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Assessing Cognitive Function in Chronic Sport-Related Head Impacts and Aging

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Abstract

Healthy normal aging and cumulative head trauma (concussion and subconcussion), can influence cognition independently and concomitantly leading to substantial late-life cognitive impairments (e.g., as seen in increased rates of dementia). With this as motivation, this dissertation explores three aspects of aging, head injury and cognition using the Cambridge Brain Sciences (CBS) cognitive battery (www.cambridgebrainsciences.com).

Study 1 (Chapter 2): Concussion-specific testing combines assessments from multiple domains to evaluate a variety of functions. While clinically relevant, their succinct nature limits the amount of cognitive information available. Eighteen male football athletes were examined at baseline using the Sport Concussion Assessment Tool (SCAT) 3, and CBS battery. SCAT3 cognition test (Standardized Assessment of Concussion) scores significantly correlated with just the verbal cognitive domain assessed by CBS. This suggests a narrow scope which may miss other aspects of cognition that could be equally vulnerable in concussion.

Study 2 (Chapter 3): It is likely that both subconcussive and concussive impacts contribute to the cognitive changes seen in retired athletes. What remains unclear is when these changes first appear and how they can be detected. This study compared 81 male football athletes (high cumulative impact burden) and matched controls (low cumulative impact burden) on cognitive test performance and response time. Results demonstrated response time deficits (slowed and more variable) without score impairments in football athletes in comparison to controls, which may represent pre-clinical compensatory mechanisms mitigating an increased cognitive demand.

To address limitations in repeating Study 2 in contact sport retirees, **Study 3 (Chapter 4)** employed discriminant function analysis (DFA) to reduce the CBS battery for better application in aging populations. 118 younger and 118 older participants were included. Five of the 12 CBS tests were necessary to retain 98% of the variance accounted for between groups in the full model. Additionally, CBS tests were divided into 3 categories based on significant differences in the full and reduced models: no significant differences (n = 2),

significant differences only on full model (n = 5), and significant differences on both models (n = 5). Results support the use of a modified CBS battery in age-related studies.

Keywords

Cognitive Function, Subconcussion, Response Time, Aging, Neuropsychological Testing, Data Reduction

Co-Authorship Statement

The written material in this thesis is the original work of the author. Danielle Brewer-Deluce participated in all aspects of the work contained herein: conception of the hypotheses, conduction of the experiments, statistical data analysis and authorship of the manuscripts. The role of co-authors is detailed below by chapter.

Chapter 1: Using the SCAT3 and CBS Cognitive Battery to Assess Cognitive Dysfunction in Non-Concussed American Footballers

The development of this research study was shared by D Brewer-Deluce, TD Wilson and AM Owen. Data were collected by D Brewer-Deluce in partnership with the Fowler-Kennedy Sports Medicine Clinic. Statistical analysis, data interpretation and manuscript preparation were completed by D Brewer-Deluce with input from TD Wilson and AM Owen.

Chapter 2: Slowed and Variable Response Times in Collegiate American Footballers

This study was developed by D Brewer-Deluce, TD Wilson and AM Owen. Data were collected by D Brewer-Deluce with support from J Brooks and K Campbell in partnership with the University of Western Ontario Football and Rowing Teams. Data were analyzed by D Brewer-Deluce and interpreted by all authors. The manuscript was composed by D Brewer-Deluce with input from TD Wilson and AM Owen.

Chapter 3: Reducing the CBS Battery to Explore Age-Based Differences in Cognitive Function

D. Brewer-Deluce developed the premise and hypotheses for this research study. Statistical methods consultation was provided by M Speechley and A Johnson. CBS Data were mined from the CBS data base by C Wild, analyzed by D Brewer-Deluce, and interpreted by all authors. D Brewer-Deluce prepared the manuscript with input from TD Wilson and AM Owen.

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"the pessimist complains about the wind; the optimist expects it to change;
the realist adjusts the sails"

- William Arthur Ward

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Annotated List of Abbreviations

AD: Alzheimer's Disease

A progressive neurodegenerative disease characterized by a subtle and graded progression. Characteristically, patients experience early and severe declarative memory deficits as well as later deficits in attention, language and reasoning.

ADHD: Attention Deficit Hyperactivity Disorder

A brain disorder marked by an ongoing pattern of inattention and/or hyperactivity-impulsivity interfering with functioning or development

BESS: Balance Error Scoring System

The balance component of the SCAT, comprised of 3 X 20s trials of double, single and tandem leg stances. Max score = 30

BOLD: Brain Oxygen Level Dependent

An fMRI measure detecting changes in blood oxygen levels which correspond to energy use in local cells

CBS: Cambridge Brain Sciences

The neuropsychological testing platform used throughout this dissertation. Available at www.cambridgebrainsciences.com

CRT: Concussion Recognition Tool

The lay-persons equivalent to the SCAT, designed to aid in concussion recognition and transfer of care to medical professionals

CT: Computed Tomography Scan

A standard clinical imaging protocol which combines many x-ray measurements at different angles to produce cross-sectional images

CTE: Chronic Traumatic Encephalopathy

A neurodegenerative tauopathy diagnosed post mortem through the identification of abnormal hyperphosphorylated tau (p-tau) accumulating in neurons and astroglia around small blood vessels in cortical sulci.

DDA: Descriptive Discriminant Analysis

A form of DFA which explains differences between compared groups

DFA: Discriminant Function Analysis

An alternative statistical approach to MANOVA, focused on how different weighted linear combinations of the dependent variables predict group membership or explain differences between groups. Used in this dissertation as a method of variable selection. Includes predictive (PDA) and descriptive (DDA) components

DMN: Default Mode Network

A cortical network thought to primarily active during wakeful rest (eg. mind-wandering, day dreaming)

DTI: Diffuse Tensor Imaging

A specialized type of MRI used to map white matter tractography in the brain by measuring the restricted diffusion of water in neural tissue

FA: Fractional Anisotropy

A DTI measure expressing the extent to which water is impeded. High value = decreased neuronal structural integrity (unimpeded movement). Can be divided in to axial and radial components

fMRI: Functional Magnetic Resonance Imaging

A specialized MRI which measures brain activity by detecting changes associated with blood flow

g: gravitational force

A unit denoting acceleration, typically measured with an accelerometer. Equivalent to 9.8 newtons of force per kilogram of mass

"g" : General Ability

Defined by Spearman in 1904 in describing human intelligence – represents a unitary dominant factor accounting for correlations in performance between cognitive tasks

"g_f" : Fluid Intelligence

A sub-component of g later defined by Cattell (1941). Refers to the ability to solve new problems, use logic in new situations, and identify patterns. Similar to Mechanics of Cognition (Baltes 1987) and Biological Component of Intelligence (Lövdén et al 2004)

"g_c" : Crystallized Intelligence

A sub-component of "g" later defined by Cattell (1941) Refers to the ability to use learned knowledge and experience. Similar to Pragmatics of Cognition (Baltes 1987) and Cultural Component of Intelligence (Lövdén et al 2004)

HTT: Hampshire Tree Task

A CBS cognitive task requiring participants to arrange numbered beads in ascending order on a tree-shaped frame

ImPACT: Immediate Post-Concussion Assessment and Cognitive Testing

A computerized concussion assessment tool primarily assessing cognitive function

LD: Learning Disability

a condition giving rise to difficulties in acquiring knowledge and skills to the level expected of those of the same age, especially when not associated with a physical handicap

LOC: Loss of Consciousness

An interruption of awareness of oneself and one's surroundings

MACFIMS: Minimal Assessment of Cognitive Function in Multiple Sclerosis

A 90-minute clinical neuropsychological test battery used to assess for cognitive change in MS patients including processing speed, working memory and recall

MCI: Mild Cognitive Impairment

A transitional stage between normal aging and dementia where patients complain of memory problems, but do not meet diagnostic criteria for AD

MD: Mean Diffusivity

A DTI measure expressing the extent to which water displacement is directionally dependent in its flow along a cell. High value = intact white matter microstructure

MEG: Magnetoencephalography

A neuroimaging technique similar to EEG which records magnetic fields produced by electrical currents occurring in the brain

MMSE: Mini Mental State Exam

A clinically valid test for assessing cognitive dysfunction in dementia requiring 5-10 minutes. It includes 11 questions and is scored out of 30

MoCA: Montreal Cognitive Assessment

A brief cognitive screening tool for mild cognitive impairment. It takes approximately 10 minutes to administer and is scored out of 30

MRI: Magnetic Resonance Imaging

A non-invasive imaging technique used to form pictures of anatomy and underlying physiology using strong magnetic fields, electric field gradients, and radio waves

mTBI: Mild Traumatic Brain Injury

Synonymous with Concussion.

NFL: National Football League

A professional American football league

PCA: Principal Components Analysis

A statistical exploratory analysis used to describe relationships among variables by identifying a relatively small number of themes, dimensions, components or factors common amongst the dependent variables

PD: Parkinson's Disease

A neurodegenerative motor disorder characterized by resting tremor, cogwheel rigidity, bradykinesia and postural reflex impairment. Characterized by reduce processing speed, decreased working memory and deficits in strategic memory

PDA: Predictive Discriminant Analysis

A form of DFA which predicts group membership based upon predictor (dependent variable) values

RT: Response or Reaction Time

The time taken to complete a task

SAC: Standardized Assessment of Concussion

The cognitive component of the SCAT. Comprised of orientation, immediate memory, concentration and delayed recall tests. Max Score = 30

SCAT: Sport Concussion Assessment Tool

A clinically valid side-line concussion assessment tool assessing cognitive, behavioural and symptomatic changes in athletes. Included numbers denote test version. Child (ages 5-13), and Pocket (miniaturized, replaced by CRT) versions also exist

STM: Short Term Memory

A CBS cognitive component derived from completing the CBS cognitive battery

TBI: Traumatic Brain Injury

An insult to the brain, not of degenerative or congenital nature, but caused by external physical force impairing cognitive abilities or physical functioning.

TOL: Tower of London

A cognitive task developed by Shallice (1982) where participants order numbered balls within sock-like containers

WAIS-R: Wechsler Adult Intelligence Scale – Revised

A general test of intelligence for adults. This reduced form of the WAIS consists of six verbal and five performance subtests.

Chapter 1

1. Literature Review

The focus of this dissertation is to better understand the influence of head injury and aging on cognitive function. While impactful individually, their concomitant consideration is necessary to fully appreciate long-term consequences. This is a complicated circumstance for study, however, and understanding their independent influence is necessary. As such, each study within this dissertation focusses on a single aspect that lays the ground work for future studies. Specifically, I aimed to:

1) better understand how cognitive function is clinically assessed in acute concussion,
2) determine if behavioural changes in cognitive function are measurable in non-concussed varsity football athletes
3) prepare a suitable battery for use age-related studies such that aspects of chapter 3 might be replicated in an aged population (namely sport retirees)

The following literature review will introduce and situate three critical topics. Specific sections will speak to: Cognitive Function, Head Injury and Cognitive Function, and Aging and Cognition while highlighting the literary gaps addressed by the three studies undertaken in this dissertation. I close the literature review with a Summary of the Dissertation to provide an outline of the studies. Finally, since Chapter 4 relies upon advanced multivariate statistical methods, a statistics overview is offered in Appendix 5.

1.1 Cognitive Function

1.1.1 A Brief History of Unitary vs Multifactorial Views

Broadly, cognitive function represents one's ability to draw upon appropriate cognitive processes to perform a given task or test. Perhaps as we better know it, intelligence, is described to be an "emergent property of anatomically distinct cognitive systems, each of which has its own capacity."[1] This understanding has evolved since intelligence was first described in 1904 by Charles Spearman.[2] Originally, intelligence was thought of as a unitary, dominant general factor, termed "g." It accounted for correlations in

performance across several cognitive tasks,[1] and could be assessed from test scores which serve as indicators.[3] Evidence supporting the theory of "fluid" and "crystalized" abilities, (1941[4]) which sub-divides "g" into two components, then began to emerge.[5] Cattell proposed that these two factors were so similar in their loading patterns that dissociating them was exceedingly difficult and that what had been previously measured as "g" was indeed fluid and crystallized abilities together.[5] He described these abilities as differing yet complementary facets of cognition as outlined in Table 1.1.[5] Though other authors described these two components with slightly different headings, the main consideration is that each of these components is differentially subject to age and injury, and can be used to explain patterns of cognitive change over time. In terms of long-term cognitive changes, cognitive function undergoes two phases: early development, then a gradual decline. The timing of each phase, however, depends upon the types of cognitive skills in question. For example, Figure 1.1 describes the age-associated trajectories of the two previously described cognitive components.[6] Essentially, the biological, "fluid" part of cognition is expected to decline after maturity, while the cultural, "crystallized" component increases with age as long as knowledge maintenance and acquisition outweigh age-based losses.[6]

There are, however, limitations to this type of factorial analysis when using behavioural data alone. Through leveraging the spatial segregation of functional brain networks,[1] functional Magnetic Resonance Imaging (fMRI) has enabled new perspectives on intelligence. For instance, in a 2012 paper published by our lab, the Cambridge Brain Sciences (CBS) cognitive battery was used to measure a range of cognitive skills. Using principal components analysis (PCA) on behavioural and fMRI data, three significant components were extracted showing that intelligence as a whole could be broken down into three cortically distinct areas supporting reasoning, short term memory, and verbal abilities.[1] These regions, and their anatomical components are pictured in Figure 1.2. From these results, the authors concluded that these components reflect the way in which the brain regions "are organized into functionally specialized networks, and moreover… the tendency for cognitive tasks to recruit a combination of these functional networks."[1]

Table 1.1: Summary of 2-Component Intelligence. Columns represent contiguous ideas expressed in various models

	Fluid Intelligence (g_f)	Crystallized Intelligence (g_c)
Cattell (1968)[5]	• More important for tasks requiring adaptation to new situations	• More important for tasks which solidify previously learned skills/habits
	• Ability maximum around age 14-15	• Ability increases to age 18, to 28 or beyond depending upon the cultural learning period
	• Ability declines continuously from age 22 onwards	• Ability declines later and to a lesser degree than g_f over time
	• Physiologically/biologically determined	• Product of environmentally varying changes in g_f
	• Stronger influence of general brain damage	• Stronger influence of localized brain damage
	• Ability determined by present and operative influences in the current moment	• Ability is determined by and representing history
	• "A capacity to perceive relations and educe correlates"	• Function of previous time applying fluid ability; memory; and specific, problem solving aids
	Mechanics of Cognition	**Pragmatics of Cognition**
Baltes (1987)[7]	• Age-based maturation, stability and decline	• Further advances and function at peak levels with aging
	• Basic architecture of information processing and problem solving	• Context- and knowledge-related applications of mechanics
	• Perceiving relations and classification	• Language, social intelligence, occupational expertise
	Biological Component	**Cultural Component**
Lövdén, Ghisletta, & Lindenberger (2004)[8]	• Fundamental organization properties of CNS; basic information processing	• Acquisition and expression declarative and procedural knowledge transmitted through socialization
	• Speed, accuracy, coordination of elementary processing	• Verbal knowledge, specialized expertise, pragmatic knowledge/wisdom
	• Tested by tasks requiring: discrimination, categorization, selective attention, reasoning in novel domains	• Tested by tasks requiring: reading/writing skills, everyday problem-solving, knowledge of self, and daily conduct[6]
	• Episodic memory (eg. autobiographical facts)	• Semantic memory (eg. general world knowledge)

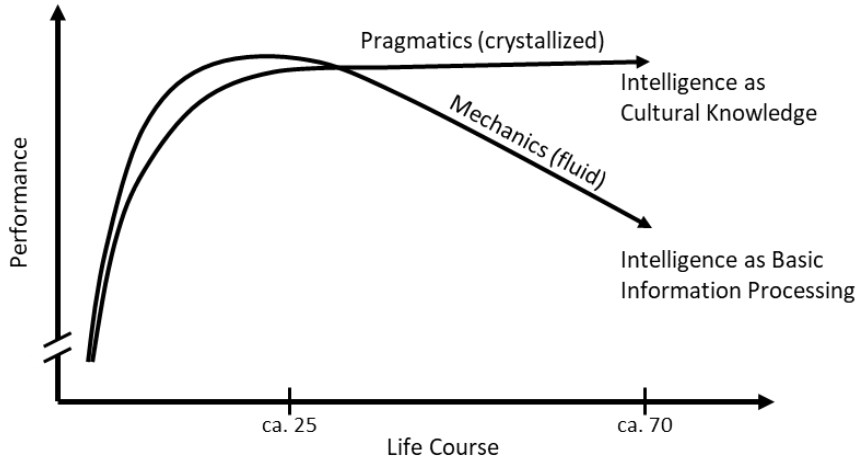
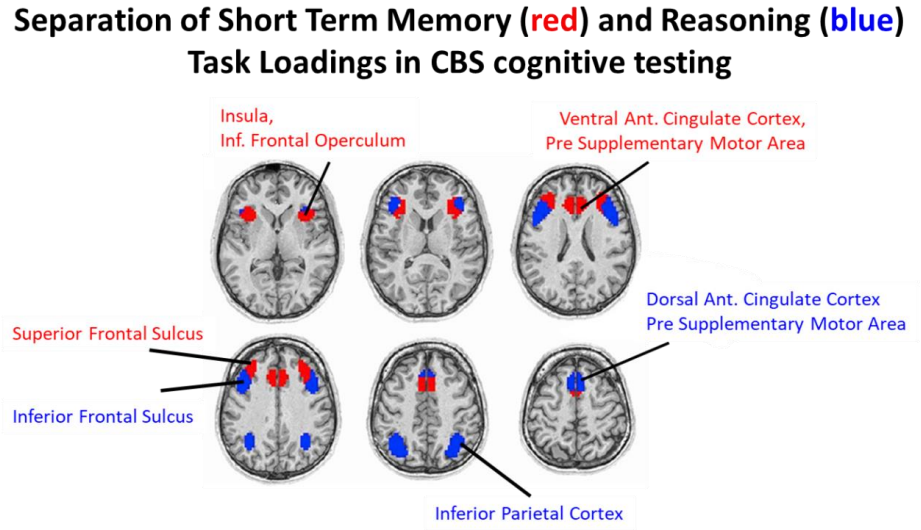


Figure 1.1: Trajectories of the two-component model of cognitive development throughout the lifespan. From Lindenberger 2001, used with permission from Elsevier © 2001



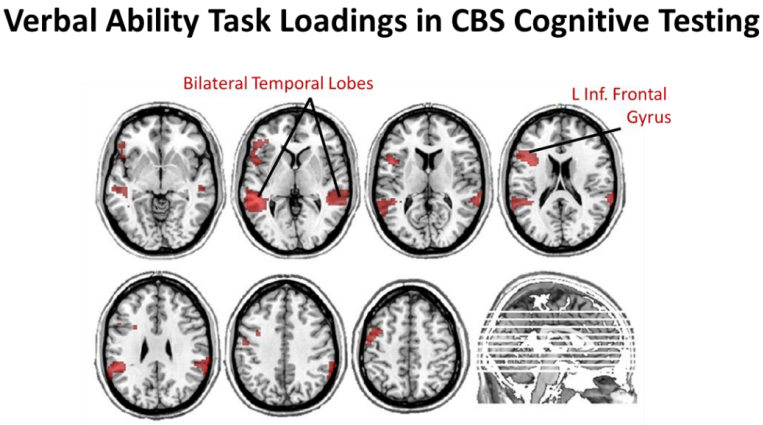


Figure 1.2 Cambridge Brain Sciences Cognitive Network Anatomy - adapted from Hampshire et al 2012 and used with permission from Elsevier © 2012

1.1.2 Reasoning, Short Term Memory and Verbal Abilities

As demonstrated by Hampshire et al, reasoning, short term memory, and verbal abilities are of specific interest throughout this dissertation. In exploring what these concepts represent, it is important to consider different models of memory or intelligence.

First, Baddeley & Hitch's multicomponent model of working memory (Figure 1.3) has provided a relatively stable depiction of how memory might work over the past 30 years. In its current form, the model consists of 4 components: the central executive, two short term memory buffers (the phonological loop, and visuo-spatial sketchpad) which operate independently of each other, and the episodic buffer.[9]

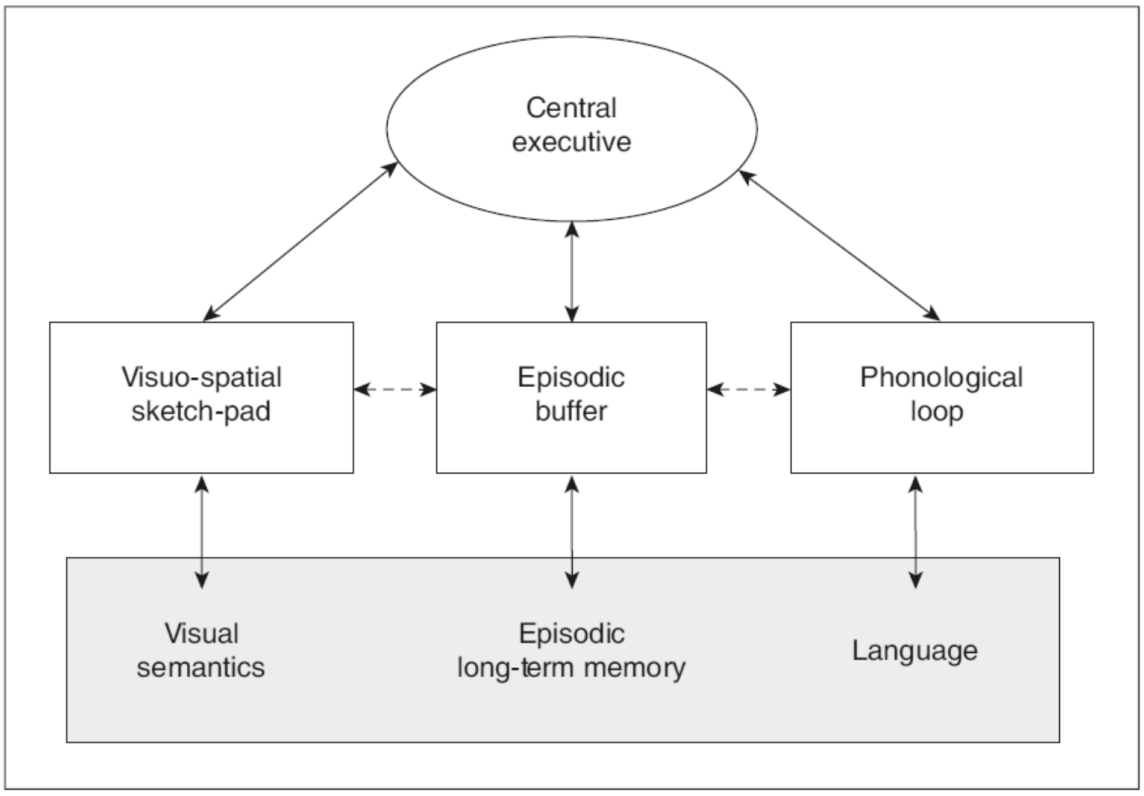


Figure 1.3: The Multicomponent Model of Working Memory designed by Baddeley and Hitch. From Baddeley 2010, used with permission from Elsevier © 2010

Based on their model, the central executive represents the attentional control of working memory or "executive function." Together, the visuospatial sketchpad and phonological loop represent short-term memory stores corresponding to spatial and verbal information respectively. Finally, the episodic buffer acts as a temporary store to combine sensory

information with long term memory for the central executive to then use to facilitate performance. Each of these systems is limited, either in the capacity of information they can hold, or manage which imposes limits on human function. Typically, short term memory can hold ~7 pieces of information,[10] the episodic buffer can hold ~ 4,[11] and the central executive is limited by attentional demands.

More recently, state-based models (Figure 1.4) have taken on increased prominence. In this form, models assume that attending to a long-term memory representation allows its transition into working memory where it can be manipulated and retained by short term memory. Further, it is this attentional selection which can explain capacity limitations.[12] The idea is that the central executive processes that manage the focus of attention to select relevant information from the short-term store, and retrieve information from the long-term store, are under effortful voluntary control.[13]

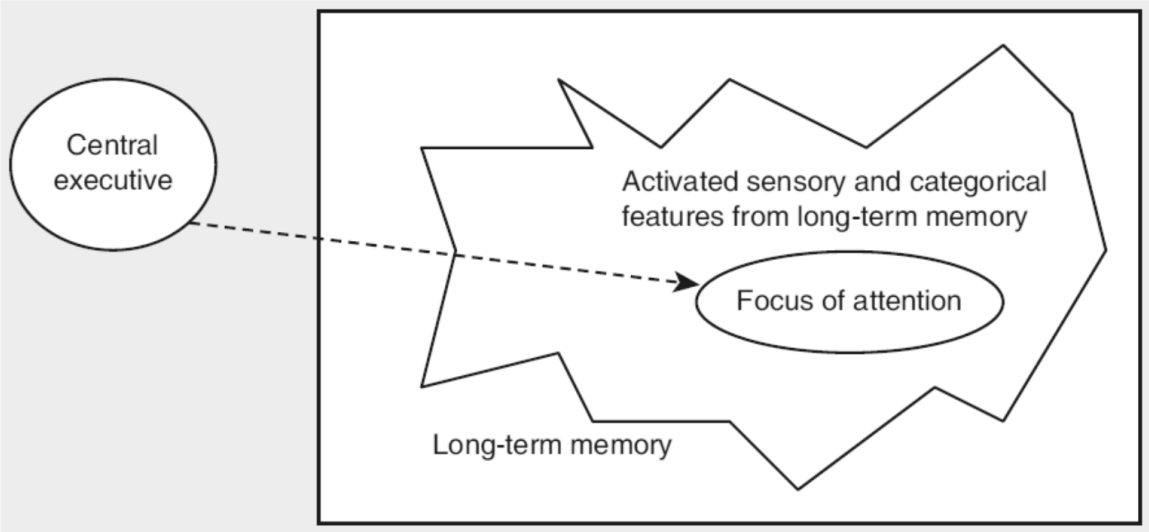


Figure 1.4: Cowan's Model of Memory. An example of "state-based" models which treat working memory as the temporary activation or long-term memory through attention. From Baddeley 2010, used with permission from Elsevier © 2010.

From this perspective, short term memory represents all activated information from long-term memory above baseline (jagged polygon outlined in Figure 1.4), while working memory can be thought of as short term memory plus the limited-capacity, attention processes associated with the central executive that maintain attentional focus.[14]

More recent models, such as Duncan's model of multiple demands (MD) have paired behavioral cognitive measures with neuroimaging to better link cortical structure with function. As pictured in Figure 1.5, Duncan notes a "common pattern of activity that is a salient part of the brain's response to many different kinds of cognitive challenge" similar to that activated by tests of fluid intelligence.[15] Anatomically, the MD cortex extends through the prefrontal and parietal cortices specifically including the: inferior frontal sulcus (IFS), anterior insula/frontal operculum (AI/FO), the pre-supplementary motor area/dorsal anterior cingulate (pre-SMA/ACC), and the intraparietal sulcus (IPS), and occasionally the rostrolateral prefrontal cortex (RPFC). In Duncan's model, problem solving requires that goals are broken down into a series of sub-tasks which are separately defined and solved. Doing so has several requirements including focusing on relevant parts of the current sub-step including identifying strategies for novel aspects, and task switching as steps are completed and a maintenance of results to carry forward between tasks – all of which the MD cortex is posited to be well suited to.[15] Importantly, two cognitive networks, reasoning and short term memory, explored by the Cambridge Brain Sciences cognitive battery (see section 1.1.5) are found within the MD cortex.[1]

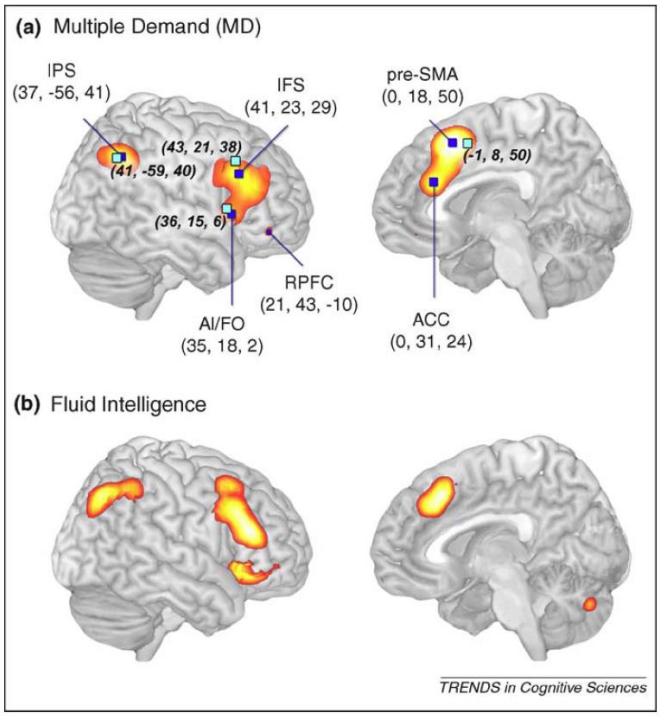


Figure 1.5: MD and Fluid Intelligence patterns of activation. From Duncan 2010, used with permission from Elsevier © 2010

Overall, in a more general sense, working memory describes how we assemble and remember relevant information to perform a complex task. It aids in tasks requiring planning, initiation, sequencing and monitoring of complex goal directed behaviour.[16] Short term memory represents the "type of memory we use when we wish to retain information for a short time to think about it" and exists as a subset of working memory for storage.[14] Finally, verbal abilities represent tasks which employ numerical or verbal stimuli. [1]

1.1.3 Speed & Cognition

A final model to explain cognitive function introduces a linkage between cognitive function and speed as a means to better understand information processing, particularly in aging. Speed itself represents an interesting variable is it is "objective, yields absolute ratio-scale values rather than arbitrary norm-referenced values, and is inherently meaningful across many different disciplines."[17] As described by Salthouse, (1985), This model of cognitive networks is expressed as a series of nodes, existing at various hierarchical levels (see Figure 1.6).[17] It is assumed that nodes are stimulated by a physical stimulus, and that activation spreads upwards to all connecting nodes, only if the total level of activation at a given node exceeds a threshold. Activation is assumed to dissipate over time, and thus activation between connected nodes must converge in a limited time interval to aggregately sum. Critically, nodes at higher levels generally have fewer inputs than their lower counter parts. Thus, the higher the node level, the more complex or abstract processing undertaken, and support required from earlier nodes. With these assumptions and limitations in place, those with faster processing have a greater ability to sum neural responses across nodes which may have otherwise asynchronously decayed in slower individuals. Importantly, in a simulation of a neural network with this structure, Salthouse noted that "pronounced effects of processing rate may occur only when the speed differences are evident beyond the input phase of processing."[17] Cleary, speed has "important consequences for both quantity and quality of responses,"[17] a critical notion given the generalized slowing expected in normal aging as discussed in section 1.3. Importantly, speeded measures on different tasks seem to correlate about 0.3 with each

other, which suggests correlations between speed and cognitive function should be around the same level.[17]

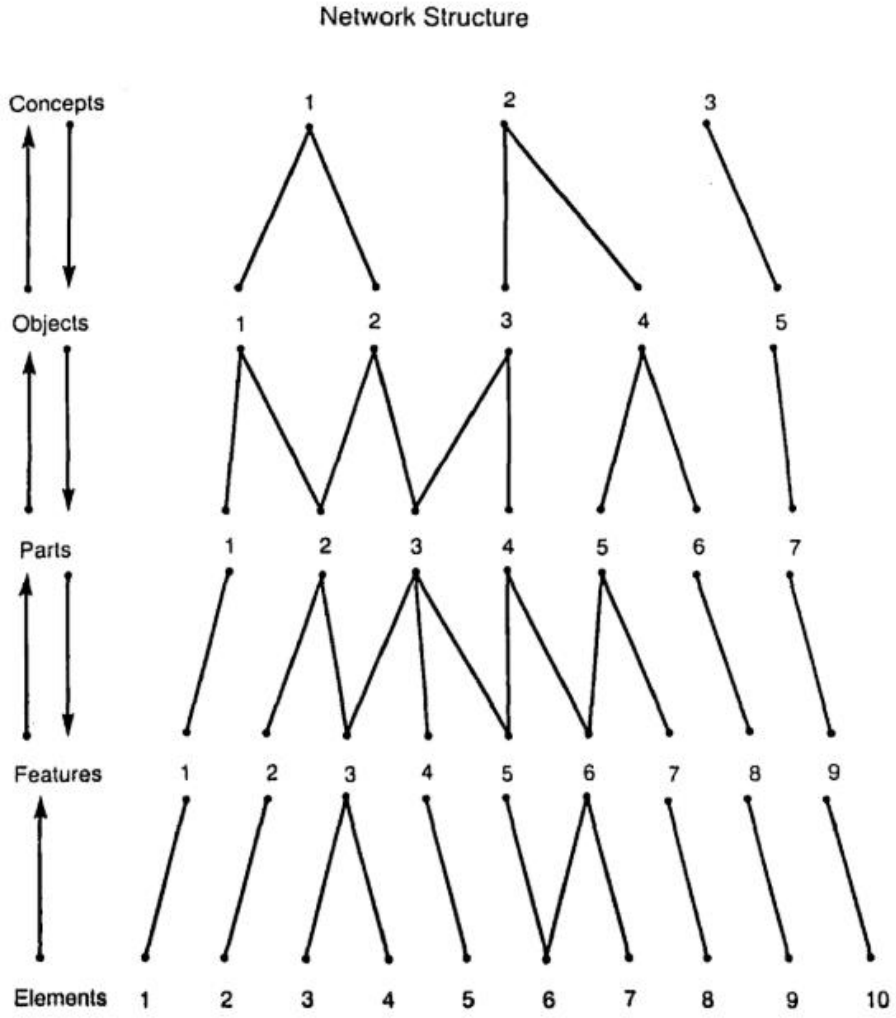


Figure 1.6: Simple Hierarchical Network Structure. Higher levels represent progressively more abstract processing. From Salthouse 1985, used with permission from Elsevier Limited © 1985/2000

1.1.4 Assessing Cognition – Neuropsychological Tests

Neuropsychological tests are a key tool for assessing cognitive function. Typically, scores on a single test are combined with other tests to form aggregate battery scores, though they can be, and sometimes are, compared directly. Generally, testing is restricted to a fairly short time span, thus tests must be short and easy to administer, while remaining valid, reliable and sensitive.[18]

1.1.4.1 Neurocognitive Test Formats & Administration

There are three formats of neurocognitive tests: Pen & Paper, Computerized and Hybrid.

Traditional Pen & Paper tests have been available to clinicians for the longest period of time.[19] They offer a more flexible task-specific approach to testing with more overt behavioural observation of effort and assessment of auditory-based processing.[19] They are, however, time-intensive and highly subject to administration/scoring variation as well as practice effects[20] due to the limited versions of tests available. Examples of pen and paper tests include: the Sport Concussion Assessment Tool (SCAT), Montreal Cognitive Assessment (MoCA), Mini Mental State Exam (MMSE), and Wechsler Adult Intelligence Scale – Revised (WAIS-R).

Computerized tests typically offer a more brief period of assessment with standardized administration and scoring and the capability to assess differences in reaction time and processing speed.[19] The Immediate Post-Concussion Assessment and Cognitive Testing (ImPACT) tool is an example of a computerized test.

Hybrid methods use a greater number of test measures across a more broad range of cognitive domains as they pull from both pen & paper and computerized techniques.[20,21] While this may harness some added benefits, this approach is not always feasible due to cost or time restrictions, or the lack of a neuropsychologist to interpret the results.[19]

1.1.4.2 Understanding Neuropsychological Test Scores

A fundamental principle of neuropsychological testing is that what is measured over time is "presumed to reflect true changes in the construct being measured by the test."[22] While this is of course the ideal circumstance, in actuality, several factors beyond natural ability can influence test scores. For example, over 75 years ago Cattell et al (1941) described that test performance, or rather the inter-individual variation in such a measure as intelligence, is reliant upon several factors including:[3]

- ***G***: Genetic Variation
- ***dG***: Environmental Variation (post-conceptually)
- ***c***: Cultural Variation (cultural appositeness aligned with test)

- ***t***: Variability of test familiarity (training, practice, exposure to similar formats)
- ***f***: Normal fluctuations in ability (through physiological and other variables)
- ***fv***: Changes in performance ability and volition
- ***e***: Chance errors
- ***K***: Special factors
- Age (systematic trend)

$$Performance = G + dG + c + t + f + fv + e + K$$

These factors and their influence on score interpretation are outlined below. While some of these sources of error are random and cannot be controlled, others are systematic and may be accounted for with good test design and administration. Regardless, understanding how outside factors may influence results is important for those looking to interpret neuropsychological test scores.

1.1.4.3 Participant-Specific Factors Affecting Test Scores

Sex and history of previous concussion[23], age, and mental health status including depression, anxiety, ADHD and learning disabilities[24] are shown to influence neuropsychological scores at baseline or post-injury in test-specific ways. Additionally, these characteristics may also influence practice effects in repeated test administration.

1.1.4.4 Test Sensitivity and Reliability

Ideally, a good test allows administrators to conclude that changes observed between sessions or groups reflect concrete changes in performance rather than normal variability in the test or individual. This is a key consideration in the use of neuropsychological tests for diagnosis and injury detection[25] and relies heavily on both test sensitivity (ability to measure deficits or change when present) and reliability (stability of measures over time and across groups).[20] Importantly, there are psychometric factors that influence both of these facets, some of which are controllable (see Table 1.2) through experimental design.

Table 1.2: Psychometric Factors Influencing Test Sensitivity and Reliability[25]

Psychometric Factor	Controllable Aspect	Rationale
Number of Observations	↓ Measurement Error & ↑ test reliability with ↑ observations	Influence of single unrelated error minimized
Continuous vs. Interval Variables	Continuous variables (e.g. response time) are more sensitive to subtle change	More degrees of freedom
	Tests with a ceiling effect are less able to detect mild cognitive changes	Even mildly impaired individuals will continue to perform well
Response Hardware in Computerized Tests	Increased hardware (e.g. mouse & keyboard vs touchscreen) = poor reliability	↓response time accuracy and ↑ variability
Difficulty Across Alternate Test Forms	Multiple forms prevent cheating, must ensure equal difficulty	Translated forms are especially prone to issues

1.1.4.5 Practice Effects

In clinical practice, neuropsychological tests are used through repeat administrations to offer a longitudinal assessment of performance over time (baseline testing), or occasionally in rapid succession to assess acute injury and rehabilitation.[26,27] In doing so, however, a distinction must be made in determining whether score changes reflect improvement due to recovery or repeated test-administration. Additionally, in the event where no change is found, researchers will want to know if it is it because there in fact is no change, or that practice effects mask an observable decline.[28,29] Importantly both participant specific factors like age[29] and clinical status[30], and test-specific factors like inter-test interval,[31,32] and type of test[33] can all influence practice effects (see Table 1.3).

Practice effects are defined as "score increases due to factors such as memory for specific test items, learned strategies, or test sophistication,"[22,34] and are hypothesized to exist independent of true changes in an individual's ability.[22] This concept is different from reliability as it is less concerned with how consistently a test can measure a certain metric, but rather how a person's performance changes on that metric for reasons beyond ability. When not taken into account, practice effects can compromise the validity of an assessment or research finding.

Table 1.3: Subject and Test Characteristics Influencing Practice Effects

		Influence	Rationale/Evidence
Subject Characteristics	**Age**	Practice effects may become smaller with age[22] - Attention/concentration, visual perception, naming ability, and verbal learning least affected[29] - Serial recall insensitive to age[29] - Memory for logical passages declines after age 75[29]	Older adults may fail to encode or store test-relevant information[22]
	Clinical Status	Practice effects in non-clinical populations may not be transferable to clinical groups[22]	- previous TBI pts ↑performance on letter fluency task to lesser degree than controls[28] - Pt populations may show greater gains on tests with ceiling than controls already performing near ceiling[22]
Test Characteristics	**Type of Test**	Score gains larger for processing speed vs verbal tasks[22]	Identifying advantageous test-taking strategies cause discrete initial gains [22]
		Negative effect of memory test items with short delay[26]	Interference similar remembered information[26]
		Visual memory > Executive Function > Visuospatial ability tasks in practice effects[22]	
	Retest Interval	Effects decrease with increasing interval[22]	Difficult to disentangle practice from change or individual variability over long time periods[35]
	Number of Trials	No consistent pattern – complex function of many factors (subject and test)	Evidence for - $1^{st} \rightarrow 2^{nd}$ trial increases[35] - Continuous improvement[28] - Quadratic then decline[22]

Reducing Practice Effects

Several strategies exist to minimize the influence of practice effects. Since most practice effect learning occurs between the first and second test administrations, offering baseline practice sessions or dual-baselines in which the second test scores are used[36] may be effective. This method, however, can be costly in terms of time and resources, and may be tiresome for participants which could compromise scores. As previously mentioned, alternate test formats offer reduced potential to memorize test answers,[22] and thus have been shown to be effective in lowering the size of practice effects related to memory components.[22] Caution is, however, advised as it doesn't combat the effects associated with understanding how to complete the test itself, multiple test versions are often

unavailable, and when they are, ensuring equivalent difficulty between versions is paramount.[22] Comparison to normative scores has also been proposed as a method for reducing practice effects; however, since much literature on normative test values either focuses on scores from the first two test administrations,[28] and therefore fails to report how normal results are expected to change over time, this approach is limited. Comparing an intervention group with a placebo group is another common practice though brings with it potential limitations of differing clinical status. A quick note on assessing clinical populations is that sometimes the failure to demonstrate practice effects may serve as valuable clinical knowledge in terms of both assessing current problems or in providing prognostic potential.[22,37,38]

1.1.4.6 Invalid Tests

A second key understanding in neuropsychological testing is that tests administered "do not directly measure cognition: they measure behaviour from which we make inferences about cognition."[39] Thus determining whether acquired data is invalid is paramount. Invalid data may be the result of unintentional factors like problems understanding the questions or testing in a distracting environment, or even intentional efforts to perform poorly[40–42] to potentially hide later injury-related impairments, particularly in sporting environments. Given the broad variability in participant scores, identifying invalid data is not straightforward. Although some tests (e.g. ImPACT[41]) incorporate measures of validity into their scoring such that probable invalid scores will be flagged, or cut off scores to eliminate implausible trials (e.g. CBS, see Appendix 1) recognition by examiners is necessary.

1.1.4.7 Considerations in Analyzing Reaction Time Data

Reaction time (RT) data typically reflects cognitive performance in terms of attention.[43] Historically, and most popularly, reaction time has been analyzed using general linear model methods (eg. ANOVA) to assess changes in the central tendency of the data. This offers performance information and a relatively simple analysis protocol. It can, however, be limited in that hypothesis testing of a population's central tendency using data that is skewed, contains outliers, or is heteroscedastic (raw RT data typically have the first two)

reduces power and can result in a failure to detect a real difference between conditions.[44,45] With these limitations in mind, researchers may choose to: delete some proportion of extreme trials (outliers), or transform the data.[44]

Cutoffs represent the most powerful[44,46] and common strategy employed in RT analysis Specifically, unlikely RTs representing processes other than the one being studied are eliminated based on a prescribed value.[46] RT outliers fall into one of two categories:

Short: result of fast guesses

- A lower thresholding of 100ms is necessary[47] to allow sufficient time for stimulus perception and motor response[44]

Long: due to multiple runs of the same process under study, subject inattention or guesses based on a failure to reach a decision[46]

- More difficult to identify
- Eliminating <5% of the data is reasonable

Data Transformation: Transforming RT to speed (reciprocal of latency) somewhat normalizes the RT distribution to maintain good power. The final interpretation, however, is often difficult as relationships within the data have changed.[44,46]

Managing Error Responses

A final consideration in RT data analysis is managing error responses. Errors can have different distributional properties from correct responses,[48] and thus have been classically treated in one of two ways: 1) exclude error trials from analysis or 2) replace error responses with mean or median of the condition. Excluding trials may carries the risk that too little valid data will remain in trials with a high proportion of errors, and replacing error values can reduce data variability.[46]

1.1.5 Cambridge Brain Sciences (CBS) Cognitive Battery

The Cambridge Brain Sciences (CBS) cognitive battery is the primary neuropsychological test employed across all three studies within this dissertation. The battery is "more diverse than those applied in classical IQ tests"[1] and contains 12 non-

verbal, culturally independent tests[1] that can be administered in 60 minutes.[49] The computerized adaptive platform allows tests to increase or decrease in difficulty to quickly iterate towards a participant's peak ability, and change with each administration to limit cheating attempts. Final scores reported are calculated based on the number of correct vs incorrect responses, the number of trials completed and the difficulty level reached. Validated in over 44 000 participants,[1] the test has been used to assess cognitive change in NHL Hockey[50] and NFL Football Alumni.[51] CBS scores also correlate with the Minimal Assessment of Cognitive Function in MS (MACFIMS)[52] and have been used to differentiate cognitively intact from cognitively impaired (scores of 23-26 out of 30) on the Montreal Cognitive Assessment (MoCA).[53]

Through Principal Component Analysis, we also know that the CBS primarily loads on three cortically distinct and functionally specialized cognitive networks that support reasoning, short term memory and verbal abilities (see Figure 1.2 for anatomical representations).[1] As cortical networks may offer a higher level assessment of cognitive function beyond single test scores alone, "CBS Cognitive Composite scores" representing these reasoning, short term memory and verbal components were calculated as linear composite scores based on PCA factor loadings (Table 1.4) determined by Hampshire et al (2012).

Table 1.4: CBS PCA Linear Component Factor Weightings (from Hampshire et al. Used with permission from Elsevier © 2012)

CBS Tests	PCA Linear Components		
	Short Term Memory	Reasoning	Verbal
Spatial Span	0.69	0.22	-
Monkey Ladder	0.69	0.21	-
Self Ordered Search	0.62	0.16	0.16
Paired Associates	0.58	-	0.25
Hampshire Tree Task	0.41	0.45	-
Spatial Rotations	0.14	0.66	-
Feature Match	0.15	0.57	0.22
Interlocking Polygons	-	0.54	0.30
Odd One Out	0.19	0.52	-0.14
Digit Span	0.26	-0.20	0.71
Verbal Reasoning	-	0.33	0.66
Color Word Remapping	0.22	0.35	0.51

1.1.5.1 CBS Tasks

A pictorial representation of each test is provided below alongside a brief description of the testing methods (adapted from Hampshire et al, supplementary materials[1]), and its application in broad clinical and control populations. A more succinct summary is found in Appendix 1.

Monkey Ladder

This test of visuospatial working memory is based on a task from the non-human primate literature.[54] During this task, numbered squares are displayed at random locations within an invisible 5*5 grid (Figure 1.7). After a variable interval (number of squares * 900 ms), the numbers are removed leaving the squares blank and a tone cues the participant to respond by clicking on the squares in ascending numerical order. The test finishes after three errors.

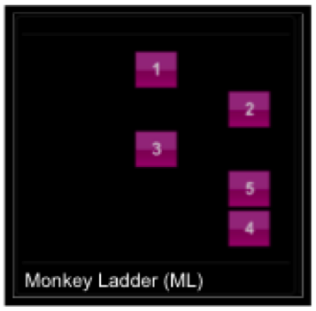


Figure 1.7: Pictorial Representation of Monkey Ladder CBS Task

The human capacity for processing information for one-dimensional judgements (eg. remembering a number, or the size of an object) is known to be limited at 7 ±2 items, which tends to increase when other dimensions are employed.[10] Since the Monkey Ladder task requires memory in three dimensions (number and a 2-dimensional location), based on the findings of Miller,[10] we might expect the peak of human performance on this test to be centred slightly higher than 7 -- which in fact it is at 8.04.

Finally, based on the findings of Inoue et al, performance on this task is liable to decrease with age due to its dependence on eidetic imagery – "memory capability to retain an accurate detailed image of a complex scene or pattern," which is known to decrease in aging.[54]

Self Ordered Search

This self-ordered sequence task is based on a test widely used to measure strategy during search behaviour.[55] Boxes are displayed on the screen in random locations within an invisible 5*5 grid. The participant must find a hidden 'token' by clicking on the boxes

one at a time to reveal their contents (Figure 1.8, token = green circle). Once found, the token is hidden within another box. On any given trial, the token will not appear within the same box twice and the participant must search the boxes until the token has been found once within each box. If they search the same empty box twice whilst looking for the token, or search a box in which the token has previously been found, an error is recorded and the trial ends. After three errors the test ends.

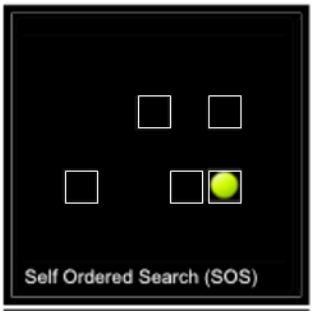


Figure 1.8: Pictorial Representation of Self Ordered Search CBS Task

This task requires three cognitive abilities: active working memory, inhibitory control, and the ability to plan/organize a sequence of responses.[55] Performance in several patient groups and their respective controls is positively correlated with the degree to which they employ a repetitive searching strategy – importantly, patents with prefrontal cortex damage are less efficient in their use of this strategy.[55,56] In addition, medicated Parkinson's disease patients (mild and severe) show increased "between search" (returning to a box where a token had been previously found) errors, but no difference in search strategy in comparison to controls.[57] Given the notable improvements seen with employing a repetitive search strategy, this task is liable to show increases between the first session and subsequent sessions when this strategy is discovered.

Hampshire Tree Task

This task is an adaptation based on the Tower of London (TOL) Task,[58] which is widely used to measure executive function. Numbered beads are positioned on a tree shaped frame (Figure 1.9) and the participant repositions the beads into ascending numerical order running from left to right and top to bottom. To gain maximum points, the participant must solve as many problems as possible, in as few moves as possible within 3 minutes. Problems become more difficult with correct solutions by increasing both the total number of moves and planning complexity required. Trials are aborted if the participant makes more than twice the number of moves required to solve the problem. After each trial, the total score is incremented by adding the minimum

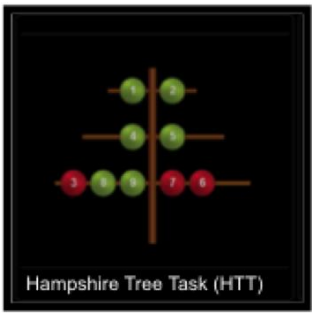


Figure 1.9: Pictorial Representation of Hampshire Tree Task

number of moves required * 2 – the number of moves actually made, thereby rewarding efficient planning.

A key difference between the TOL task and the Hampshire Tree Task (HTT) is the number of moves required to solve each problem. While both increase in difficulty over time, the TOL difficulty plateaus at a 5-move solution,[56] whereas the HTT difficulty level can exceed 20-move solutions. From the TOL literature, we know that participants completing these tasks (which are equivalent to easy levels of the HTT) require an "active search of possible solutions, placing a significant load on spatial working memory,"[56] followed by a significant loading on spatial short-term memory while the solution is transposed into a motor sequence.[57] Since the more difficult HTT trials can be thought of as a series of TOL tasks strung together, we would suppose that high level performance requires an ability to reset the sequence and engage ongoing working memory processes to continually adapt the new plan to what has been completed, and what remains to be done in the solution. Importantly, this task requires both the production and execution of a sequence (by contrast, spatial span requires just reproduction).[56]

On the TOL task, patients with frontal lobe injury have problems with producing an accurate solution prior to solving the problem as evidenced by inefficient solution patterns as well as equivalent times to first response as controls, but delayed processing times despite no differences in the number of problems successfully solved.[56] Conversely, medicated Parkinson's disease (severe) patients demonstrate decreased performance accuracy (fewer perfect trials, and fewer trials solved) as well as prolonged initial thinking times with no impairments in processing time.[57] We suspect a similar pattern would be found using the HTT in these populations, though these studies have not yet been completed.

Finally, the HTT offers some significant advantages over the TOL task as it better captures performance inefficiencies by incorporating a score reward for efficient planning, and employing adaptive changes to increase or decrease task difficulty (altering minimum number of moves required).

Spatial Span

This short term memory test is based on the Corsi Block Tapping Task[59], a classical tool for measuring spatial short-term memory capacity. To start, 16 squares are displayed in a 4*4 grid. A sub-set of the squares flash in a random sequence (Figure 1.10) and the participant is then cued to repeat the sequence by clicking on the squares in the same order in which they flashed. The test finished after 3 errors.

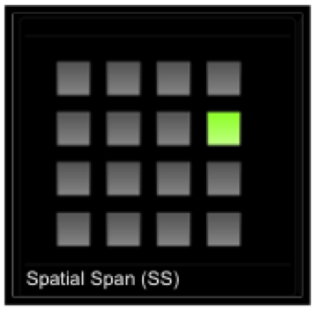


Figure 1.10: Pictorial Representation of Spatial Span CBS Task

In a similar task, medicated patients with severe Parkinson's disease were significantly impaired.[57] Through having more alternative spatial positions to select from, spatial span places a greater load on short term memory than the Hampshire Tree Task.[56]

Digit Span

This test of immediate memory span is a computerized variant on the verbal working memory component of the WAIS-R intelligence test.[60] Participants view a sequence of digits appearing one after another (Figure 1.11). They then repeat the sequence of numbers by entering them on the keyboard. The test ends after 3 errors.

Figure 1.11: Pictorial Representation of Digit Span CBS Task

As previously noted, the human capacity for processing information for one-dimensional judgements (eg. remembering a number,) is known to be limited at 7 ±2 items.[10]

Paired Associates

This task is based on a test commonly used to assess memory impairments in aging clinical populations[61] and tests episodic memory.[8] Boxes are displayed at random locations on an invisible 5*5 grid and then open one after another to reveal an enclosed object (Figure 1.12). The objects are then displayed in random order in the center of the grid and the participant clicks on the box that contained them. After three errors the test ends.

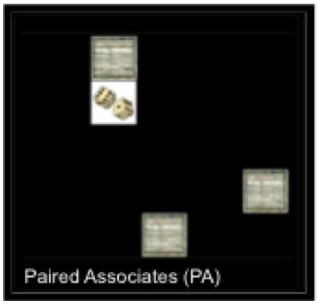


Figure 1.12: Pictorial Representation of Paired Associates CBS Task

During successful trials (independent of task difficulty) of a similar task, lateral and medial frontoparietal and occipital regions were engaged, suggestive of recognition and retrieval processing (lateral), imagery and retrieval success (medial) and perceptual and recognition processes (occipital), in both healthy and Alzheimer's disease patients when controlling for task difficulty.[61] As expected, controls were able to perform significantly more difficult tasks than patients, and differences in activation between groups was suggestive of functional compensation (eg. recruiting and activation more regions in patients outside of control response).[61]

Spatial Rotations

This test is a 2D assessment, loosely based on the Vandenberg and Kuse Mental Rotations test[62] often used for measuring the ability to manipulate objects spatially in mind.[63] In this variant, two grids of coloured squares are displayed to either side of the screen with one of the grids rotated by a multiple of 90 degrees (Figure 1.13). The grids are either identical or differ by the position of just one square. Participants must indicate whether the grids are identical, solving as many problems as possible within 90 seconds.

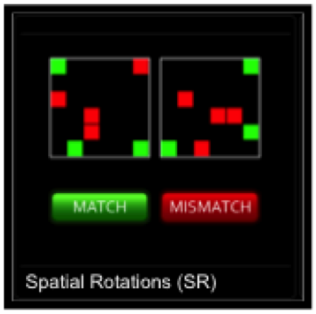


Figure 1.13: Pictorial Representation of Spatial Rotations CBS Task

It is a test of spatial ability, and specifically its sub-division entitled "mental rotation ability" which is "generally described as an individual's intrinsic ability to maintain a mental image of a two-dimensional or three-dimensional object turning in space[64]."[65] In general, there appears to be an effect of sex on tests of this type, with males generally out performing females.[63]

Feature Match

This task is based on classic feature search tasks historically used to measure attentional processing.[66] Two grids are displayed on the screen, containing a set of abstract shapes (Figure 1.14). In half of the trials the grids differ by just one shape. Participants must indicate whether or not the grids'

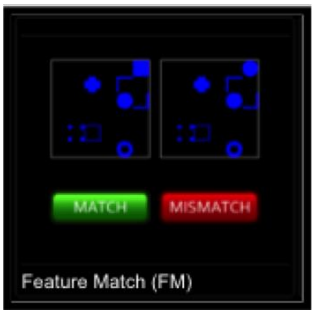


Figure 1.14: Pictorial Representation of Feature Match CBS Task

contents are identical, solving as many problems as possible within 90 seconds.

The test is based on the "feature-integration theory of attention" which suggests that a newly perceived scene is coded early in terms of colour, orientation, spatial frequency and brightness, and that objects within are later identified separately and paired with aforementioned codes to form a single object that correctly represents stimulus locations and features.[66] This secondary "combination step" is heavily reliant upon focal attention which is subject to memory decay and interference.[66] Understanding the role attention plays in this task is particularly important in assessing patients with visual agnosia who appear to have difficulties in assembling different components or properties of objects[66] as it links to describing and "impairment in simultaneous synthesis – in the capacity to pull the relevant elements together into a coherent unity."[67]

Interlocking Polygons

This test is based on a task taken from the Mini-Mental State where participants are asked to copy a design of overlapping polygons, often used in the assessment of age related disorders.[68] A pair of overlapping polygons is displayed on one side of the screen and participants must indicate whether a polygon displayed on the other side of the screen is identical to one of the interlocking polygons (Figure 1.15). The task lasts 90 seconds.

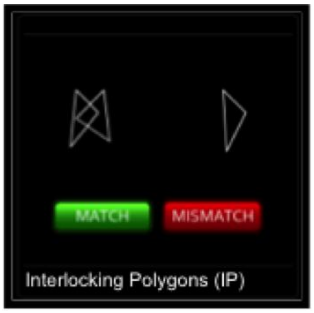


Figure 1.15: Pictorial Representation of Interlocking Polygons CBS Task

Odd One Out

This is a test of deductive reasoning, based on a sub-set of classification problems from the Cattell Culture Fair Intelligence Test.[69] A 3* 3 grid of cells is displayed on the screen with each containing a series of coloured shapes (Figure 1.16). The features that make up the objects in each cell (colour, shape, number of copies) are related to each other according to a set of rules. The participant must deduce the

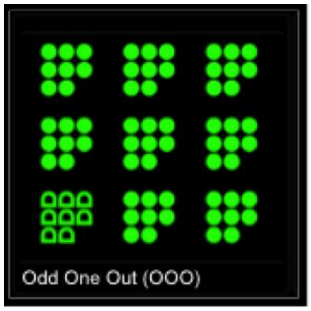


Figure 1.16: Pictorial Representation of Odd One Out Task

rules that relate the object features and select the one cell whose contents do not correspond to those rules solving as many problems as possible within 90 seconds.

Color Word Remapping

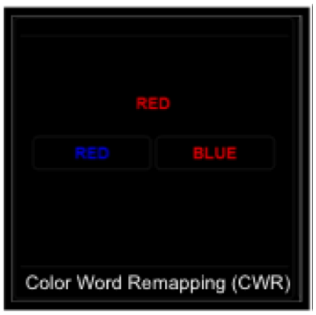


Figure 1.17: Pictorial Representation of the Color Word Remapping CBS Task

This task is a more challenging variant of the Stroop test[70] designed to assess ones response to interference in the presence of conflicting stimuli. In this task a word appears at the top of the screen, and two at the bottom (Figure 1.17). Participants must click the word at the bottom that describes the ink colour of the top word. Based on the colour combinations, words printed may be congruent ("red" printed in red ink) or incongruent ("red" printed in blue ink) which means that trials may represent congruent, incongruent stimulus, incongruent response, or doubly incongruent scenarios. This is a timed task lasting 90 seconds.

As a gold-standard test of attention selection,[71] the original Stroop task requires conflict identification, followed by top-down attentional control[72] to support task-relevant processes and dampen task-irrelevant processes. Neuroanatomically, this task would recruit the anterior cingulate cortex and the dorsolateral prefrontal cortex[71] respectively. In aging, when top-down control is compromised, similar modified Stroop tasks (which use a shape-colour pairing as opposed to word-colour pairing) have demonstrated decreased performance paired with increased activity in posterior processing regions that handle task-irrelevant information and inferior prefrontal regions involved in maintaining working memory information.[71]

Verbal Reasoning

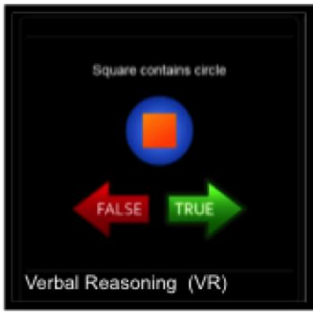


Figure 1.18: Pictorial Representation of Verbal Reasoning CBS Task

Based on Alan Baddeley's 3 minute grammatical reasoning test,[18] this reasoning task requires participants to determine if a written statement correctly describes the pair of displayed objects (Figure 1.18). The task lasts a total of 90 seconds, in which total score increases or decreases by 1 depending upon

whether responses are correct.[1] Historically used for native English speakers, scores on this test are quite stable over time making it a suitable test for repeated measurement.[73]

1.1.5.2 CBS Outliers

Outliers from CBS data are assessed in three ways. First, any response scores that exist below the level of chance are deemed implausible and are removed. The valid ranges of scores are included in Appendix 1. Second, any reaction times below 100ms are removed[47] to allow sufficient time for stimulus perception and motor response.[44] Finally, prior to data analysis, all data is screened for statistical outliers.

1.1.5.3 CBS Limitations

As previously noted, the CBS battery can be administered in 60 minutes.[49] While certainly reasonable in comparison to other in –depth neuropsychological test batteries, its length may pose problems when the battery is used in conjunction with other metrics including history surveys or imaging protocols. This limitation is specifically addressed in chapter 4. Additionally, while comprehensive, CBS does not offer a measure of long-term memory (for example, delayed recall) or orientations, which are commonly noted impairments in concussion. This is a critically important understanding in comparing CBS test results to concussion-specific tests (as in chapter 2). Finally, while appealing for mass distribution, the online nature of CBS presents some limitations, specifically in that testing environments are not consistent between participants, or even trials, and that researchers are fully reliant upon participants to read and independently understand the test instructions. These specific limitations are combated with strict screening to eliminate implausible (success rates below chance, or response times <100ms) or invalid/incomplete data sets, which may account for the significant participant exclusions in studies 1 and 2.

With the foundation of cognitive function and neuropsychological testing now set, our attention shifts into its application to better understand cognitive changes in head injury and aging.

1.2 Head Injury and Cognitive Function

1.2.1 Concussion/mild Traumatic Brain Injury (mTBI)

Concussion, or mild traumatic brain injury (mTBI), is "a complex pathophysiological process affecting the brain, induced by biomechanical forces"[74] to the head or body. Despite being highly underreported,[75,76] concussion represented 5.8% of all collegiate athletic injuries across 180 colleges in a 2007 study, with football and soccer exhibiting the highest concussion rates in comparison to other sports.[77] The injury may result in neuropathological changes, but historically has reflected a functional disturbance rather than a structural injury.[74] Though progress is being made, standard clinical imaging scans (MRI and CT) are unable to measure concussion-related structural damage on a macroscopic level.[78,79] Injuries are often referred to structurally as "diffuse axonal injury" resulting in some degree of transient functional cognitive impairment with deficits lasting approximately 7-10d after concussion[80] in 80-90% of cases[74]. Symptoms are often not specific to concussion, and may be delayed in onset,[81] representing strong heterogeneity in injury profile. As such, some hypothesize the existence of various sub-types of concussion, which may represent differences in "clinical manifestations, anatomical localization, biomechanical impact, genetic phenotype, neuropathological change or an as yet unidentified difference."[82] Identified clinical sub-types include: vestibular, oculomotor, cognitive fatigue, posttraumatic migraine, anxiety/mood, sleep and cervical,[83] as outlined in Table 1.5, and specified rehabilitative strategies to target specific concussion subtypes may also be beneficial.[84]

In terms of cognition, despite varied methods for accounting for the cumulative magnitude of traumatic head injuries, studies show a correlation between the number and severity of sustained concussions and cognitive function.[75,85,86] Critically, long-term cognitive outcomes remain poorly understood limiting our ability to prevent, diagnose and treat concussive injuries.[79] With no definitive diagnostic test available, and varied presentations likely, concussion remains a clinical diagnosis subject to variability between physicians and across subspecialties.[79] Consequently, it is considered to be among the most complex injuries in sports medicine to diagnose, assess and manage.[74]

Table 1.5: Clinical Concussion Subtypes and Manifestations[83]

Subtype	Clinical Manifestation		
Vestibular	Disequilibrium, impaired balance	Dizziness, vertigo, blurred/unstable vision, discomfort in busy environments, nausea	**Vestibulo -Ocular**
Oculomotor	Blurred vision, diplopia, difficulty reading, eyestrain, headache, reading difficulties, visual scanning problems		
Cognitive Fatigue	Difficulty concentrating, memory problems, attentional issues, decreased vigor, headaches worsening throughout the day		
Posttraumatic Migraine	Headache, nausea, photo-sensitivity, phono-sensitivity, dizziness		
Anxiety/Mood	Frustration, feelings of isolation and loss of control, anxiety, depression		
Sleep	Persistent sleep disruptions (commonly permeates across other clinical subtypes)		
Cervical	Abnormal afferent input to CNS – dizziness, imbalance impaired oculomotor control, headaches, sensory information mismatch		

1.2.1.1 Proposed Concussion Mechanisms and Pathophysiology

Axonal Injury is the primary neuropathology associated with TBI[87] and can range from microscopic diffuse injuries, to macroscopic focal lesions superimposed on diffuse injury depending on severity.[88] These acute functional disturbances may be attributed to 2 distinct, yet interrelated neuropathological mechanisms that happen over time:[89]

1. Primary Brain Injury: Upon impact, the acceleration/deceleration of the brain and ensuring physical shearing and stretching of axons beyond tolerance[87] results in the primary injury.

2. Secondary Brain Injury: The neurometabolic cascade, following a primary injury results in a transient state of excitotoxicity leading to neuronal exhaustion[90] and may progressively lead to axonal disconnection over time.[91] Specifically, trauma causes axolemma structural changes causing a loss of ionic homeostasis and eventual disruption of axonal transport.[92] In mild cases, these changes are reversible, however, in more severe cases, changes may progress to axonal swelling and secondary axotomy over the course of days to months in humans. Overall, TBI neuropsychological outcomes are thought to be related to the degree to which white matter neural network functioning is disrupted and how well those networks are able to recover or adapt.[93]

Perhaps even more concerning clinically is the recent neuroimaging finding that concussion repercussions on brain structure and function tend to worsen when athletes

get older,[94–96] which suggests that concussion pathophysiology outlasts the above described neurometabolic cascade.[89]

1.2.2 Neuropsychological Testing in Concussion

Concussion test batteries typically exploit a multimodal approach to assess the multifactorial changes in behaviour, mood, physical abilities and cognitive function expected in concussion. In doing so, they serve three major functions:

1. aiding in concussion diagnosis[74],
2. facilitating effective medical management of patients after concussion (including return to play decision making) and
3. better understanding the subservient brain regions responsible for a certain behaviour or impairment.[25]

Clinically, various practice guidelines and position statements note a role for neuropsychological testing in the appropriate management of concussion.[74,97] Importantly, it may be used as a baseline measure for future comparisons, a sideline assessment of acute injury, or a clinic-based test to diagnose concussion and assess recovery. For research, the same tests are often used for assessing decline or recovery. With this in mind, the influence of test-retest bias is an important consideration should athletes have several exposures to the same tests (baseline, time of injury, follow-up and rehab), though the magnitude of these effects has not been well studied.

Baseline Testing

The goal of baseline testing is to provide a pre-injury cognitive profile of athletes to aid clinicians and therapists in identifying post-injury neurocognitive deficits,[98] and pre-existing risks.[99] It provides the "most accurate representation of an athlete's pre-injury cognitive status," which is important as individuals differ in cognitive performance.[100] As a practice, however, the value of baseline testing remains controversial. Many cite problems with standardizing testing and scoring, an inability to modify risk of participation,[101] and failing to provide added value beyond normative data.[102] Perhaps more troubling is that one study on collegiate football athletes found that > 25% of all baseline tests suggested suboptimal effort either due to invalid responding or intentional

efforts to falsely perform poorly to disguise later injury-induced impairments (termed "sandbagging" in concussion literature)[103] and only ~50% of athletic trainers report screening for invalid baseline data despite ~95% using the tool as a baseline measure.[100] In alignment with these concerns, the most recent iteration of the Sport Concussion Assessment Tool, the SCAT5, suggests that while "baseline testing can be useful for interpreting post-injury test scores… [it] is not required for that purpose."[104]

Baseline testing, however, seems salient in subpopulations of athletes predisposed to conditions affecting cognition including learning disabilities and ADHD,[105] and in young athletes who are experiencing rapid cognitive skill development.[19] In addition, "screening for psychological disturbance during baseline and post-injury assessments is an important element of concussion management, not only because of the prevalence of psychological difficulties, but also because the early identification and treatment of pre-existing or comorbid psychological issues associated with concussion may prevent the development of persistent post concussive symptoms in vulnerable individuals."[102,106]

Sideline Concussion Evaluation

A sideline assessment is designed to aid a clinician in making an immediate decision "in the midst of competition with a time constraint and the athlete eager to play."[74] In most cases, practitioners use a sideline assessment tool (eg. SCAT) that has been previously used as a baseline test so that athlete-specific comparisons can be made. While a sideline neuropsychological test cannot replace necessary clinical judgment,[74] it remains a major resource for clinicians and must assess broad areas of potential deficit to ensure that injured athletes are removed promptly from play to prevent further injury for which they would be at increased risk.

Delayed Evaluation and Ongoing Concussion Monitoring

Neuropsychological testing also plays an important role during in-office evaluations of concussion as cognitive deficits may appear several hours following a concussion.[74] Various factors may predict the potential for prolonged or persistent symptoms in concussion[74] which ultimately delay recovery, or increase the risk of a secondary insult. In general, most people tend to recover from concussion clinically (symptoms, cognitive

and balance measures) within 5-7 days,[107] though children and adolescents sometimes have a slower recovery than adults.[108–111] Previous concussion history also influences recovery rates. Youth sustaining one or more concussion in the year prior to a new concussion reported more prolonged symptoms[112] which may suggest a possible 'window of vulnerability' putting previously injured youth at a high risk of delayed recovery times.[79] As such, beyond initial diagnosis, the major goal in ongoing concussion monitoring is determining a suitable return to play timeframe.[74] During a graded return to play assignment (see Table 1.6), athletes progress step-wise through a protocol, moving to the subsequent, more challenging level only when they remain asymptomatic for one day at the current level. In children, completing a return to learn/think protocol to support academic reintegration prior to a return to play protocol is recommended.[24]

Throughout, neuropsychological testing may aid clinicians in determining progress, rehabilitation or recovery of injured athletes. It's use as a marker of recovery is, however, controversial as physiological deficits may persist after cognitive recovery.[113–115]

Table 1.6: Graded Return to Play Protocol from McCrory et al 2013 used with permission from BMJ Publishing Group ©2013

Rehabilitation Stage	Functional Exercise at Each Stage of Rehabilitation	Objective of Each Stage
1. No activity	Symptom limited physical and cognitive rest	Recovery
2. Light aerobic exercise	Walking, swimming, or stationary cycling keeping intensity <70% maximum permitted heart rate. No resistance training	Increase HR
3. Sport-specific exercise	Skating drills in ice hockey, running drills in soccer. No head impact activities	Add movement
4. Non-contact training drills	Progression to more complex training drills, eg. passing drills in football and ice hockey. May start progressive resistance training	Exercise, coordination and cognitive load
5. Full-contact practice	Following medical clearance participate in normal training activities	Restore confidence and assess functional skills by coaching staff
6. Return to play	Normal game play	

1.2.2.1 Common Test Measures in Concussion Tests

Though multiple concussion-specific neuropsychological tests are available, many offer assessment in common areas of function outlined here:

Symptoms

Symptoms describe any manifestation of a condition that is solely apparent to the patient but not otherwise outwardly observable. They are commonly assessed via self-report using a list of symptoms paired with a Likert scale to denote severity experienced. While highly subject to non-disclosure, when used in combination with other neuropsychological metrics, researchers have reported a 19% increase in sensitivity to detect concussion.[116]

Balance

Balance measures are typically used as a proxy for the motor domain of neurological functioning.[74] As such, many concussion-specific tests include balance as a functional measure (eg. Balance Error Scoring System - BESS, or force plate technology). Indeed, postural stability deficits have been identified following concussion lasting approximately 72hrs following the incident,[74] and is a particularly reliable and valid addition to concussion assessment when symptoms or signs indicate a balance component.[113,117–122]

Reaction Time (RT)

Reaction time is broadly defined as "the time taken to complete a task."[44] Within the confines of neuropsychological testing it is a measure typically restricted to computerized testing, and has the potential to offer a specific measure of impairment that is outside of an athlete's control and thus, is less susceptible to cheating. In addition, reaction time variability has been referred to as a "dynamometer of attention"[123] with high variability indicating attentional lapse[124] or impairment of sustained attention.[125] Importantly, increased variability in reaction time for patients sustaining TBI[126] and mTBI[125] as well as differences in reaction times[125] have been noted in the absence of score differences.[127] As head injured patients are known to be able to meet the demands of a cognitive task,

this consistency disturbance is useful for identifying deficiencies in single-assessments (where the inability to sustain performance cannot be assessed).[125] Essentially, reaction time measures may serve to offer pre-clinical insight for when an impairment may exist, but is not yet clinically relevant, and may identify a window for which intervention is most ideally timed.

Cognitive Function

Cognitive function is the most prevalently assessed ability in concussion-centered neuropsychological testing. Given its broad scope, however, many neuropsychological tests choose to address cognitive function through administering a variety of sub-tests or by generating a composite score to reflect function in a specific cognitive domain. As many neuropsychological tests are available, yet differ in the specific tasks employed, developing ways to equate or relate scores and sub-scores across tests and cognitive functional domains is a priority for researchers. A recent study assessing the critical elements for sideline concussion screening suggest that cognitive evaluation tests demonstrate lower sensitivity but relatively good specificity, though all types of sideline tests demonstrate high risk of bias due to diagnosis inconsistency and imprecision.[128]

1.2.3 The Sport Concussion Assessment Tool (SCAT)

Three main clinical tests; the Sport Concussion Assessment Tool (SCAT), the Immediate Post-Concussion Assessment and Cognitive Testing (ImPACT) and the King-Devick Test, have gained popularity in measuring dysfunction in concussion. All take a multimodal approach to assess a wide range of skills and attributes which may be disturbed in concussion. The following discussion, however, centers on the SCAT as it is the most widely used concussion assessment test,[129] and was employed in **Chapter 2**.

Debuting in 2004, SCAT was designed to provide an objective and standardized assessment for concussion at the sideline.[130] Since then, it has undergone several revisions (see Table 1.7), through which its scope has expanded to include monitoring an athlete's recovery over the course of subsequent clinical assessments[130–132] and as part of a baseline assessment before injury.[130,133] Scores are best interpreted in the context of what is normal for an individual athlete,[74,134–136] though normative values are available

for comparison should a baseline value be unavailable. Additional tests including the Child SCAT and Concussion Recognition Tool (CRT) have also been developed for use in those aged 5-12 and by laypersons, respectively. Critically, due to varying test components, and robust development of cognitive function during adolescence, direct comparisons cannot be made between the SCAT and Child SCAT.[74]

The SCAT3, the version of the test employed in chapter 2, encompasses eight components pictured in Figure 1.19. From these tests, three composite scores are generated reflecting patient symptomatology, cognitive status (standardized assessment of concussion – SAC) and balance (balance error scoring system – BESS) (see greyed boxes in Figure 1.19). The major component of interest in this dissertation is the cognitive assessment, the SAC. Literature shows that after injury, a decline in SAC is 94% sensitive and 76% specific in accurately classifying injured and uninjured athletes on the sideline. [137] Although now replaced by the SCAT5 which debuted in 2017 (after the data for chapter 2 was collected), changes to the cognitive assessment portion were minor. Therefore, the results obtained using SCAT3 remain valid and useful.

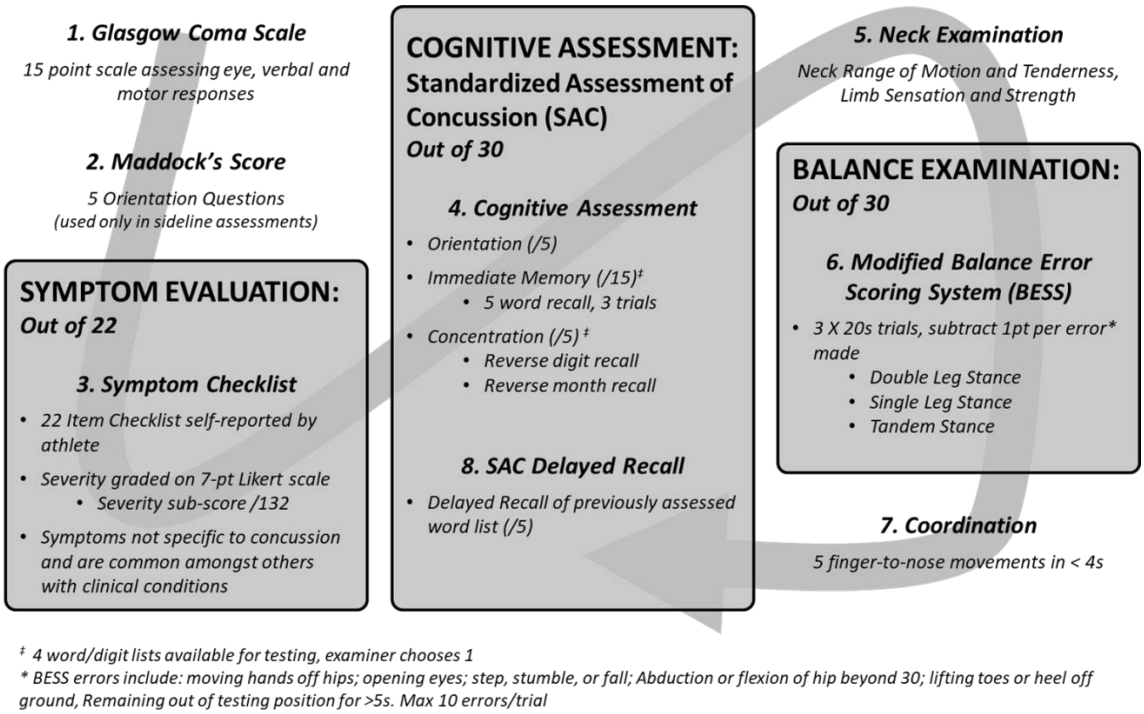


Figure 1.19: SCAT3 Test Components. Greyed boxes represent composite scores generated for symptoms, cognition and balance sub-scores

Table 1.7: Summary of SCAT Development and Revisions

	Version	Date	Purpose	Major Changes from Previous Version
Sport Concussion Assessment Tool	SCAT	2004	Public and medical use. Combined separate approaches to concussion assessment as "pass"/"fail"	
	SCAT 2	2008	Ages 10+	• 8 subscales, max total score /100
	SCAT3	2013	Ages 13+ Use by medical professionals to aid in concussion diagnosis.	• No total score, GCS added • Foam option for BESS + tandem gait alternative
	SCAT5	2017		• Indications for emergency management in "Rapid Neurological Screen" • Post- vs Pre-injury questions • Delayed recall lists of 10 words option added, 6 word/digit lists available • Return to school progression
Child Sport Concussion Assessment Tool	Child SCAT3	2013	Aged 5-12 Evaluation by medically trained personnel for suspected concussion.	*Modified from SCAT2* • Maddock's questions changed for use with children • Health and Behaviour Inventory for child and parent reported symptoms • No time- based orientation question • "2" digit backwards string, months changed to days of week-backwards • No single-leg balance test • Return to school information
	Child SCAT5	2016		• Potential signs became "red flags", Rapid Neurologic Screen (RNS) added • No Maddock's or orientation questions • Rating of function /10 for child report, /100 for parent report • Delayed recall lists of 10 words option added, 6 word/digit lists available • Single leg stance for 10-12 aged patients
Concussion Recognition Tool	Pocket SCAT	2005	Assist non-medically trained laypersons to recognize signs and symptoms of concussion, remove athlete and seek medical attention. Not for use in medical diagnosis	• Miniaturized version of SCAT/SCAT2 including symptoms suggesting concussion, memory via orientation questions and balance testing.
	Pocket SCAT2	2008		
	CRT5	2017		• Red flags to call ambulance • Signs & Symptoms list divided into different types with simplified language • Memory function changed to "awareness" questions

There is no version 4 for any test. All version numbers increased to 5 in 2016 to match across tests & meeting where SCAT was initially developed/revised (int'l conference on concussion in sport)

1.2.3.1 SCAT Normative Scores

Thomas et al conducted a systematic review to compare baseline SCAT2/3 scores, from 26 studies and 4978 athletes to determine the following weighted means (see Table 1.8). In general, SCAT scores remain similar across high school and collegiate athletes, with little variation between sexes.[129] There was, however, limited data in assessing post-concussion scores, professional athletes, and adult non-collegiate athletes.[129] In another study on Finnish Hockey athletes, Hänninen et al found that total scores on SCAT3 components had no significant association with age, years of education, history or number of past concussions, history of headache or migraine, or recovery time after last concussion.[134] Their findings suggest similar normative values of other athlete populations and unusual score cut off values (found in <10% of their sample)[134] noted in Table 1.8. Finally, a study by Zimmer et al found a significant main effect of sex such that female collegiate athletes performed significantly better than their male counterparts on the SAC, with equal performance on all other measures.[138]

Table 1.8: SCAT 2/3 Normative Weighted Means & Cut Off Scores

Population	Symptoms (max 22 ±SD)	BESS (max 30 ±SD)	SAC (max 30 ±SD)	Reference
High School	18.46	26.14	26	Thomas et al [129]
Collegiate	20.09	25.54	27.51	
Collegiate – Male	20.31 ±2.87	25.49 ±4.14	26.97 ±2.05	Zimmer et al [138]
Collegiate – Female	20.09 ±3.29	25.94 ±3.90	27.63 ±1.87‡	
Unusual Score Cut Off	*<18**	*<24*	*<24*	*Hänninen et al* [134]

‡ indicates sig diff from males

**total symptom severity of >6 also considered unusual (max 132)*

SCAT Meaningful Change in Score

Barr and McCrea (2001) suggest that a 1 point decrease on SAC is clinically significant.[137] While this offers a strict guideline promoting a cautious approach, Zimmer et al (2015) emphasize that this may result in many false positives and instead suggest that a decline in performance larger than 1 SD from the mean should be cause for caution in return to play and performance decrements of 1.5 standard deviations are indicative of a real impairment.[138] Other interpretations of meaningful changes in score are outlined in Table 1.9 which align well with the findings of Zimmer et al.

SCAT Psychometric Properties

SCAT test reliability, sensitivity and specificity have been addressed in a number of studies and compiled by Guskiewicz et al.[139] An adaptation of their summary is provided in Table 1.9.

Table 1.9: SCAT2 Psychometric Properties (from Guskiewicz et al 2013, used with permission from BMJ Publishing Group Ltd. © 2013)

Test Component	Reliability (ICC)	Sensitivity	Specificity	Measures of Difference/Change
Symptom Scale 140–145	0.88-0.94	0.64-0.89	0.91-1.0	3-5x Baseline symptoms at time of injury; reliable change indicated as 6-8 points on severity
SAC 137,146–152	0.42-0.71	0.80-0.94*	0.76-0.91	2-4 points lower at time of injury relative to baseline
BESS 118,147,153–157	0.54-0.98	0.34-0.64	0.91	Concussion vs control score typically 6-9 points lower; overall BESS decreased 3-6 points from baseline at time of injury

** sensitivity highest within 48 hrs of injury*
All data provided on SCAT2

1.2.3.2 SCAT Strengths

SCAT is particularly useful as it is short and easy to administer, taking less than 15 minutes total. Its pen and paper nature requires limited resources, keeping cost and barriers to administration low. It also follows a relatively intuitive scoring system that requires little training for interpretation. Studies have found it to be valuable in both a baseline-post injury assessment model, but also in comparison to normative group data in the absence of a patient-specific baseline.[158]

1.2.3.3 SCAT Limitations

A lack of non-athletic normative values, insufficient data on the longitudinal normative and abnormal range of SCAT performance in athletes,[129] and unestablished minimum clinically important differences in scores,[159] limits SCAT's current use as a prognostic tool. Thus it should be used cautiously for clinical and return-to-play decision processes and supplemented with clinical and other neuropsychological assessments. In addition, SCAT was not developed with the intent of evaluating change scores from pre-season to post-season,[159] thus research studies looking to examine longitudinal changes may not be

able to adequately assess them using this tool alone. Sandbagging (intentional efforts to perform poorly to disguise a later impairment), is a major problem for the SCAT since the test is readily available online, and a portion (symptom scores) is completed via athlete self report. Finally, due to the pen-and-paper nature of this test, a higher "network" analysis of cognitive domains impaired, akin to what the CBS test offers, is unavailable. In fact, in considering the composition of the SAC, one is quick to note that 2/3 of the score is derived from verbal recall alone, which is fairly one-dimensional. As such, using SCAT as a tool to measure broad cognitive function, and specifically decrements or improvements therein is highly problematic and an issue I address with **Chapter 2.**

1.2.4 Subconcussion

While concussion is an important clinical diagnosis and concern in contact sport, subconcussive impacts (head impacts not causing a diagnosed concussion injury) are far more common, yet remain poorly understood. Though once considered harmless, subconcussive trauma may affect cognitive function[80,85,160] and is recognized as contributing to the cumulative long-term neurological consequences noted in chronic traumatic encephalopathy (CTE).[161] With this realization, many studies have sought to examine the effects of chronic subconcussion in isolation from concussive episodes and strong evidence supporting cumulative deleterious effects is mounting. For instance, Koerte et al examined a population of elite soccer athletes in comparison to swimmers using DTI to assess changes in white matter integrity. Importantly, only participants without previous symptomatic concussion were included. Soccer players demonstrated increased radial and axial diffusivity, indicative of decreased white matter integrity, such that age and years of training had no significant association with diffusivity value.[162] Another 2016 study found changes in white matter integrity as well as functional changes in a population of non-concussed high school football athletes after a single season of play.[163] Similar findings of neurocognitive and neurophysiological changes in asymptomatic, non-concussed high school footballers were reported by Talavage et al in 2010.[164] Together, these studies highlight the presence of an unexpected new population of non-concussed yet neurologically impaired athletes which underscores the importance

of considering subconcussion as a viable mode of injury.[164] Further to this, retroactive study design[85,86,165] and selection bias for only patients with severe concussion has meant that subconcussion is largely understudied. Recognizing that athletes sustaining subconcussion are often missed in the clinic altogether as they don't present with overt impairments, yet may still be at risk for future neurological injury[164] underscores the need to continue study in this area.

1.2.5 Football: A Case-Study for Repetitive Head Trauma

Serving as a natural circumstance for repetitive head trauma, football athletes are a key population in concussion and subconcussion studies. Quantifying head impact exposure in football has become a major research stream as understanding how an average impact profile might change throughout a career, may provide insight on the most vulnerable time points for injury, as well as the most effective time points for intervention. Most literature is divided into four career stages: youth, high school, collegiate and professional; all of which are important to consider in the context of an athlete's cumulative lifetime exposure. Table 1.10 summarizes research findings by level of play on common measures of head impact exposure. While biomechanics methodology and reporting vary substantially between studies, it is particularly striking to note the robust similarities across these three levels of play (youth, high school, and varsity). Considering that ~70% of all football players in the US are below high school age,[166] this is key for understanding cumulative impact exposures. Although not explored in this dissertation, impact profiles also vary substantially across positions played with several studies finding that skilled positions (backs/receivers) typically sustain few high magnitude hits while linemen sustain frequent low magnitude hits.[167–169] This is an important consideration for stratifying participants in future studies while recognizing the tendency for athletes to change their primary position played throughout their career.

Table 1.10: Summary of Head Impact Exposure in Football by Level of Play

	Youth		High School	Collegiate/ Varsity
	Aged 6-9 [170]	Aged 12 [166]		
Average Linear Acceleration (g)	18	25.5	25.9 ± 15.5 [171]	**20.43** [168] (median)
Peak Linear Acceleration (g) (95th percentile)	40	57.3	> 56.2 [169]	**36.13** [168], > 58.8 [169]
Average Angular Acceleration (r/s²)	901	1691.8	1694.9 ± 1215.9 [171]	**1724.4** [168] (median)
Peak Angular Acceleration (r/s²) (95th percentile)	2347	3929.0	2519.8 [172]	**3029.62** [168]
Average Impacts/Season	107	306	652 [173] - 774 [171]	1022-1444 [174]
Concussion Incidence (AE = games + practice)	0.99 [175]- 1.76 [176] /1000 athletic exposure		0.92 [175] - 4.08 [177] /1000 athletic exposures	0.83 / 1000 athletic exposures [175]
Practice vs Game Impact Magnitude	game < practice [170]		game > practice [171]	game > practice [168]
Bolded varsity values highlight measures from the same athletic team as assessed in studies 1 and 2				

Unfortunately, there is very limited information on head impact profiles in professional sport. The closest proxy comes from the series of "concussion in professional football" studies, where authors reconstructed NFL collisions where a concussion was suspected. They concluded that biomechanics differ between the striking and struck player, and in cases with and without injury. A brief summary of their linear and rotational acceleration findings is presented in Table 1.11. These values are in general higher than those outlined in Table 1.10, though only reflect high magnitude impacts suspected of causing a concussion, and thus do not take into account routine subconcussive impacts, or those occurring in practices.

Table 1.11: Head Biomechanics of Struck and Striking Players in Lab Reconstructions of NFL Collisions where concussion is suspected

	Struck Player		Striking Player
	Concussion	No Concussion	No Concussion
Peak Linear Acceleration (g)	94.3 ± 27.5 [178]	67.9 ± 14.5 [178]	56.1 ± 22.1 [179]
Peak Rotational Acceleration (r/s²)	6432 ± 1813 [178]		4255 ± 1405 [178]

1.2.5.1 Incidence of Head Injury in Football

In football, the head and neck sustain a relatively small proportion of all reported injuries ranging from 5%-13%.[180] Although the risk of catastrophic injuries is low, between 0.19

and 1.78 for every 100 000 participants,[181–183] this rate is higher than most other team sports outside of gymnastics and hockey.[182] In addition, the risk appears to increase with age of participants from youth, to high school to collegiate players.[181,183] For youth, most concussions tend to occur during practice (53.9%) while for high school and collegiate athletes most concussions occur during games (57.7%, 57.6% respectively) despite the rate of concussion being higher in games for all 3 levels of competition.[175] Unsurprisingly, the majority of concussions, and injuries in general, result from tackling or being tackled.[177]

1.2.6 Cognitive Impairments in Concussion and Subconcussion

The focus of this dissertation is on better understanding cognitive function. In the first two studies, we explore cognitive function changes in sub-concussive head trauma. In the literature, cognitive changes are primarily considered in two domains: acutely in the moments and months after a concussion, and in the long-term years and decades after the event. In all, "how the long-term neurobehavioural, neurocognitive and neurological consequences of concussion interact with one another to create subclinical and clinical changes is not as well understood as the extant research might indicate."[89]

Acute Cognitive Function: Studies measuring cognitive function in terms of behavioural neuropsychological test scores have found that participants with acute concussion typically perform as well as controls.[115] While it is encouraging that many of those experiencing an isolated concussive injury seem to be capable of resuming normal cognitive function, recent studies suggest that neuropsychological testing may not be the best option in identifying recovery in concussion. For example, several studies examining concussed individuals have noted that despite a return to a neuropsychological test baseline, other physiological measures including cerebral blood flow[114], postural stability[113], and BOLD responses[115], demonstrate persistent, prolonged or inadequate recovery. From this, two major conclusions could be drawn: either cognitive function recovers at a faster pace than other related physiological measures after a concussion, or neuropsychological tests represent an inadequate method for assessing concussion recovery.

As evidenced through the above sections on concussion pathophysiology and modifiers of concussion recovery, it is imperative that clinicians establish timely and accurate concussion diagnoses that capture heterogeneous concussion presentations. Further, given the ongoing challenges in using neuropsychological tests to identify concussion recovery, new test versions should allow for a better assessment of recovery and changing cognitive function over time. This issue is the primary target for **Chapter 2** of this dissertation and will be important for future diagnoses and understanding clinically important changes.

Long Term Cognitive Function: The cumulative effects of concussion and subconcussive effects remain an important injury mechanism to consider both inside and outside of sport. Some evidence suggests that long-term cognitive deficits can be attributed most often to chronic head trauma exposure as a whole, including both concussive and subconcussive incidents. In terms of concussion, those with a history of chronic, and multiple incidents, tend to show long-term deficits[75] that appear after second and subsequent concussions. Studies comparing athletes with a history of even one concussion to controls have not found statistically different behavioural test measures, but rather a correlation between baseline reaction time and the number of years played[184] suggesting that reaction time may offer a more sensitive measure of altered cognitive function in concussion than neuropsychological test scores themselves. Further, aging seems associated with accelerated cognitive decline in episodic memory and attention in retired athletes with a remote history of sports concussion,[94] as well as in significant declines in motor execution speed and sequential motor learning.[185] These changes have been paralleled with electrophysiological and metabolic anomalies in brain regions responsible for the generating these behaviours.[96]

Beyond concussion test measures, dementia-related diagnosis,[186] including Alzheimer's disease,[187,188] MCI,[189]and Parkinson's Disease[190] may be related to concussive and subconcussive exposure. Specifically, some studies of NFL players have found that retirees aged 30-49 are diagnosed with dementia at a rate 20 times the rate of age-matched populations, while players over age 50 receive a dementia-related diagnosis five

times more frequently than the American national average.[186] Additionally, some studies have demonstrated impaired reaction time, decreased hippocampal volume,[184] and impaired visual processing up to seven years post injury in football athletes.[184,191] Critically, both altered physiological function and neuroimaging findings have been noted in athletes with and without a concussion diagnosis. For instance, collegiate level football athletes without a diagnosed concussion history have shown cerebral white matter changes six months into the post-season as a result of subconcussive repetitive head impacts,[192] and a study in high school football athletes across a single season found that those with head injuries without concussive symptoms or diagnoses had both lower scores in visual working memory and decreased activation in the dorsolateral frontal cortex on fMRI.[193]

This theme of identifying the influence of chronic impact exposure is the focus of **Chapter 3** of this dissertation where we assess cognitive function in non-concussed varsity football athletes. We also employ response time measures to ensure the most sensitive approach to identifying cognitive change.

1.3 Aging and Cognition

Age-related cognitive decline is inevitable and characterizing such change has been an important ongoing task in establishing what "normal" means for comparison to diseased or injured states. As pictured in Figure 1.2, cognitive change isn't linear, and is complicated by variability in both between cognitive domains and across individuals.

1.3.1 Age-Related Change across Cognitive Domains

As noted in section 1.1, we generally expect the classic aging pattern[194] to include a linear "decline across adulthood for the fluid mechanics (eg. working memory, and processing speed) accompanied by stability or increases in the crystallized pragmatics (eg. verbal knowledge)"[8] into very old age. The exact age-related timing of these changes, however, is difficult to quantify, owing to inconsistent study methodologies since there are no standardized age-based cut offs denoting specific age categories (eg. young, old and very old). Sex, and sociobiographical status can also influence cognitive

function,[195] though seem unassociated with the rate of cognitive change.[8] Regardless, cognitive functions in aging are often divided into three primary categories:

Life-Long Declining Functions: Broadly, these functions (processing speed, working memory, inductive reasoning) fall under the term "executive function" and are "required to coordinate several processes in order to achieve a goal."[196] Decline seems long-term and linear based on cross-sectional studies from those aged 20-80,[197,198] although longitudinal comparisons[199] suggest more rapid declines in late life.[200] Since the incidence of pathologies increases with age, this late-life accelerated decline may represent the influence of pathology, whereas the earlier linear decline may be more representative of normal aging.[200] This is particularly evident after age 70.[17] The main premise behind this decline is a reduction of attentional resources along with a general slowing in information processing which is supported by the frontal lobes.[196]

Late-Life Declining Functions: Tasks that are well practiced or involve knowledge show general preservation of performance until very late life.[200] One example is vocabulary and semantic knowledge which demonstrate stability in both cross-sectional and longitudinal studies, with decline beginning after age 60.[198,199] One way to explain this relative stability is that older adults may "use preserved knowledge and experience to form more efficient or effective strategies when performing tasks in which younger adults rely on processing ability."[200–203]

Life-Long Stable Functions: Not all cognitive abilities decline in aging. For example, autobiographical memory,[204] emotional processing,[205] and automatic memory processes[206] are typically well preserved.

More generally, "age effects are generally greatest on tasks requiring the acquisition or transformation of information (sometimes referred to as fluid intellectual activities), but are minimal to non-existent on tasks involving the retrieval or utilization of previously acquired information (sometimes designated as crystallized intellectual activities)."[17]

1.3.1.1 Age-Related changes in Speed

Importantly, despite a relatively modest proportion of variance accounted for between cognitive function and speed (r = 0.3), and a generalized lack of evidence supporting a "central speed factor" underlying performance, speed remains a very important factor accounting for cognitive changes in aging.[17] Specifically, speed variables demonstrate some of the strongest relations to age across adulthood[207] with weighted-average correlations noted as high as 0.52.[208] Three main factors modifying this relationship have been extensively studied. Specifically, health status demonstrates a small main effect with healthier individuals performing faster. Practice or test exposure demonstrates little to no interaction with age as everyone seems to get better with practice to the exception of initial trials in older adults who show more robust improvements.[207] Finally, task characteristics (eg those testing more fluid or more crystallized aspects of intelligence) seem to show variability in their age-specific relationships such that crystallized-based tests (eg. arithmetic and lexical) demonstrate less slowing.[207] Indeed, while the absolute magnitude of effects of age on speed vary test-wise, for many variables, the proportional difference between those aged 60 vs 20 is between 20%-60%.[17]

1.3.1.2 CBS Task Performance in Aging

Previous work shows that the CBS battery is sensitive to age in terms of cognitive composite scores. Performance in the Short Term Memory (STM), Reasoning and Verbal domains assessed by CBS follows a similar pattern (see Figure 1.20) as predicted by age-related changes in fluid and crystallized intelligence. More specifically, both the short term memory and reasoning composites demonstrate continual, nearly-linear decline with age while the verbal composite demonstrates relative stability over time.[1] Age-specific changes on each CBS test have not been published.

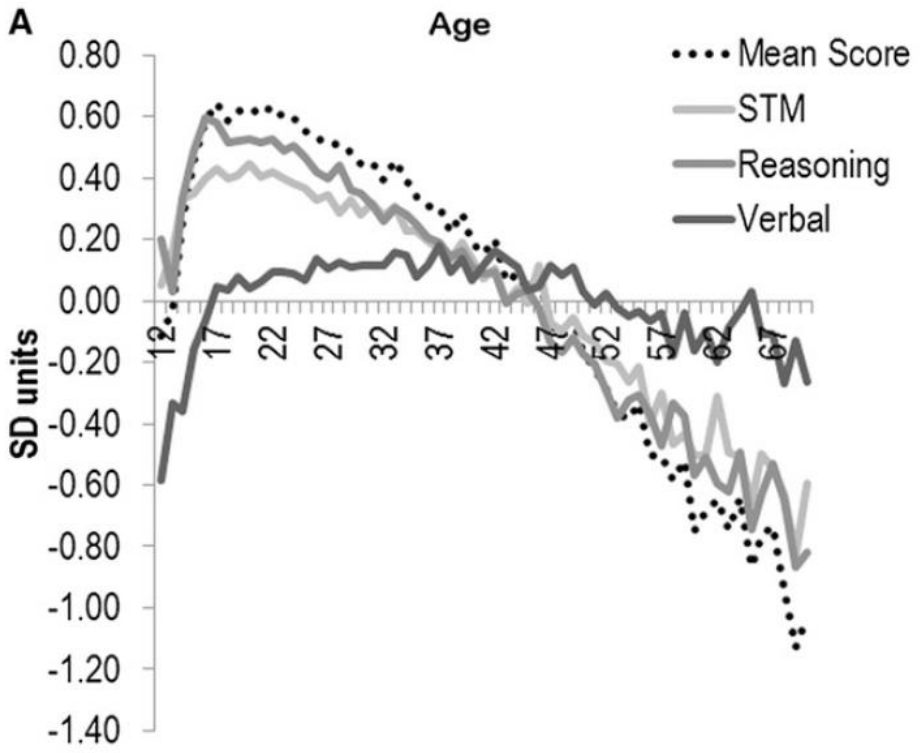


Figure 1.20: The Relationship of Behavioural Components of the CBS Cognitive Battery to Age - from Hampshire et al 2012, used with permission from Elsevier © 2012

1.3.2 Cognitive Reserve in Aging

Paralleling preserved function in some cognitive areas, some individuals show remarkable preservation of cognitive function over time[209] in comparison to others. One hypothesis supporting this variation regards cognitive reserve. It suggests "that individual differences in how tasks are processed provide reserve against brain pathology."[210] Specifically, high cognitive reserve may allow for more flexible strategy usage (thought to be important in executive function), greater neural efficiency and capacity, as well as compensation via recruiting additional brain regions.[210] This last concept of neural recruitment has been shown in fMRI studies assessing cortical activation during executive processing tasks in young and old individuals. Although an expected age-related deficit is sometimes coupled with less prefrontal activation in older adults in comparison to younger adults,[211] other times, areas of increased activity exist

contralateral to those activated in younger individuals indicating that additional activation may aid processing in older adults (see Figure 1.21 for an example).[212,213]

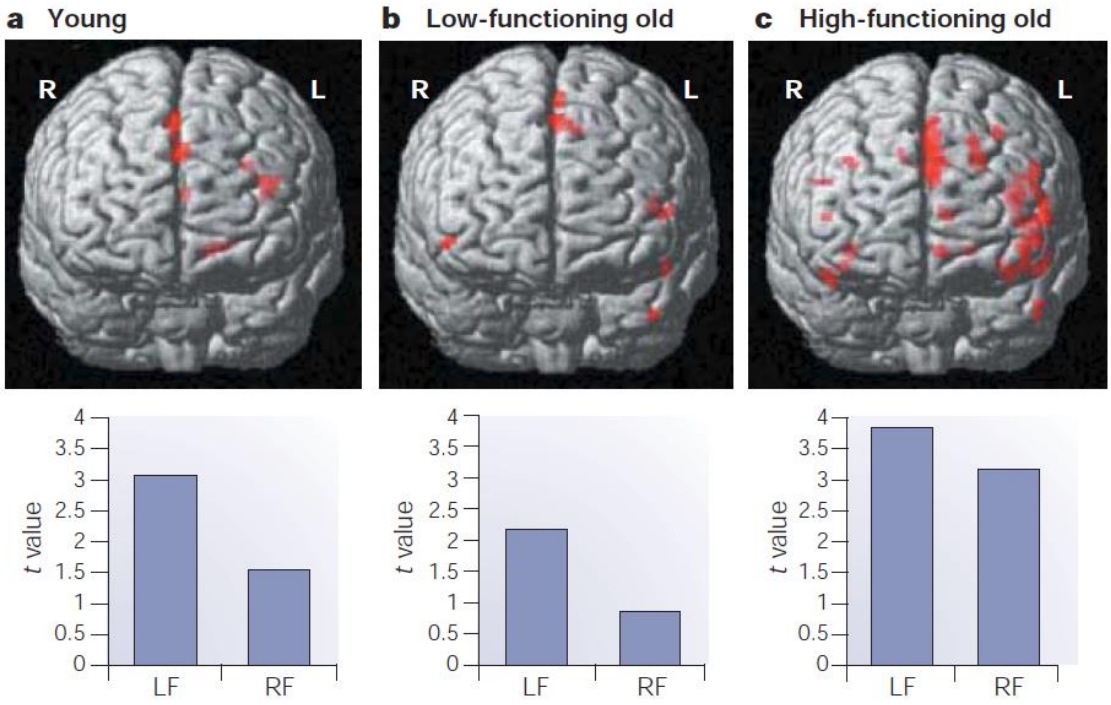


Figure 1.21: Neural Activations in prefrontal cortex during a memory encoding task. Activations are shown for young adults, low-performing older adults and high-performing older adults. Low-performing older adults exhibit a pattern similar to young adults with lower overall levels of activation. High-performing adults exhibit greater bilateral activation. RF: right frontal, LF: left frontal. From Hedden & Gabrieli 2004. Used with permission from Springer Nature © 2004

1.3.3 Anatomical Changes in Aging

Anatomically, healthy normal aging is associated with significant changes in both grey and white matter, with both experiencing overall volumetric losses.[96] Grey matter loss is particularly evident in the dorsolateral prefrontal cortex, while the hippocampus and medial temporal lobes are relatively spared.[196] White matter loss is estimated at about 45% between the ages of 20-80.[214,215] This type of loss in particular is thought to underlie the cognitive decline typical of healthy normal aging including information processing speed, psychomotor speed, postural stability, memory, attention and executive function.[216,217] Specifically, this does not indicate robust neuronal loss, but rather a decrease in synaptic integrity or neurotransmitter levels in normal aging.[218] Essentially,

the white matter "wiring" throughout the brain loses integrity impeding neural transmission which manifests with the above symptoms of cognitive decline.

1.3.4 Late-Life Implications of Early-Life Head Trauma

One theory of learning and intelligence suggests that individual differences in ability are the result of biological propensities and at which stage learning occurs.[219] While the formal structure of cognitive abilities is partly due to biological factors, the development of "generalized solution instruments," or approaches which aid an individual in future problem solving mechanics[5,220] contribute greatly to the variability between individuals' cognitive abilities.[220] Thus, early-life head trauma may hinder the development of these habits which means that "early learning or its lack may have a permanent and generalized effect in the adult."[219] To further contextualize, clinical reports suggest residual problems in intellectual ability, attention and memory after severe childhood brain injury[221] and young people recovering from concussion can experience challenges of altered social and academic development[79] disadvantaging them relative to their peers.[222] In terms of concussive and subconcussive exposure in sport, one study found that those beginning football play before the age of 12, as opposed to those above age 12 experienced a greater cognitive decline post professional (NFL) retirement.[223] Overall, understanding the role that aging plays as a modifier of cognitive outcomes in cumulative head impact exposure will be important both of identifying the onset of injury, but also in predicting a course of decline, and how it might best be ameliorated.

1.3.5 Considerations for Age-Related Studies

A key consideration in assessing aging populations is that older individuals typically have a reduced capacity for completing cognitive tasks due to straying attention, impaired comprehension, and short retention.[73,81] Pilot testing of aged controls and retired athletes completed by the author demonstrated robust challenges with participant retention and recruitment. Due to poor protocol adherence, the data from this pilot project (n = 11), are not presented here. In total, however, 43 people were recruited, with 32 individuals choosing to stop part way through the assessment. Anecdotally, many participants expressed concern with the one-hour time commitment required to complete the

cognitive battery and history survey and there was concern over the appropriateness of a computerized test for this population. Fortunately, previous work in our lab has suggested that the computerized administration of the CBS test is appropriate for use in aged populations,[49,53,225,226] but that all tests may not equally useful. For example, in one study of individuals over age 65, 98% of those tested were able to complete five CBS tests (Paired Associates, Feature Match, Odd One Out, Color Word Remapping and the Hampshire Tree Task).[53] Additionally, while two tasks (Odd One Out and Color Word Remapping) were useful for categorizing those with borderline cognitive impairment (on the MoCA) as unimpaired or impaired, the Hampshire Tree Task demonstrated no discriminating power and the Paired Associates Test was deemed too difficult for an elderly population.[53]

Overall, offering a shorter test may be necessary to promote recruitment and retain aged participants. The possibility of optimizing test battery to include only the most relevant and salient tests may be an ideal approach to solve this external confound. This is the objective of **Chapter 4**.

1.4 Summary of the Dissertation:

In total, three studies were completed as a part of this dissertation. Their rationale and specific objectives are as follows:

Chapter 2 – A Comparison of SCAT3 and CBS Tests to Assess Cognitive Dysfunction in Non-Concussed American Footballers

> **Objective:** Assess which aspects of cognition are measured by the SCAT3 through CBS test score correlations

Concussion is an important and frequent injury in contact sport. To help standardize its clinical diagnosis, miniaturized neuropsychological cognitive tests have been paired with assessments of balance, coordination and symptoms to generate concussion-specific tests. The Sport Concussion Assessment Tool 3 (SCAT3) is the most widely used concussion assessment and can be applied in several clinical settings to aid in diagnosis. One aspect of the SCAT3, the Standardized Assessment of Concussion (SAC), is focused on

cognition. Since concussion patients can present with a myriad of cognitive symptoms, the limited scope of the SAC calls into question how adequately broad cognitive deficits can be identified or assessed. Additionally, in recognizing that the SCAT3 has limited diagnostic ability beyond 3-5 days,[227] and that prolonged and persistent physiological disturbances exist beyond neuropsychological recovery,[113–115] we must reconsider the relevancy and usefulness of current behavioural tests, like SCAT3, in assessing cognitive change in concussion. Critically, if concussion-specific tests are unable to adequately measure cognitive change, clinicians and researchers will miss impairments or suggest premature recovery putting athletes at increased risk.

Chapter 3 – Slowed and Variable Cognitive Response Times in Footballers

> **Objective:** Determine the influence of cumulative head trauma (measured as seasons of contact sport played) on cognitive function through comparing neuropsychological test results (scores and response times) of varsity football athletes to matched controls.

A myriad of studies suggest a link between early-life head impact exposure, and late-life cognitive changes, though there remains a lack of understanding regarding the onset of decline. Specifically, some studies show increased rates of dementia diagnoses post retirement,[186] while others have noted CTE diagnoses in those as young as 18 years of age,[228] suggesting that some individuals are either resilient, or spared from cognitive decline, for reasons which are currently not understood.[229] As such, the premise behind this study was that identifying early-career cognitive changes, would offer the best options for intervention. For this study, we selected varsity football athletes as our population of interest for a number of reasons including:

1) They represent an extraordinary case of chronic head impact exposure,
2) Football athletes are the population most commonly diagnosed with CTE,
3) Collegiate athletics is a common career step for both professionals and recreationalists,
4) Most individuals playing collegiate football have participated in the sport for a number of years, suggesting a nominal impact burden at this career stage, and

5) Cognitive,[186] mental-health[230] symptoms, and neuroanatomical changes[231] have been identified in some retirees, but the onset remains unknown

Study 4 – Optimizing the CBS Battery & Applications in Aging

Study 4A Objective: Examine how previously determined cognitive composites (Hampshire et al 2012) applied to both young and old populations, and then exercise Principal Component Analysis methods to reduce the battery while maintaining the integrity of the 3 previously established cognitive components.

Following chapter 3, we wanted to expand our work to include older contact sport retirees. This, however, came with some logistical considerations that needed to be addressed, which became the goal of this study. First, we noted a shortcoming with participant retention and protocol adherence in chapter 3 that we attributed to the relatively long-time commitment we asked of participants participating remotely. Additionally, we recognized that older individuals typically have a reduced capacity for completing cognitive tasks.[68,224] To address these challenges, data reduction methods presented a common solution through offering better data acquisition economy, improved participant recruitment/retention and more targeted and stable scoring[232,233] as both time to completion and extraneous error are reduced.

The initial goal was to examine CBS tests for redundancy in order to identify specific tests for removal. Previous work by Hampshire et al (2012) suggested a known 3-component structure for CBS (representing cortically distinct networks supporting reasoning, short term memory and verbal abilities) which would be ideal to preserve. This however relied upon a preservation of the previously established factor structure, which did not exist in our sample. Thus, in order to be able to apply the CBS tasks in an aging population, we took another approach to data reduction that would identify tests that discriminate best between younger and older populations. As such we chose to:

Chapter 4B Objective: Employ Discriminant Function Analysis data reductions strategies to determine how many tests were necessary to discriminate between

groups of varying age while preserving the amount of variance accounted for in the test.

Discriminant function analysis is focused identifying how the different weighted linear combinations of the dependent variables predict group membership or explain differences between groups[232] and are useful in choosing subsets of original variables for future use.[234] Through employing a stepwise model, we aimed to exploit a data-driven approach to data reduction such that variables contributing least to group separation (based on age) are removed.

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Chapter 2

2. Using the SCAT3 and CBS Cognitive Battery to Assess Cognitive Dysfunction in Non-Concussed American Football Players

2.1 Introduction

Concussion is a prevalent diagnosis for those partaking in contact sport, generally considered a functional, rather than structural cortical injury.[1] While research efforts are making progress in imaging the effects of concussion,[2] standard clinically available imaging scans (namely, MRI and CT) do not typically show concussion-related structural changes[3,4] which can make diagnosis difficult. Additionally, symptoms in concussion are varied and can include deficits in attention, working memory, and speed of information processing, headaches, dizziness, and irritability,[3] which are not unique to concussion. Additionally, symptoms may be delayed in onset[5] and normally last 7-10 days[6] in 80-90% of cases,[1] further complicating diagnosis. As such, identifying concussion is based on clinical judgement based on interpreting a patient-specific[6] report that may include a description of how they became injured and their symptom severity,[7,8] combined with medical details of physical signs, and cognitive impairment,[1] rather than a definitive biological or physiological test. Thus it is considered an "imperfect art"[4] and to be among the most complex injuries in sports medicine to diagnose, assess and manage,[1] and is subject to variability between clinicians and across subspecialties.[4]

2.1.1 Neuropsychological Testing

Neuropsychological testing is a well-established method for assessing cognition in clinical populations[9] that is sensitive to decline, recovery and interventions (e.g. pharmaceutical, lifestyle). Importantly, many clinical practice guidelines and position statements emphasize a role for neuropsychological testing in the appropriate management of concussion.[1,10] Their ease of use and ability to detect changes both between and within individuals across serial administrations make them an appealing tool. A limitation however, is that full neuropsychological test battery requires 4-8 hours

to administer, and concussion generally results in multimodal deficits beyond cognition. Thus, in an effort to support clinicians, aspects of these cognitive tests have been combined with assessments of behaviour, mood and physical abilities to create shorter concussion-specific tests that serve three major functions:

1. aiding in concussion diagnosis[1],
2. facilitating effective medical management of patients after concussion, including return to play assignments
3. a better understanding of the brain regions responsible for a certain behaviour or impairment.[11]

Neuropsychological assessments in sport typically occur at three different clinically relevant time points: a pre-season baseline, at the sideline immediately after a suspected injury, and in the clinic to assess recovery and rehabilitation. They are also used in research to better understand concussion etiology, diagnosis and recovery patterns. Often the same test is used across multiple instances, meaning that concussion-specific tests should be robust against cheating/sandbagging (intentional efforts to falsely perform poorly to disguise later injury-induced impairments[12]), exhibit low test-retest bias so that they may be used multiple times and be quick and easy to administer and score.[13] However, to remain brief, many existing assessments are inadequate with respect to the breadth of cognitive domains that they able to consider. For instance, many concussion studies have attempted to assess broad aspects of cognitive function such as reasoning,[7] short-term memory,[7,14–16] and verbal abilities,[7,14] but have done so by extrapolating from performance on just a few tests. This limits understanding to test-specific impairments, which are incapable of describing broader cognitive deficits if they are present.

2.1.2 Importance and Limitations of Neuropsychological Testing in Concussion

In research, neuropsychological tests are often used alongside physiological or biomechanical assessments to broadly assess concussion deficits. Several studies have noted that, despite a return to baseline on neuropsychological tests (or equivalent performance in comparison to matched controls), other aspects of health and physiology

including cerebral blood flow,[17] postural stability,[18] BOLD responses,[14] and MRI changes,[2] demonstrate persistent, or prolonged changes. In essence, this means that symptom resolution does not necessarily define complete recovery from concussion.[19] From this, one of two major conclusions might be drawn:

1. Cognitive function recovers at a faster pace than other physiological measures after a concussion or,
2. Neuropsychological tests may be insensitive to the longer-term effects of concussion

While the first option is certainly possible, and is supported by the results of several studies,[2,14,17,18] a larger concern is the second as it not only impedes our ability to assess the first, but may exacerbate the risk for asymptomatic athletes who are prematurely cleared to return to play. Therefore, it is important to evaluate whether performance on cognitive tests, such as the Sport Concussion Assessment Test (SCAT) 3, is adequate for assessing the cognitive effects of a sports-related concussion and whether such tests are sensitive to changes that might occur over time.

SCAT3

The Sport Concussion Assessment Test (SCAT) is the most widely used concussion assessment tool[20,21] and represents a current 'gold-standard' for assessing for concussion. It was developed to provide an objective and standardized assessment of concussion, primarily at the sideline.[22] SCAT was first described at the second international conference on concussion in sport in Prague in 2004,[23] and underwent subsequent revisions to become the SCAT2 and SCAT3 in 2008[24] and 2013[1], respectively. With these revisions, the scope of the test began to expand to include monitoring an athlete's recovery over the course of subsequent clinical assessments[22,24,25] and as part of a baseline assessment before injury.[22,26] The test consists of 8 components, the results of which are combined to generate Cognition, Balance, and Symptom Scores as outlined by the grey boxes in Figure 2.1. Of particular note for the current study is the test's cognitive assessment entitled the "Standardized Assessment of Concussion (SAC)" which consists of four sub-scores: orientation, immediate memory, concentration and delayed recall.

The SCAT5 (there is no SCAT4) was released in 2017 after data for this study had been collected. Changes to the updated 5th edition were limited to offering 10 word/digit lists alongside the conventional 5 word/digit lists to reduce ceiling effects, and suggesting that although still helpful, baseline testing is not required for interpreting post-injury test scores.[27] Test administration and scores are otherwise consistent, which maintains the usefulness of this study for future comparisons.

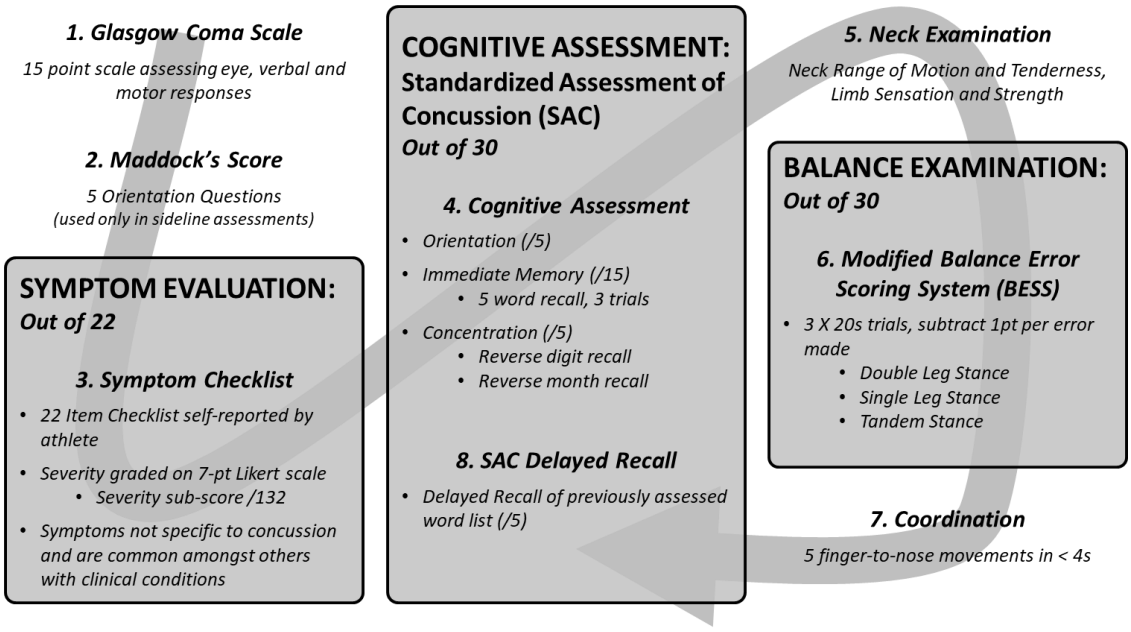

Figure 2.1: SCAT3 Components, and the Composition of Symptom, Cognition and Balance Scores. Greyed boxes represent specific scored aspects of the test representing symptom, cognitive and balance abilities

Previous research has established normative scores (see Table 2.1) for the SCAT2 and SCAT3 editions of the test, for which SAC and balance component scoring remained consistent.[28] In general, baseline SCAT scores remain similar across high school and collegiate athletes[20] and a small main effect of sex has been found for the SAC.[29] Scores on SCAT3 components appear to have no significant association with age, years of education, history or number of past concussions, history of headache or migraine, or recovery time after last concussion.[30] There is, however, limited data available for professional athletes, and adult non-collegiate athletes tested post-concussion.[20]

Table 2.1: SCAT2/3 Normative Weighted Means, Cut Offs and Meaningful Changes Scores

Population/ Notable Measure	Symptoms (max 22 ±SD)	Cognition: SAC (max 30 ±SD)	Balance: BESS (max 30 ±SD)	Reference
High School	18.46	26	26.14	Thomas et al[20]
Collegiate	20.09	27.51	25.54	
Collegiate – Male	20.31 ±2.87	26.97 ±2.05	25.49 ±4.14	Zimmer et al[29]
Collegiate – Female	20.09 ±3.29	27.63 ±1.87‡	25.94 ±3.90	
Unusual Score Cut Off	<18*	<24	<24	Hänninen et al[30]
Significant Change Relative to Baseline	3-5x symptoms, 6-8 pts in severity	2-4 points decrease	3-6 points decrease	*Guskiewicz et al*[28]

‡ indicates sig diff from males
**total symptom severity of >6 also considered unusual (max 132)*
(SAC: Standardized Assessment of Concussion, BESS: Balance Error Scoring System)

SCAT3 Strengths and Limitations

Of SCAT3's many advantages, perhaps the most relevant comes though its administration. Specifically, it's short duration, often taking less than 15 minutes in total, and it pen and paper nature, requires limited resources, keeping cost and barriers to administration low. It also uses a relatively intuitive scoring system that requires little training for interpretation which limits the need for a trained neuropsychologist. Some of these features, however, may also limit the SCAT3's use in certain circumstances. For example, because the test is easily available online, it is prone to memorization tactics and sandbagging efforts,[27] and since is administered via pen and paper, there are no options for assessing response time, which is both more sensitive to cheating attempts,[31] and may offer insights about attention that cannot be gleaned from accuracy scores alone.[32,33]

Cambridge Brain Sciences

The Cambridge Brain Sciences (CBS) cognitive battery is a widely cited, online adaptive testing platform that comprises 12 non-verbal, culturally independent tests that cover four broad domains (i.e. memory, reasoning, concentration, and planning/executive function).[34,35] While not a full scale neuropsychological test, the CBS test battery is more diverse than those applied in classical IQ assessments[34] and offers a practical way to test participants in less than 60 minutes.[35] The tests are adaptive, increasing or decreasing in difficulty in response to performance, to quickly determine a participant's specific ability

with each administration, and questions are randomly generated between individual trials, which limits cheating. Validated in over 44,000 participants,[34] the tests have been used to characterize impairments in multiple sclerosis patients[36] and NFL Football Alumni.[37] CBS scores also correlate with the Minimal Assessment of Cognitive Function in MS (MACFIMS),[36] the Montreal Cognitive Assessment (MoCA),[38] and both Cattell's Culture Fair and Raven's Progressive Matrices tests of fluid intelligence.[34]

Principal component analysis (PCA) has also been used to show that the CBS cognitive tests broadly assess three cortically distinct and functionally specialized cognitive networks supporting Reasoning /Executive function (planning, initiation, sequencing and monitoring of complex goal directed behaviour), Short Term Memory (short term storage and manipulation of information in working memory) and Verbal Abilities (tasks employing numerical or verbal stimuli).[34] These three cognitive components provide a means for assessing cognitive function in a way that is not bound by single test scores. For more information on the 12 tests, please consult the supplementary materials of Hampshire et al (2012)[34] and Appendix 1.

Objectives

The objective of the current study was to examine the SCAT3, the most widely used concussion assessment tool, in order to identify its strengths and weaknesses in assessing cognitive function. To do so, we compared performance on the SAC portion of the SCAT3 and its four sub-scores to performance on the CBS cognitive battery to address the following questions:

1. Is the overall SAC score correlated with any of the CBS Cognitive Composite scores and if so, which SAC sub-scores are correlated with which CBS Composite scores?
2. Is the overall SAC score correlated with CBS test scores and if so, which SAC sub-scores are correlated with which CBS tests?

Given its broad nature, we hypothesized that the SAC portion of the SCAT3 test would correlate with all three CBS cognitive composite scores (verbal, reasoning, short term memory), as well as relevant test sub-scores.

2.2 Methods

2.2.1 Participant Inclusion/Exclusion and Protocol

Participants in this study were recruited as a part of a larger study assessing cognitive function in football athletes. All completed the CBS cognitive battery prior to the start of the season. CBS tests were completed online by participants at their leisure following a short survey to gather participants' health, sport and demographic histories.

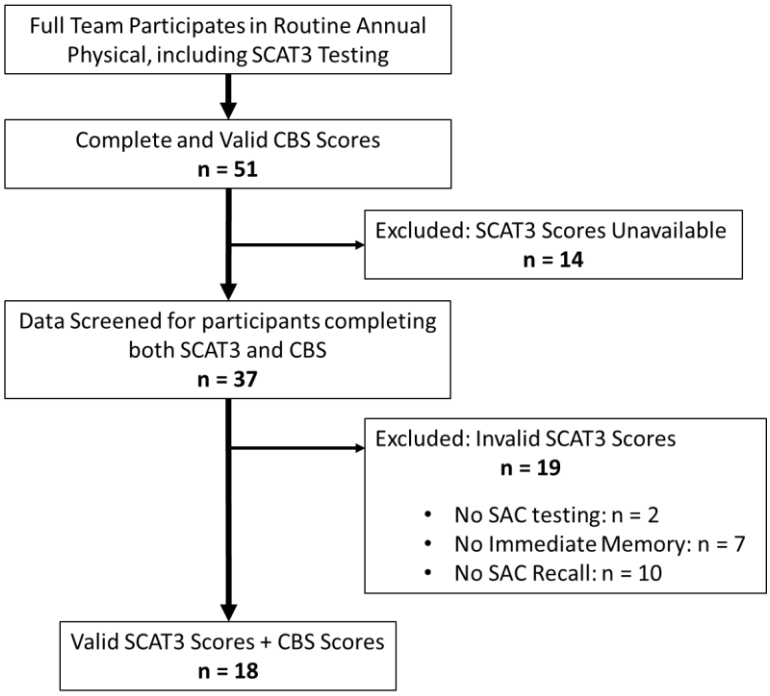

Figure 2.2: Experimental Protocol and Participant Exclusions

SCAT3 testing was administered as a routine part of the pre-season physical evaluation conducted by trained team medical staff, who were naïve to the research question. SCAT3 scores were extracted from participants' medical charts and matched to CBS scores. All participants were aged 18-23, and were current members of a local varsity football team. Informed consent was obtained in accordance with the Declaration of Helsinki and the University of Western Ontario Health Sciences Research Ethics Board. After screening data for completeness and validity, 18 complete data sets remained for analysis. The experimental protocol and the procedure used to exclude participants are summarized in Figure 2.2, while participant demographics are included in Table 2.2.

Table 2.2: Participant Demographics

	American Footballers (± SD)
N	18
Age	20.33 (± 1.71)
Years University Education	2.67 (± 1.46)
Years Physically Active	15.44 (± 3.55)
Seasons of Contact Sport Played	14.33 (± 6.49)
Seasons of Football Played	6.50 (± 2.85)
Number of Previous Concussions	0.39 (± 0.61)

2.2.2 Cognitive Composite Scores

"CBS Cognitive Composite scores" representing reasoning, short term memory and verbal components were calculated as linear composite scores based on PCA factor loadings (Table 2.3) determined by Hampshire et al (2012).

Table 2.3: CBS PCA Linear Component Factor Weightings (from Hampshire et al. Used with permission from Elsevier © 2012)

CBS Tests	PCA Linear Components		
	Short Term Memory	Reasoning	Verbal
Spatial Span	0.69	0.22	
Monkey Ladder	0.69	0.21	
Self Ordered Search	0.62	0.16	0.16
Paired Associates	0.58		0.25
Hampshire Tree Task	0.41	0.45	
Spatial Rotations	0.14	0.66	
Feature Match	0.15	0.57	0.22
Interlocking Polygons		0.54	0.30
Odd One Out	0.19	0.52	-0.14
Digit Span	0.26	-0.20	0.71
Verbal Reasoning		0.33	0.66
Color Word Remapping	0.22	0.35	0.51

2.2.3 Statistical Analyses

The Statistical Package for the Social Sciences (SPSS 25) was used for all statistical comparisons. More specifically, Pearson bi-variate correlations were calculated between SAC and its sub-scores, as well as CBS tests and cognitive composites. Multiple comparison bias was addressed through the use of Holm-Bonferroni adjustments to the alpha within family comparisons (see Table 2.4). With this adjustment, no significant correlations were found for any comparison. The exploratory nature of this analysis

however warrants considering these comparisons individually without correction, as is presented subsequently.

2.3 Results

2.3.1 CBS Cognitive Composite Score Correlations

CBS Cognitive Composite scores were first compared to the SAC. Significant composites were then assessed in comparison to the SAC sub-scores. There was a significant uncorrected correlation between the Verbal Composite Score and the SAC (Figure 2.3A: $r = 0.516$, $n = 18$, $p = 0.028$), as well as the Verbal Composite Score and the Immediate Memory SAC sub-score (Figure 2.3B: $r = 0.506$, $n = 18$, $p = 0.032$).

2.3.2 CBS Test Score Correlations

CBS Test scores were compared to the SAC, Significant tests were then compared to the SAC sub-scores. There was a significant uncorrected correlation between the Paired Associates Test and SAC (Figure 2.3C: $r = 0.523$, $n = 18$, $p = 0.026$), as well as the Paired Associates test and the Delayed Recall SAC sub-score (Figure 2.3D: $r = 0.522$, $n = 18$, $p = 0.026$).

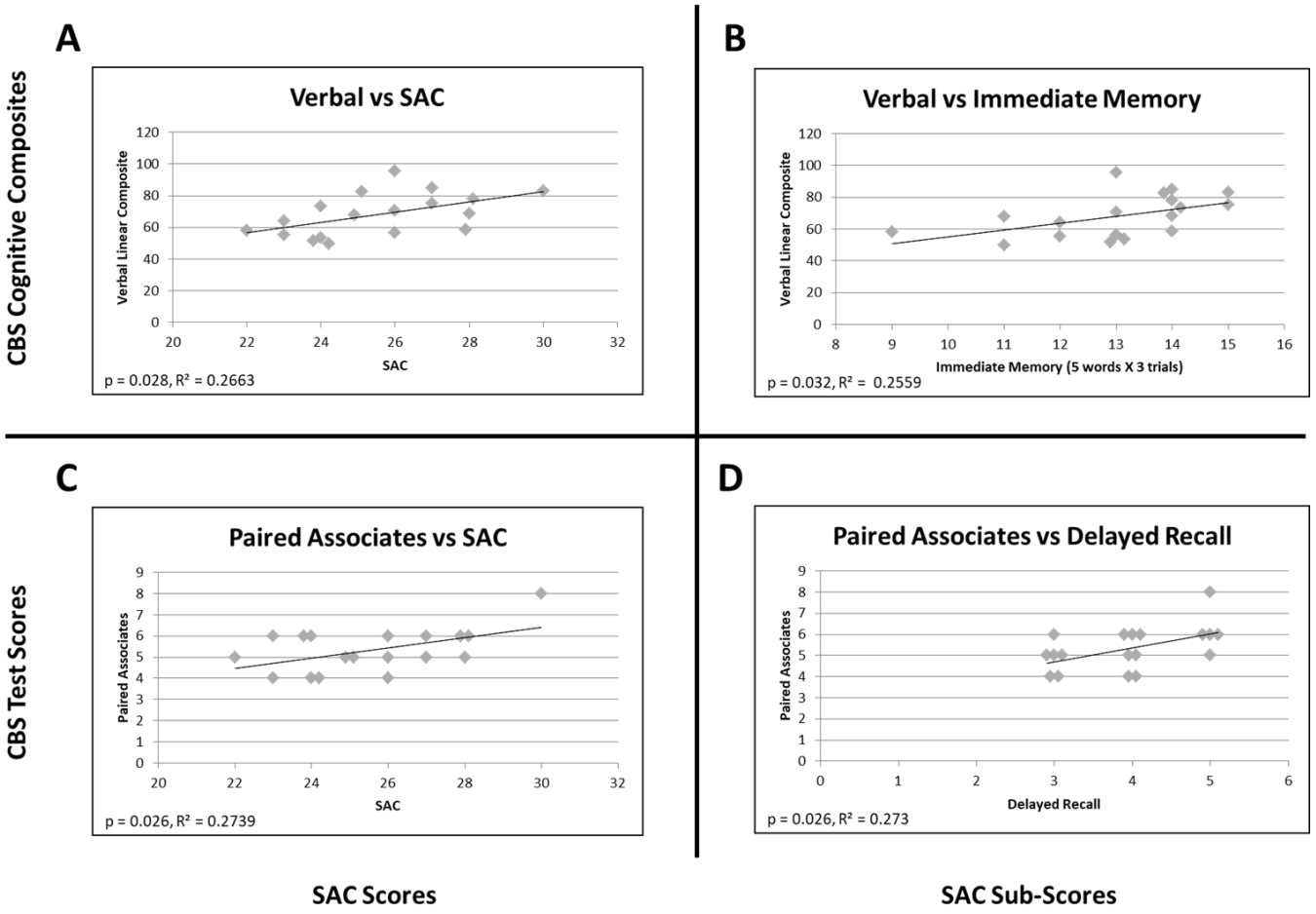

Figure 2.3: Significant Pearson Bi-variate Correlations representing:
A) CBS Cognitive Composite vs SAC **B) CBS Cognitive Composite vs SAC Sub-Scores**
C) CBS Test Scores vs SAC **D) CBS Test Scores vs SAC Sub-Scores**

Pearson Bi-variate (r) and significance values for all tested correlations are detailed in Table 2.4.

Table 2.4: Pearson Bi-Variate Correlations for all CBS and SAC Comparisons
*** indicates significant uncorrected correlations (p < 0.05). H-B familywise corrected α is listed below.**

		SAC	SAC Sub-Scores				
			Orientation	Immediate Memory	Concentration	Delayed Recall	
CBS Cognitive Composites	Short Term Memory	r = 0.274 p = 0.270 *α = 0.05*					*Composites Family*
	Reasoning	r = 0.400 p = 0.100 *α = 0.025*					
	Verbal	**r = 0.516** **p = 0.028*** *α = 0.017*	r = -0.107 p = 0.673 *α = 0.05*	**r = 0.506** **p = 0.032*** *α = 0.013*	r = 0.249 p = 0.319 *α = 0.017*	r = 0.124 p = 0.624 *α = 0.025*	
CBS Test Scores	Spatial Span	r = -0.199 p = 0.429 *α = 0.05*					*Short Term Memory Family*
	Monkey Ladder	r = 0.221 p = 0.378 *α = 0.025*					
	Self Ordered Search	r = 0.367 p = 0.134 *α = 0.017*					
	Paired Associates	**r = 0.523** **p = 0.026*** *α = 0.013*	r = -0.059 p = 0.816 *α = 0.025*	r = 0.447 p = 0.063 *α = 0.017*	r = 0.035 p = 0.889 *α = 0.05*	**r = 0.522** **p = 0.026*** *α = 0.013*	
	Hampshire Tree Task	r = 0.014 p = 0.955 *α = 0.05*					*Reasoning Family*
	Spatial Rotations	r = 0.317 p = 0.201 *α = 0.013*					
	Feature Match	r = -0.221 p = 0.377 *α = 0.017*					
	Interlocking Polygons	r = 0.383 p = 0.117 *α = 0.010*					
	Odd One Out	r = -0.187 p = 0.457 *α = 0.025*					
	Digit Span	r = 0.116 p = 0.648 *α = 0.05*					*Verbal Family*
	Verbal Reasoning	r = 0.291 p = 0.241 *α = 0.025*					
	Color Word Remapping	r = 0.465 P = 0.052 *α = 0.017*					
			SAC Family				

2.4 Discussion

In this study, the relationship between performance on the Standardized Assessment of Concussion (SAC) portion of the SCAT3 and performance on the CBS battery was assessed. The results demonstrated that SAC performance correlated only with the verbal cognitive composite score of the CBS battery. As noted in Figure 2.1, the SAC consists of orientation, immediate memory, concentration and delayed recall sub-scores. Importantly, both the immediate memory and delayed recall sub-scores, accounting for 2/3 of the SAC test score, require the participant to recall the same list of five words. On this basis, it is unsurprising that the correlation between SAC performance and the verbal component of the CBS battery is driven by SAC immediate memory performance. This correlation accounted for ~30% of the variance between these tests. It is important to realize that the SCAT and CBS tests represent assessment in some non-overlapping areas. In particular, SCATs ability to assess orientation, simple attention and long term memory exceeds that of CBS. As such, it is likely that the remaining ~70% of variance may be accounted for by these differences in assessment (e.g. tests included), a difference in data collection methods (pen & paper vs computerized), variability and noise in the data or something else, beyond cognitive function.. Considering that the SAC is the primary method for assessing cognition offered acutely to many concussion patients, it is necessary to recognize which aspects of cognitive function are and are not adequately assessed. Critically, if the SCAT is unsuitable for comprehensively assessing cognition, its use in an injured or rehabilitative state will be ineffective.

In addition to assessing cognitive composite scores, CBS test scores were compared with the SAC and its sub-scores. As illustrated in Figures 3C and 3D, the CBS Paired Associates task was significantly correlated with both the SAC and its delayed recall sub-score. In the Paired Associates task, participants view boxes containing pictures of everyday items which open one after another to reveal the item, and then close. Participants are then given a target item for which they are to find its match. Both the CBS Paired Associates task and most of the SAC tasks require that information be recognized and retrieved, likely accounting for the high correlation between these

performance scores. The fact that the SAC correlated with a single CBS test score confirms that its scope is relatively narrow.

Overall, individuals should exercise caution when interpreting international consensus statements on player assessment, suggesting that the SCAT3 assesses attention and memory,[1] and be aware of the limited scope of the SAC in assessing cognition. Finally, it is worth noting that concussion is shown to produce long term deficits in executive function and speed of information processing,[7] neither of which are specifically assessed by the SAC. These results suggest more comprehensive cognitive testing, which is generally offered in the clinic as part of a more comprehensive neuropsychological test, is warranted.

2.4.1 SCAT3 Administration

Invalid or partial baseline testing is a known issue for the SCAT3, and it was no different in this study; nearly 50% of all available SCAT3 tests were incomplete due to partial immediate memory scores, or the absence of a delayed recall score. Assessing these specific components requires that the same five words are retested several times. It is unclear why adherence was so poor; it may reflect time constraints or the belief among clinicians that additional iterations of the tests were without value. In this regard, it is important to note that our data was collected in a true-to-life fashion by clinicians administering a routine pre-season exam, so this problem may be ubiquitous across other teams and sports as well. Compounding this issue, evidence suggests upwards of 25% of all baseline tests are inaccurate due to invalid responding or sandbagging.[12] Overall, this is a problem because ~95% of athletic trainers use baseline testing, but only ~50% screen for invalid baseline data.[39] Although current guidelines no longer require baseline testing,[27] this is an important consideration for clinicians who still rely upon this practice. Further research on which aspects of the SCAT3 test are most important clinically is necessary to streamline the test and mitigate this known issue. Based on our findings and those of others, we also recommend that a secondary screening protocol be put into place for those administering baseline SCAT3 assessments to ensure both data completeness and validity.

2.5 Conclusions

Although previous work has established normative scores and reliability estimates, the validity of SCAT3 (that is, the extent to which it accurately measures what it intended), is widely assumed, but not previously systematically tested. The results of the current study suggest that the SAC cognitive component of the SCAT3 is focused too narrowly on verbal abilities and may miss important components of cognition that are equally vulnerable to brain injury. The main issue is *not* that the SCAT3 is incapable of identifying acute concussion where it occurs, but rather, that it's use as a measure of cognition is likely to be misleading and does not take account of deficits in higher order functions. Still, SCAT remains useful as a mental status exam even if it lacks the sensitivity to detect more subtle cognitive change. In conclusion, whether on the field, in a clinic, or the lab, a more comprehensive set of tests may be more appropriate for fully documenting the effects of concussion and for understanding the long-term cognitive consequences of repeated head impacts in athletic populations.

2.5.1 Limitations

This study was conducted using a sample of male contact sport athletes aged 18-23. These athletes represent an important and high-risk population to consider for concussion, results presented here should be replicated with other populations to ensure consistent applicability. Secondly, all participants in this study were healthy and non-concussed, completing all testing at as a pre-season baseline. While we acknowledge that the SCAT3 is primarily used as a rapid assessment for the presence or absence of concussion, it still must be able to capture broad cognitive abilities at baseline in order to be effective at managing these concerns post-injury. As such we believe that this baseline comparison is adequate though suggest future studies compare changes in test results in the presence of concussion. Finally, future comparisons of concussion-specific tests should include computerized versions like ImPACT or CogSport which offer more similar metrics to those used in CBS.

2.6 Acknowledgements

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Chapter 3

3. Slowed and Variable Response Times in Collegiate American Footballers

3.1 Introduction

While concussion is an important clinical diagnosis and concern in contact sport, subconcussive impacts are far more common, may affect cognitive function[1–3] and are recognized as contributing to the cumulative long-term neurological consequences noted in chronic traumatic encephalopathy (CTE).[4] Beyond this, the literature is rife with other examples of subconcussion-related cognitive changes including cerebral white matter changes six months into the post season in non-concussed collegiate football atheltes,[5] and decreased visual working memory and dorsolateral frontal cortex activation in non-concussed high school footballers after a single season.[6] More chronically, dementia-related diagnosis,[7] including Alzheimer's Disease,[8,9] Mild Cognitive Impairment, (MCI),[10]and Parkinson's Disease,[11] may be related to concussive and subconcussive exposure, with NFL retirees demonstrating increased diagnosis rates in comparison to the general population.[7] Given their extraordinary impact exposure of upwards of 900 impacts/player per season,[3] as well as decreased hippocampal volume,[12] and impaired reaction time[12] with concussive exposure, determining when head-trauma related cognitive changes start and what they might mean long-term is increasingly important for American football athletes. Critically, it seems that cumulative head impact burden (both concussive and subconcussive impacts) contribute to these cognitive changes, though what remains unclear is when these changes first appear, when they can first be detected and what form they take. Establishing this understanding is key as early pre-clinical intervention essential for slowing or stopping disease progression and ensuring that contact sport participation decisions are made from a well-informed perspective.

Traditionally, cognitive abilities are assessed using paper and pencil neuropsychological tests, although in recent years computerized assessment batteries have become more common. One advantage of computerized tests is that response times and their variabilities can be accurately measured[13] offering important insights into potential

cognitive deficits. Importantly, differences in reaction times[14] and increased variability are frequently observed in patients who have sustained traumatic brain injury[15] and concussion,[14] even in the absence of neuropsychological test score differences.[16]

3.1.1 Hypothesis

The goal of this study was to compare cognitive function, as assessed by neuropsychological test scores and response times between football athletes (high cumulative head impact burden) and matched healthy controls (low cumulative head impact burden).

We hypothesized that varsity American football athletes experiencing chronic head impacts would demonstrate impaired cognitive function compared to matched control group. Because participants were assessed at pre- and post-season time points we were also able to estimate the effects of chronic (i.e. pre-season performance versus matched controls) and acute (i.e. post-season performance versus pre-season performance) head impacts in the participants.

3.2 Materials and Methods

3.2.1 Participants

A total of 81 male university-level American Football Athletes, and 101 matched controls completed the Cambridge Brain Sciences Battery as a part of this study. American Football participants were current members of a local university team, and controls were recruited both from the community and online via Amazon's Mechanical Turk. Informed consent was obtained in accordance with the Declaration of Helsinki and the University of Western Ontario Health Sciences Research Ethics Board. As this study was administered fully online, all assessments were completed at participants' discretion on their personal computer. To ensure study eligibility, all participants were screened using a brief questionnaire (see Appendix 2) designed to assess concussion, athletic and basic demographic history. All participants were male, aged 18-25, and were excluded if they self-reported having a history of concussion within the previous year (including the time period of the tenure of the study). Concussion information for athlete participants was compared to available Sport Concussion Assessment Tool 3 (SCAT3) tests administered

by team-affiliated athletic trainers to ensure accuracy. Participants were also excluded if their CBS scores were implausible, or they did not complete both testing time points. A single footballer was excluded as he did not play a contact-based position (kicker). After all exclusions (outlined in Table 3.1) 32 American football sets of pre-post season data were matched with 32 control sets of data selected from an available pool of participants.

Table 3.1: Participant Inclusion/Exclusions

	Football
Completed CBS	81
Excluded:	49
Implausible CBS Scores	*24*
Completed 1 Time Point Only	*20*
Concussion within Last Year	*4*
Non-Contact Position	*1*
Included:	32

Contact sport participation was documented in terms of seasons played and serves as a proxy for exposure to head impacts. Open-ended descriptions of athletic involvement were coded by a single examiner to derive this measure by including seasons of American football, rugby, lacrosse, hockey and combat sports. Demographic, sport and health information of both the American football and control groups were compared via independent samples t-tests. Data and significant comparisons are highlighted in Table 3.2.

Table 3.2: Participant Demographic, Sport and Health Information

	Control (± SD)	Football (± SD)	Significance
N	32	32	
Age	**22.68 ± 1.69**	**20.31 ± 1.38**	*** t(62) = 6.154, p < 0.001**
Years University Education	2.78 ± 1.43	2.22 ± 1.04	NS
Years Active	13.71 ± 7.10	15.22 ± 3.19	NS
Lifetime Concussions	0.31 ± 0.64	0.78 ± 1.96	NS
Seasons Contact Sport ‡	**2.88 ± 3.82**	**13.16 ± 7.54**	*** t(62) = -6.882, p < 0.001**
Hours/week of Activity	**8.06 ± 4.83**	**17.44 ± 7.21**	*** t(62) = -6.115, p < 0.001**
‡ Contact Sports: American Football, Rugby, Lacrosse, Hockey, Combat * Indicates Significant difference between groups			

3.2.2 Experimental Design

Based on an a priori power calculation for a moderate effect size (0.6), a total of 64 participants were required to achieve a power of 0.80 with alpha of 0.05.

American football participants had the opportunity to engage in neuropsychological testing every two weeks throughout the course of the athletic season for a total of 8 testing sessions. On average, 3.4 sessions were completed by American football participants, though only time points 1 (pre-season) and 8 (post-season) were included in the analysis, because participation in the intervening sessions was too variable across players to be of any analytical value. These pre- and post-season time points were approximately 100 days apart. Control participants only completed time points 1 and 8 at a 100-day interval. The effect of test repetition was considered as a covariate for analyses.

Cambridge Brain Sciences Cognitive Battery

The Cambridge Brain Sciences (CBS) cognitive battery was used to broadly assess cognitive function in this study. It consists of 12 short tests (1-3min duration each) based on classical neuropsychological paradigms.[17] In total, the CBS cognitive battery requires approximately 30 minutes to complete. Tests are adaptive in nature, increasing in difficulty with correct answers and decreasing in difficulty with incorrect answers to quickly iterate towards a participant's peak level of performance. Test questions also change with each administration to prevent cheating attempts. Final scores are calculated based on the number of correct and incorrect answers and the number of responses completed. A pictorial representation, and short outline of each test is included in Appendix 1. For a more in depth explanation of each test, please see Hampshire et al (2012), supplementary materials. Each test within the battery is measured on an independent scale, thus all participant scores were transformed into Z-scores based upon normative means and standard deviations generated from a population of >18 000 previously assessed participants aged 18-23.

Cognitive function has been described previously as an "emergent property of anatomically distinct cognitive systems, each of which has its own capacity."[17] Identified using neuroimaging and the CBS battery, Hampshire et al note 3 primary components supporting the following abilities:[17,18]

- Reasoning (executive function): tasks including planning, initiation, sequencing, monitoring complex goal-directed behaviour

- Short Term Memory: tasks requiring short-term storage and manipulation of information in working memory
- Verbal: tasks employing numerical or verbal stimuli

Together, these components reflect the way in which brain regions "are organized into functionally specialized networks, and moreover… the tendency for cognitive tasks to recruit a combination of these functional networks."[17] By extension, these cognitive networks have the potential to offer a more salient measure of the effects of injury as, while deficits on a single test may be noteworthy, globalized deficiencies are much more clinically relevant in terms of identifying impaired capabilities, developing rehabilitation strategies and understanding the cortical underpinnings of injury/disease. As such, three CBS Composite Cognitive scores representing Short Term Memory, Reasoning and Verbal abilities were generated from the 12 test scores using the PCA factor loadings determined by Hampshire et al (2012).

Response Times & Variability

Participant response times were measured for 5 of the 12 tests as identified in Appendix 1. All response times were coded as occurring for correct or incorrect responses. Incorrect responses can have different distributional properties than correct responses;[19] thus, the analysis of response times was restricted to correct responses only. A lower threshold was set to exclude all responses of less than 100ms,[20] as shorter response times are physiologically implausible and likely to be artifacts.[21] Variability comparisons were made using coefficient of variation ($CV = \sigma/\mu \times 100$) to account for differences in RT distributions across individuals.

3.2.3 Statistical Analyses:

All statistical comparisons were made using the Statistical Package for the Social Sciences (SPSS 25). Data were compared between groups (Control vs Footballers) using multivariate general linear model methods. Multivariate outliers, determined using Mahalanobis distance scores (chi^2 evaluated based on test df and $p = 0.001$), were removed from further analysis. In all comparisons, sample sizes were relatively equal. As such, accommodations for violations of covariance matrices (Box's M), equality of error

variances (Levene's Test)[23] and multivariate normality (Shapiro Wilk W)[24] were not made, as with equal sample sizes, MANOVA is robust to violations of this nature. All comparisons were made using a doubly repeated measures MANCOVA (group X time X test). Specific comparisons include:

- CBS Test and Composite Cognitive Z-Scores
- Response Time
- Response Time Variability (Standard Deviations)

Statistically significant omnibus tests were assumed to operate under a protected-F[25] and thus were followed up with uncorrected ANOVAs as the experiment-wise error rate was adequately controlled near the nominal alpha level.[26] Finally, two-tailed Pearson Bi-variate correlations were assessed between participants' age and all neuropsychological test and response time measures following the respective omnibus tests.

3.3 Results

3.3.1 CBS Test and Network Z-Scores

A doubly repeated measures MANCOVA, accounting for the effects of repeated test exposure, demonstrated no significant effects of group $F(12, 50) = 0.999$, $p = 0.464$, $\eta^2 = 0.193$), or pre- vs post-season sessions $F(12, 50) = 1.182$, $p = 0.322$, $\eta^2 = 0.221$.

The main effect of repeated test exposure, the covariate in this analysis, was statistically significant ($F(12, 50) = 2.505$, $p = 0.012$, $\eta^2 = 0.375$), specifically for the following tests: Hampshire Tree Task, Paired Associates, Spatial Rotations, Spatial Span, Digit Span, Color Word Remapping, Odd One Out, and all cognitive composite scores (Short Term Memory, Reasoning, Verbal). Finally, age was not significantly correlated with any neuropsychological test measure.

3.3.2 Response Time Data

Correct Average Response Time (Figure 3.1A): For this analysis, data was unavailable for a single football participant, which reduced the sample size to 31 and 32 for the American football and control participants, respectively. A doubly repeated measures MANCOVA noted a significant main effect of Group ($F(5,56) = 3.847$, $p = 0.005$, $\eta^2 =$

0.256). Specifically, American football players were significantly slower than controls on the Verbal Reasoning ($F(1, 60) = 10.840$, $p = 0.002$) and Color Word Remapping Tasks ($F(1,60) = 10.291$, $p = 0.002$). Age was not correlated with any response time measure.

Correct Response Time Variability (Figure 3.1B): Sample size for this analysis was reduced to 28 and 28 for footballers and controls, due to the unavailability of data in a single case (football), and outliers as assessed by Mahalanobis distance scores. A doubly repeated measures MANCOVA, noted a statistically significant main effect of group ($F(5,49) = 2.629$, $p = 0.035$, $\eta^2 = 0.212$). Specifically, American footballers demonstrated more variable responses in comparison to controls for the Verbal Reasoning task ($F(1,53) = 9.037$, $p = 0.004$). Age was not significantly correlated with any response time variability measure.

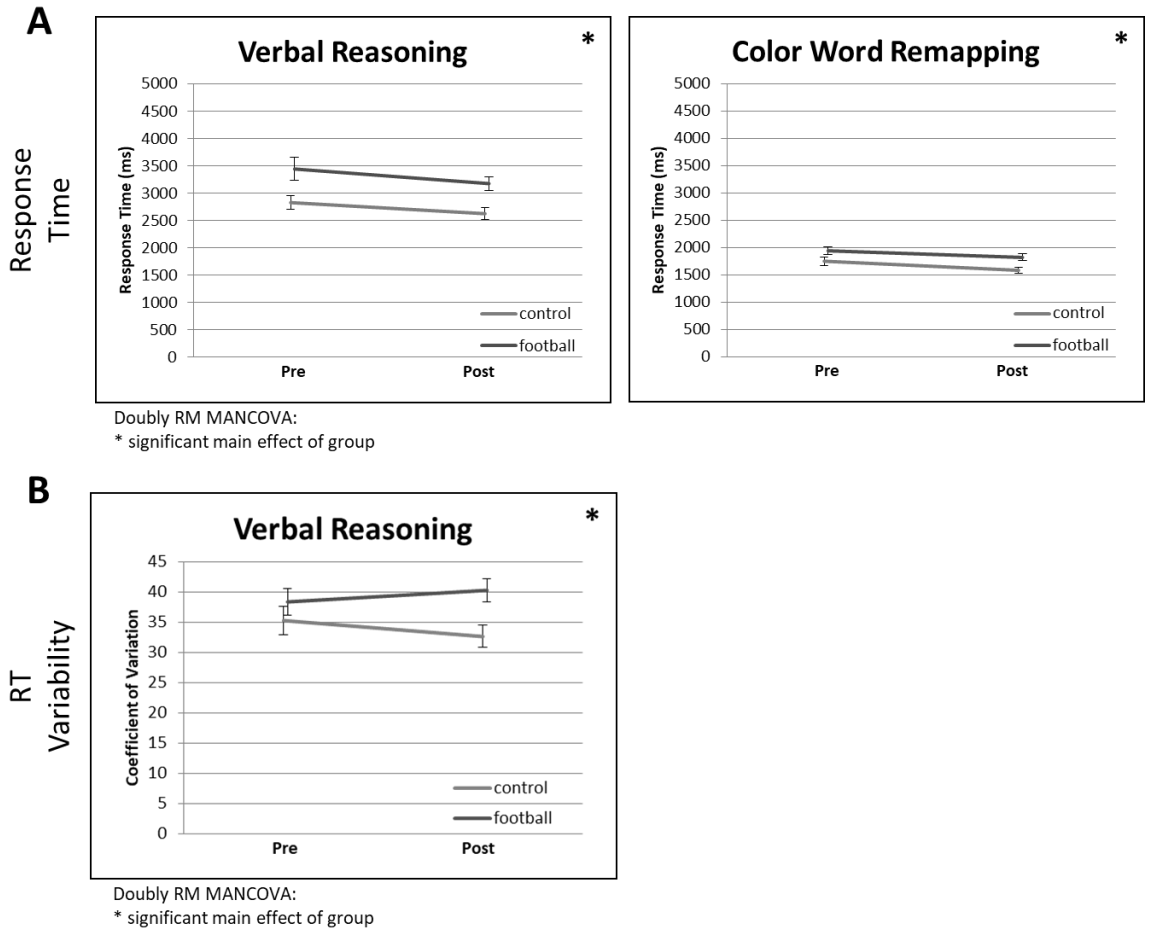

Figure 3.1: Correct Response Time and Response Time Variability by Group and Time Point. Error Bars represent SE.

3.4 Discussion

The aim of this study was to determine what the influence is of chronic head impacts, sustained through contact sport play, on cognitive function. Overall, the results confirm that cumulative head impact exposure in varsity football players is associated with cognitive impairments taking the form of prolonged reaction times in several tests of cognition.

3.4.1 Neuropsychological Test Scores

There were no significant differences in CBS test (accuracy) scores, or composite test scores, between controls and American football players pre-season or post-season. This finding adheres to the existing literature suggesting that neuropsychological test performance is maintained when assessed 1-14 months after a concussion[27] particularly given that some of our participants had no concussion history.

3.4.2 Response Time and Response Variability

Response times typically relate to the processing time required by a given task[28] and/or attentional allocation,[29] and high response variability generally indicates attentional lapses[30] or an impairment of sustained attention.[14] American footballers demonstrated both slower and more variable response times on two of five tasks that measure simple response time. Together, these results suggest that although footballers were capable of performing each task, they were less efficient in solving them. Specifically, the two tasks demonstrating response time and response time variability impairments in American Footballers (Verbal Reasoning – both, Colour Word Remapping – response time) tap aspects of cognitive flexibility, inhibition, and disinhibition thereby implying that some combination of these factors is likely driving the effects.

Previous work in this area has generally focused on the effects of concussion on response time and response time variability, and largely ignored subconcussion as a viable contributor likely due to its m nature. To our knowledge, this is the first study to document response time deficits and response time variability differences between groups

experiencing a high (football) and low (control) number of seasons of contact sport, or proxy measure for head impact exposure.

One possible explanation for the effects observed here is that the football athletes are compensating for their sub-clinical impairments by recruiting additional neurons,[27,31] or exploiting an increased cognitive reserve (bolstered by elite athletic training[32,33]), to enable consistent behavioural performance,[31,34,35] all of which manifests itself as longer times to complete these tasks. Based on our results and others, these response time deficits could be an early marker of early cognitive and functional decline.[36]

3.4.3 Limitations

As noted in the methods section, controls were on average 2 years older than football players. Although cognitive function changes with age, most cognitive abilities peak in young adulthood and are then either maintained or decline in old age.[37] Given the narrow age range of our participants, we expect a similar level of age-related function in both groups. Additionally, since, participants' age was not correlated with any test score or response time measure we conclude that age did not influence our findings.

In this study, subconcussive head impacts were quantified as "number of seasons played of contact sport," however, the age at which footballers, and controls first participated in contact sport was not controlled. Although there is no established dose-response relationship between concussive and subconcussive impacts in football,[38] some evidence suggests that those who begin playing football before the age of 12 experience more cognitive decline post retirement than those who start later.[39] Future studies should control for this "age of first exposure" to better homogenize groups, and assess the influence of chronic head impacts in youths on long-term cognitive outcomes. There is currently much debate about whether the benefits of plasticity in younger brains outweighs the costs associated with brain injury in this population,[40] and studies that take an age-centered longitudinal approach to look at the influence of concussion and subconcussion will be necessary to determine causal long-term outcomes.

Finally, though we were able to identify changes in cognitive function as a result of prolonged exposure to subconcussive impacts, the results presented here in no way suggests that those impaired in this study are destined for further decline. This type of causality would require a long-term study, which remains a key next step in exploring the etiology and progression of head-impact related cognitive decline.

3.4.4 Conclusions & Next Steps

Results from this study provide evidence of increased cognitive demand for footballers to perform at an equivalent level as age- and sex-matched controls. While this is encouraging evidence for identifying cognitive change using a low-cost, low-demand assessment, extending this study to include neuroimaging techniques would offer a better assessment of how cognitive function is potentially altered in this population. Specifically, evidence supporting areas of altered neural recruitment or deficit could identify impaired cortical networks, which when paired with functional outcomes, could help determine options for targeted rehabilitative interventions, and even idealized testing/identification strategies.

3.5 Acknowledgements

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Chapter 4

4. Optimizing the CBS Cognitive Battery & Applications in Aging

4.1 Chapter Rationale

Following chapter 3, our goal was to apply a similar methodology to look for cognitive differences between younger and older adults. From the literature, we know that aging results in a host of generalized cognitive changes[1] that differentially affect individuals[2] and cognitive domains.[3] Methodologically, the CBS battery we have used throughout appears sensitive to these age-related changes (see Figure 4.1).[3] As has been referenced throughout the literature review, finding a way to assess cognitive change in aging, particularly in those who have had early-life exposures to chronic head impacts is important. Doing so, however, presents a unique challenge, with a couple of limitations to be addressed.

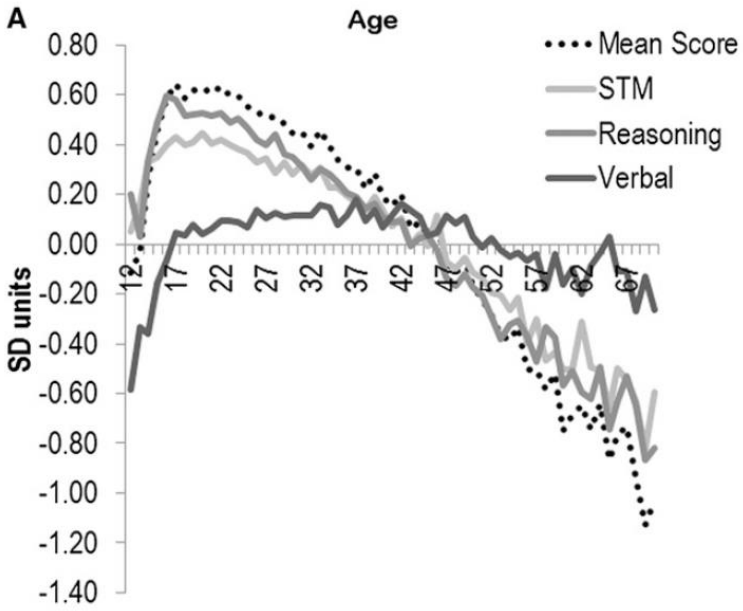

Figure 4.1: The Relationship of Behavioural Components of the CBS Cognitive Battery to Age - from Hampshire et al 2012, used with permission from Elsevier © 2012

First, both studies 1 and 2 were plagued by high drop out and exclusion rates when CBS data was considered. Specifically, in chapter 2, 51% and in chapter 3, 60% of participants were removed from the study due to incomplete data sets (including incomplete post-season data sets in chapter 3), or implausible scores (outliers or scores below chance performance). Additionally, in a brief pilot study recruiting aged former athletes and sedentary individuals from the community, a similar

rate of removal due to poor protocol adherence (66%), coupled with limited recruitment (n=32), particularly for older participants, occurred. Finally, as previously mentioned, aged individuals typically have a reduced capacity for completing cognitive tasks due to straying attention, impaired comprehension, and short retention.[73,81] Overall, this presents a significant limitation in being able to recruit and assess aged participants. As such, we targeted this final study towards rectifying this problem and felt that developing an evidence-based shorter cognitive battery may offer the best strategy.

Herein we explore two methods for optimizing the CBS battery by reducing its contents such that only the most relevant and salient tests are included. First, in study 4A, we explore Principal Component Analysis (PCA), replicating the methodology of a previous large scale study (n = 44 000)[3] in order to retain the original 3-factor structure while reducing the battery's size. If successful, this method would provide a 25% reduction in from 12 to 9 tests. Secondly, in study 4B, we explore discriminant function analysis, and its stepwise applications, to offer an alternative data-driven solution to test inclusion to separate participant groups based on age.

4.2 Introduction

Age-related cognitive decline is both well established, and an important deficit to recognize for intervention with a globally aging population.[7] Typically aging brings generalized deficits across all areas of cognition[1] which tend to vary in degree of severity both across individuals and cognitive domains. Interestingly, some domains and some individuals show remarkable preservation over time,[2] while others succumb to unfavourable deficits without a diagnosed pathology. Importantly, both understanding and preventing age-related cognitive decline begins with identifying it, which is where neuropsychological tests come in. The main barrier here is that older individuals typically have a reduced capacity for completing cognitive tasks[4–6] which makes designing a shorter yet salient battery paramount.

Cognitive function is generally interrogated through the completion of a cognitive battery; a combination of several neuropsychological tests designed to assess varied components of cognition. Their ease of administration, clinical applicability and ability to

measure change both within and across individuals make them an appealing tool for clinicians and researchers alike. One such cognitive battery, the Cambridge Brain Sciences (CBS) cognitive battery, broadly assesses cognition using a series of 12 online tests (previously explained by Hampshire et al 2012, and outlined in the supplementary materials[3]). Importantly, CBS tests iterate towards a participant's peak performance by increasing or decreasing question difficulty based on the correctness of the previous answer. In addition, individual questions change between administrations to limit cheating, and the battery has been validated in over 60 000 participants aged 13–70.[3] CBS scores correlate with the Minimal Assessment of Cognitive Function in MS (MACFIMS)[8], and both Cattell's Culture Fair and Raven's Progressive Matrices tests of fluid intelligence.[3] In total, testing requires 30-40 minutes, which while fairly short, compounds quickly with the addition of imaging or survey components, which may cause difficulties with participant recruitment, protocol adherence and increased scanning costs should MRI measures be included concomitantly.

Overall, data reduction strategies offer a productive avenue to limit the amount of data collected to that which can best discriminate between groups of interest. Specifically in cases where multivariate methods are useful in capturing the overall gestalt of a factor, the objective should move towards including "as many variables as possible so that reliable results may be obtained, and yet as few as possible so as to keep the costs of acquiring data at a minimum."[9] Beyond improving data acquisition economy, data reduction also offers improved participant recruitment/retention and more targeted and stable scoring[10,11] as both time to completion and extraneous error are reduced.

Applying data reduction in neuropsychological testing, especially in aging populations is not new. In fact, Folstein et al developed the Mini-Mental State exam in 1975 as an effort to simplify previous tests (eg. Wechsler Adult Intelligence Scale - WAIS). With the 1981 publishing of the WAIS-R (revised version), Silverstein et al (1982) created the two- and four- subtest short forms.[12] In both cases, the result was a more streamlined clinically useful test that reduced the overall cost (time, resources) for researchers. Following this historical trend, we employed two exploratory statistical methods to reduce the CBS battery. Study 4A focusses on Principal Component Analysis (PCA) methods to retain a

previously found factor structure, while Study 4B employs Discriminant Function Analysis (DFA) to determine which CBS tests best discriminate between groups of varying ages.

Study 4A: Principal Component Analysis for Data Reduction

4.3 Materials and Methods:

4.3.1 Statistics

The general purpose of PCA is to identify a relatively small number of themes, components or factors underlying a relatively large set of variables by distinguishing sets of variables that have more in common with each other than with other variables in the analysis.[10] "What the subsets of variables have in common are the underlying components."[10] Importantly, PCA is entirely data driven, meaning that each component is not determined as an a priori decision but rather through a data-driven approach. In psychological research, principal components analysis is most commonly used in test development and scoring, as well as in organizing or conceptualizing a set of measures by determining which ones might be measuring the same thing.[10] Importantly, further analyses can be conducted based on factors rather than individual dependent variables[10] which reduces the dimensionality of the data, but doesn't reduce the overall amount of data required.

Previous work by Hampshire et al used PCA to uncover 3 components (short term memory, reasoning and verbal) in normative CBS data (n = 44 000) referenced throughout this dissertation. Specifically, this was in a population of healthy controls aged 13 to 70 of both sexes. With the assumption that the components derived here are valid and reproducible, as has been shown with other large data sets in our lab (Wild, unpublished data) the first goal was to employ methods that would preserve them while still reducing the overall number of tests included.

For this analysis, the goal was to run the same PCA analysis as Hampshire et al[3] (varimax rotation), and then use an alpha if item deleted approach to reduce each component

individually. As shown in Table 4.1, component 1-STM is primarily derived from 4 tests, component 2-Reasoning from 5 tests, and component 3-Verbal from 3. At a minimum, components should be derived from 2 variables, otherwise they offer no dimension reduction, although reducing them beyond 3 can compromise the breadth of what is captured by each component.

Table 4.1: Hampshire et al PCA analysis of CBS Data (n = 44 600, ages 13-70, male + female) Adapted from Hampshire et al 2012, used with permission from Elsevier © 2012

Hampshire et al (44 600)										
	initial eigenvalues			after rotation			1	2	3	
Comp	total	% variance	cumulative variance	% variance	tot var		STM	Reas	Verb	
1	3.277	27.31	27.31	17.072	17.072	SS	**0.69**	0.22		
2	1.119	9.326	36.636	15.819	32.891	ML	**0.69**	0.21		
3	1.008	8.397	45.033	12.142	45.033	SOS	**0.62**	0.16	0.16	
4	0.876	7.303	52.336			PA	**0.58**		0.25	
5	0.828	6.9	59.236			HTT	0.41	**0.45**		
6	0.769	6.41	65.654			SR	0.14	**0.66**		
7	0.759	6.323	71.968			FM	0.15	**0.57**	0.22	
8	0.732	6.101	78.07			IP		**0.54**	0.3	
9	0.706	5.881	83.951			OOO	0.19	**0.52**	-0.14	
10	0.685	5.704	89.656			DS	0.26	-0.2	**0.71**	
11	0.658	5.485	95.14			VR		0.33	**0.66**	
12	0.583	4.86	100			CWR	0.22	0.35	**0.51**	

4.3.2 Participants:

A total of 236 complete data sets (all 12 CBS tasks completed with valid scores) were extracted from the larger CBS data base. All participants were male and were evenly divided between younger and older groups and roughly matched such that they were 50 years apart in age. Specifically, younger participants were aged 21.67 ± 1.91 while older participants were 71.67 ± 0.99.

4.4 Analysis:

The factor structure for the CBS battery was tested using a PCA, and interpretation was facilitated by a varimax rotation. The number of extracted factors was determined through the use of a parallel analysis.[13] Parallel analysis uses Monte Carlo simulation to identify the eigenvalues that would be expected due to chance, for a particular number of factor analytic items, and given a particular sample size. Our simulation was based on 1000 simulated analyses. Factors with eigenvalues that are greater than the average of the

eigenvalues across the 1000 simulated datasets are considered to be likely candidates for extraction.[14]

Two different samples were analyzed: young participants, and a combination of young and old participants. Identification of factors was conducted separately in each sample, and the factor loading matrices were compared amongst the three samples.

Given the previously established factor loadings as published by Hampshire et al[3] and replicated by Wild (unpublished data), we hypothesized that a similar structure would be extracted in both the younger and younger + older groups in this study.

4.5 Results:

Factorability of the data was estimated using the Kaiser-Meyer-Olkin (KMO) index, a metric that assesses the sampling adequacy for each variable in the model, and for the complete model. It assesses the proportion of variance among variables that might be common variance with lower proportions being more suited to Factor analysis. Scored on a scale of 0-1, values above 0.5 are deemed acceptable for factor analysis (see Table 4.2 for Kaiser's evaluation levels of Index Factorial Simplicity).[15] Bartlett's test of sphericity was found to be statistically significant, suggesting that the variables are sufficiently intercorrelated as to be acceptable for factor analysis. The KMO was found to be acceptable, at 0.67, suggesting that the data is marginally acceptable for the performance of a factor analysis. The parallel analysis conducted on the data suggested a two-factor principal components solution (see Figure 4.2). Factor loadings for this solution are presented in Table 4.3.

Table 4.2: Kaiser's evaluation levels for Index of Factorial Simplicity[15]

Index of Factorial Simplicity	Rating
0.90-1.00	Marvelous
0.80-0.89	Meritorious
0.70-0.79	Middling
0.60-0.69	Mediocre
0.50-0.59	Miserable
Below 0.50	Unacceptable

Examination of the eigenvalues suggests that the overall factor solution explains 33.45% of the variability in the original data. Factor 1 accounts for 18.78% of the variability and Factor 2 accounts for 14.68% of the variability.

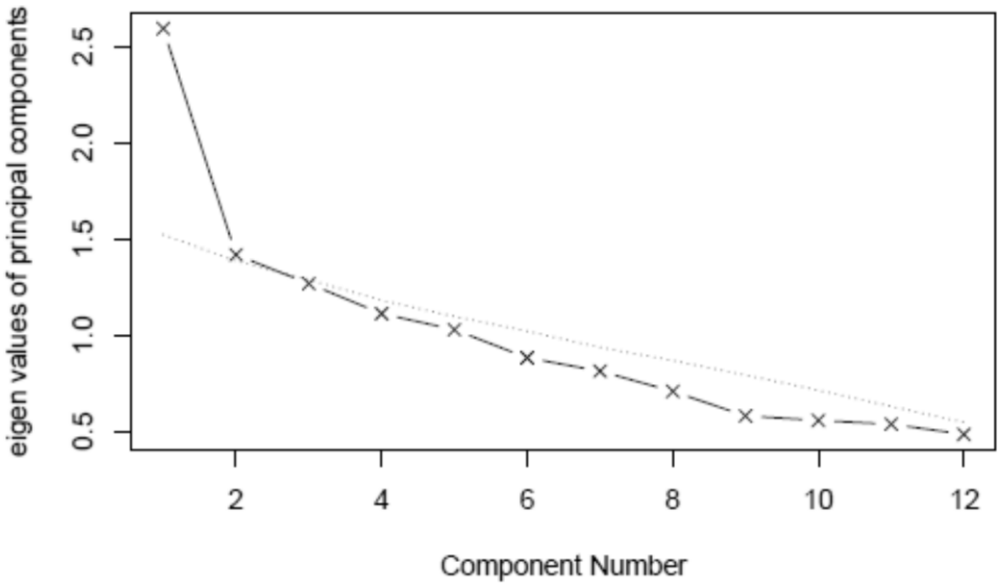

Figure 4.2: Parallel analysis for Principal Component Analysis within the Young Sample (n = 118, aged 18-24)

Table 4.3:Factor loadings for the Principal Components Analysis within the Young Sample

Test	Factor I	Factor II
Verbal Reasoning	-0.02	0.67
Self Ordered Search	0.48	0.27
Hampshire Tree Task	0.32	0.50
Paired Associates	0.68	-0.01
Interlocking Polygons	-0.20	0.42
Spatial Rotations	0.25	0.48
Spatial Span	0.33	0.57
Monkey Ladder	0.57	-0.39
Digit Span	0.46	0.10
Color Word Remapping	0.46	0.27
Feature Match	0.57	0.14
Odd One Out	0.43	0.01
Eigenvalue	**2.2**	**1.8**

Suspecting that the variability accounting for differences between our sample and the Hampshire sample could be age-related, 118 older male participants were added to the population. The analysis was replicated.

Factorability of the data was estimated using the Kaiser-Meyer-Olkin (KMO) index. The KMO was found to be acceptable, at 0.77. The parallel analysis conducted on the data suggested a two-factor principal components solution (see Figure 4.3), so we extracted and rotated two factors in our initial factor analysis. This factor solution is presented in Table 4.4. It is, however, conceivable that the scree plot could be interpreted to suggest a three-factor solution, and so we extracted that factor solution as well. This factor solution is presented in Table 4.5.

Examination of the eigenvalues for the two-factor solution suggests that the overall factor solution explains 40.51% of the variability in the original data. Factor 1 accounts for 24.09% of the variability and Factor 2 accounts for 16.43% of the variability.

Examination of the eigenvalues for the three-factor solution suggests that the overall factor solution explains 51.36% of the variability in the original data. Factor 1 accounts for 18.05% of the variability, Factor 2 accounts for 16.66% of the variability, and Factor 3 accounts for 16.66% of the variability.

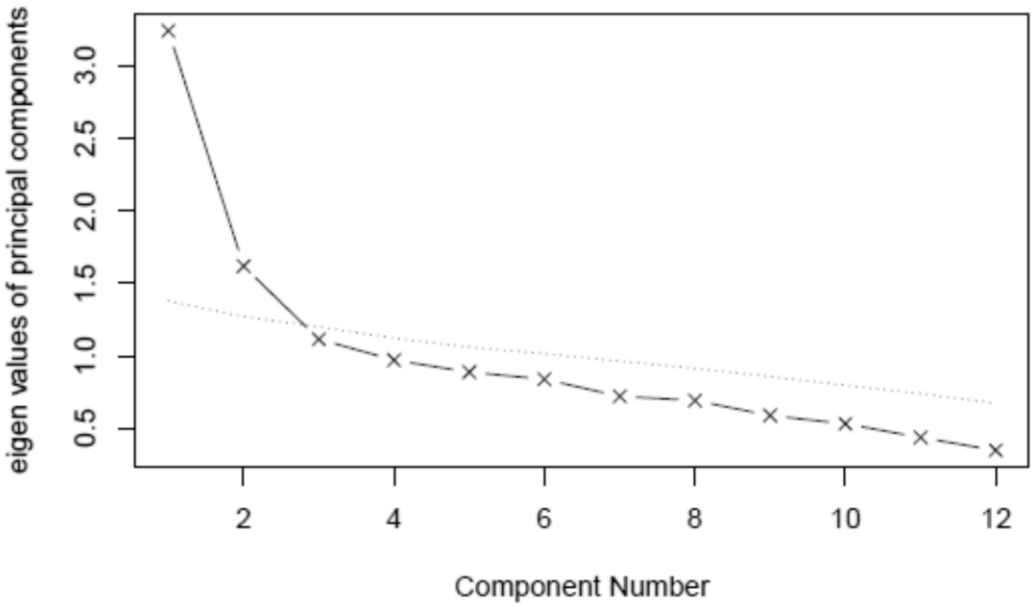

Figure 4.3: Parallel analysis for Principal Component Analysis within the Whole Sample (n = 236, ages 18-24, 68-74)

Table 4.4: Factor loadings for the principal component analysis with all data (n = 236, ages 18-24, 68-74), Two-Factor Solution

Test	Factor I	Factor II
Verbal Reasoning	0.50	-0.09
Self Ordered Search	0.50	-0.62
Hampshire Tree Task	0.58	0.01
Paired Associates	0.56	-0.22
Interlocking Polygons	0.04	0.54
Spatial Rotations	0.58	-0.03
Spatial Span	0.43	0.41
Monkey Ladder	0.51	-0.65
Digit Span	0.40	0.22
Color Word Remapping	0.63	-0.12
Feature Match	0.64	-0.04
Odd One Out	-0.04	0.76
Eigenvalue	**2.9**	**2.0**

Table 4.5: Factor loadings for the principal component analysis with all data (n = 236, ages 18-24, 68-74), Three-Factor Solution

Test	Factor I	Factor II	Factor III
Verbal Reasoning	0.34	-0.10	0.36
Self Ordered Search	0.35	-0.63	0.35
Hampshire Tree Task	0.77	0.00	-0.02
Paired Associates	0.21	-0.23	0.62
Interlocking Polygons	0.06	0.54	0.01
Spatial Rotations	0.69	-0.04	0.06
Spatial Span	0.32	0.40	0.29
Monkey Ladder	0.32	-0.66	0.39
Digit Span	-0.14	0.21	0.81
Color Word Remapping	0.41	-0.13	0.48
Feature Match	0.63	-0.05	0.23
Odd One Out	-0.05	0.76	0.03
Eigenvalue	**2.2**	**2.0**	**1.8**

Through examining the number of factors extracted, factor loadings and eigenvalues of each of these models, we determined that they differed from those originally found by Hampshire et al (Figure 4.4). Given that there was only one Three-Factor solution extracted from our sample (see Table 4.5), the subsequent discussion pertains only to this comparison.

4.6 Discussion:

As illustrated in Figure 4.4, the three-factor solution identified in the whole sample (young and old participants combined) did not map directly onto those previously found by Hampshire et al. There is considerable overlap in terms of factor loadings between samples, but there are still some significant differences in terms of component weightings and tests assigned to each component.[3] While a formal statistical comparison to determine the quantitative similarities between these models was not possible (due to the unavailability of the original Hampshire data set), based on our cursory examination, we are confident that these analyses represent different models. We suspect that the variability accounting for the observed differences may reflect sample size differences, the aging process, and the fact that we excluded female participants in this analysis. Still, noting differences between our sample and the components previously found by Hampshire et al represents an important conclusion. Specifically, it suggests that cognitive function is different between young and old individuals, and that the CBS battery is sensitive to age-related change. Based on just this cursory glimpse, however, it is difficult to quantify what that difference means, specifically in terms of cognitive aging, which is the focus of study 4B.

Finally, although the PCA methods explored in this section did not result in a meaningful reduction of the CBS battery, their application in a larger data set may prove a useful next step. Unfortunately, technical limitations in managing the CBS database have prohibited the extraction of such a sample which would be more representative of the general population, and better align with the previously published data by Hampshire et al (Male/Female, ages 13-70).[3] Once this larger-scale data extraction is possible, replicating this study may offer a better approach to uncovering redundancy amongst the CBS tasks and optimizing the CBS battery.

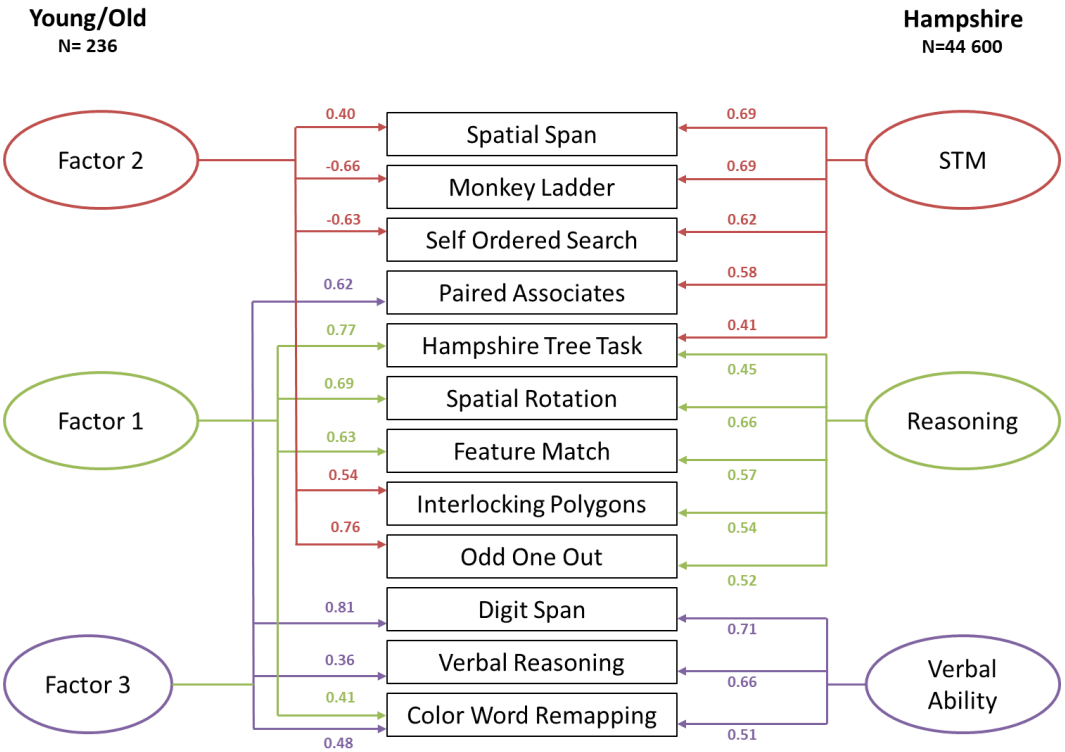

Figure 4.4: Comparison of the Three-Factor Young +Old PCA loadings vs Hampshire PCA Loadings Component weightings are listed next to each factor line

Study 4B Reducing the Cambridge Brain Science Battery to Explore Age-Based Differences in Cognitive Function

Based on the results of study 4A, and to better understand age-related changes in performance on the CBS cognitive battery, an alternative statistical approach was employed. The goal of this study was use discriminant function analysis (DFA) to leveraged well-known age-related cognitive change to investigate which aspects of the CBS battery are most salient in discriminating between younger and older groups. We hypothesized that a sub-set of the 12 CBS tests would be able to adequately discriminate between younger and older groups while maintaining the majority of the variability accounted for by all 12 tests together.

4.7 Materials and Methods

4.7.1 Statistics

Discriminant function analysis (DFA) is an alternative way to view MANOVA, and is generally focused on a slightly different outcome. In MANOVA, the focus is on differences between groups based on the means of dependent variables in the study, while discriminant function analysis is focused on how the different weighted linear combinations of the dependent variables predict group membership or explain differences between groups.[10] The main strength of discriminant analysis, however, lies beyond prediction and classification and is in choosing subsets of the original variables for future use.[16]

In practice, each measured predictor variable is entered into the DFA statistical model which creates a weighted linear discriminant score (DS) that maximally differentiates between groups.[10] In this equation (Equation 1), *a* represents the constant (y-intercept), *w* represents the discriminant coefficients and X represents individual quantitative measures. The group mean discriminant score is known as the group centroid, and the difference between group centroids represents the extent to which groups differ,[10] akin to the result achieved using an omnibus MANOVA.

Equation 1: General Discriminant Function

$$DS = a + w_1X_1 + w_2X_2 + \cdots + w_vX_v$$

In a standard (full) DFA, all predictor variables are entered into the model simultaneously, with each receiving a weighting in the created linear function. Assuming a statistically significant model, those variables which are significant in a univariate sense[9] can be carried forward for variable selection using step-wise (empirical, data driven) or step-down (a priori, conceptual ordering) methods. Respecting the complex factors which might influence age-related cognitive change, we chose to keep the analysis as data-driven as possible and thus selected step-wise methods. In a step-wise DFA, variables are entered into the model one at a time. Inclusion/exclusion criteria are set such that only those variables which significantly contribute to the equation are

included and those that don't are removed.[10] Importantly, in a comparison of six selection methods,[17] stepwise discriminant analysis yielded the best subsets and most accurate classification.[9] Additionally, in the special case of just two criterion groups that can be ordered in a quantitative sense, discriminant analysis reduces to ordinary regression analysis.[18] This means, that reduced models represent both the variables which contribute most to maximal group discrimination, and are most strongly associated with the dependent or criterion variable (in this case, age).

4.7.2 Participants

Data from 118 young (age = 21.67 ± 1.91), and 118 old (age = 71.67 ± 0.99) male participants completing the CBS battery were mined from our lab database for this study. Only complete data sets with valid scores for each test within the battery were included in the analysis. Informed consent was obtained in accordance with the Declaration of Helsinki and the University of Western Ontario Health Sciences Research Ethics Board when participants completed their initial study enrollment. All 12 cognitive tests are scored on independent scales, thus all scores were standardized to Z-scores based upon normative means and standard deviations generated from a population of > 18 000 previously assessed participants aged 18-23 before analysis.

4.8 Analysis

Data were screened for multivariate outliers using mahalanobis distance scores, which resulted in the removal of two younger participants. Additionally, there was no multicollinearity found between predictor variables.

Two separate analyses were completed on the same sample. Data were subjected first to a standard DFA such that all quantitative predictors were entered into the discriminant function equation at once. Following this, variables demonstrating univariate significance were carried forward to a step-wise DFA (Wilks' λ method) in which the discriminant function equation was built one predictor at a time. Step-wise DFA was chosen because there was no a priori rational for variable order, and we wanted to develop a more parsimonious model. Overall, this approach offered an opportunity to discern, beyond statistical significance, which cognitive tests were more salient for discriminating

between younger and older participants as well as the ability to compare the amount of variance accounted for between groups with both the full and reduced discriminant functions.

4.9 Results

A two-group discriminant function analysis was performed on young and old participants using the 12 CBS tests as discriminating (predictor) variables. The discriminant function accounted for a significant percentage of between-group differences, Wilks' $\lambda = 0.198$, X^2 (12, N = 236) = 366.538, $p < 0.01$, $R^2 = 0.802$. Group Centroids are presented in Figure 4.5. Separate one-way between-subjects ANOVAs using a Bonferroni-corrected alpha of 0.004 indicated that 10 out of 12 predictor variables were statistically different between groups.

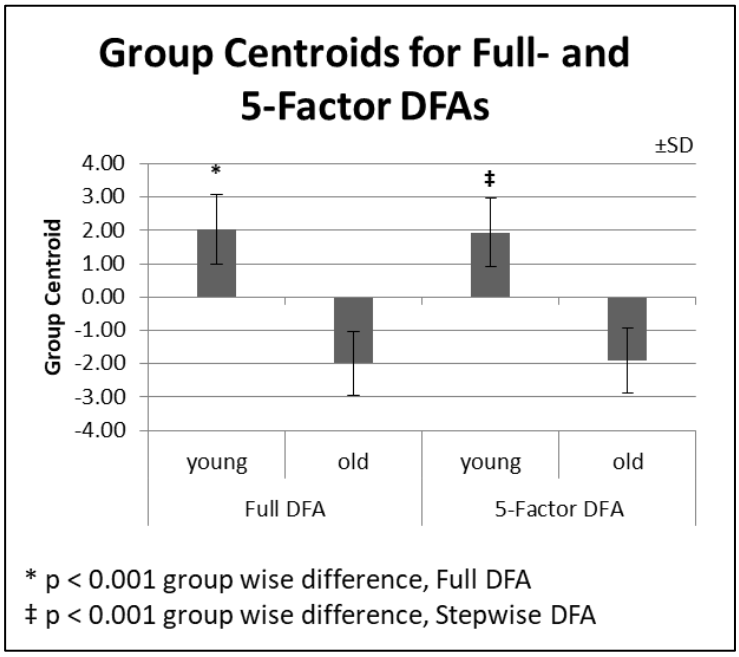

Figure 4.5: Group Centroids for Full and 5-Factor DFA Analyses

Following this significant result, a step-wise discriminant function analysis was completed using the 10 variables demonstrating univariate significance. The step-wise discriminant function (Wilks' λ method, criteria for variable entry/removal set at $p = 0.05$ and $p = 0.10$ respectively) resulted in five variables being included in the model. This discriminant function accounted for a significant percentage of between-group differences Wilks' $\lambda = 0.211$, X^2 (5, N = 234) = 357.047, $p < 0.01$, $R^2 = 0.789$. Group Centroids are presented in Figure 4.5. Separate one-way between-subjects ANOVAs using a Bonferroni-corrected alpha of 0.001 indicated that all five predictor variables were statistically different between groups.

Table 4.6 presents the discriminant function coefficients for the variables for both the full- and 5-factor discriminant functions. Standardized function coefficients describe the amount of relative credit an observed dependent variable received when creating the composite.[10,19] By contrast, structure coefficients represent the correlation between each predictor variable and the discriminant score[10,20] and denotes how strongly (higher correlation = more relevant variable) a variable indicates what the discriminant function represents.[10]

In both functions, Monkey Ladder, Self Ordered Search, and Odd One Out were most strongly weighted in the linear composite while Spatial Rotations and Interlocking Polygons were assigned moderate weights. Higher levels of the latent variable are indicated by Monkey Ladder and Self Ordered Search, and lower levels of Odd One Out in both the full and step-wise factor analyses. Overall the discriminant function appears to represent performance on executive-function/active working memory based tasks. All group means on the discriminant variables (CBS tests) are shown in Figure 4.6 with significant differences (using one-way between-subjects ANOVA) for each model noted.

Table 4.6: Standardized and Structure Coefficients for the Full- and Five-Factor Discriminant Functions

		Full DFA		Step-Wise DFA	
		Standardized Coefficients	Structure Coefficients	Standardized Coefficients	Structure Coefficients
NS	Digit Span	-0.161	-0.003		
	Spatial Span	-0.174	-0.040		
Sig. Full DFA	Hampshire Tree Task	-0.117	0.101		0.194
	Paired Associates	0.115	0.215		0.150
	Feature Match	-0.002	0.142		0.171
	Verbal Reasoning	0.111	0.146		0.078
	Color Word Remapping	0.121	0.189		0.118
Sig. Full and Step-Wise DFA	Monkey Ladder	0.608	0.603	0.596	0.628
	Self Ordered Search	0.553	0.558	0.575	0.582
	Spatial Rotations	0.229	0.156	0.239	0.163
	Interlocking Polygons	-0.171	-0.154	-0.180	-0.161
	Odd One Out	-0.520	-0.391	-0.548	-0.407

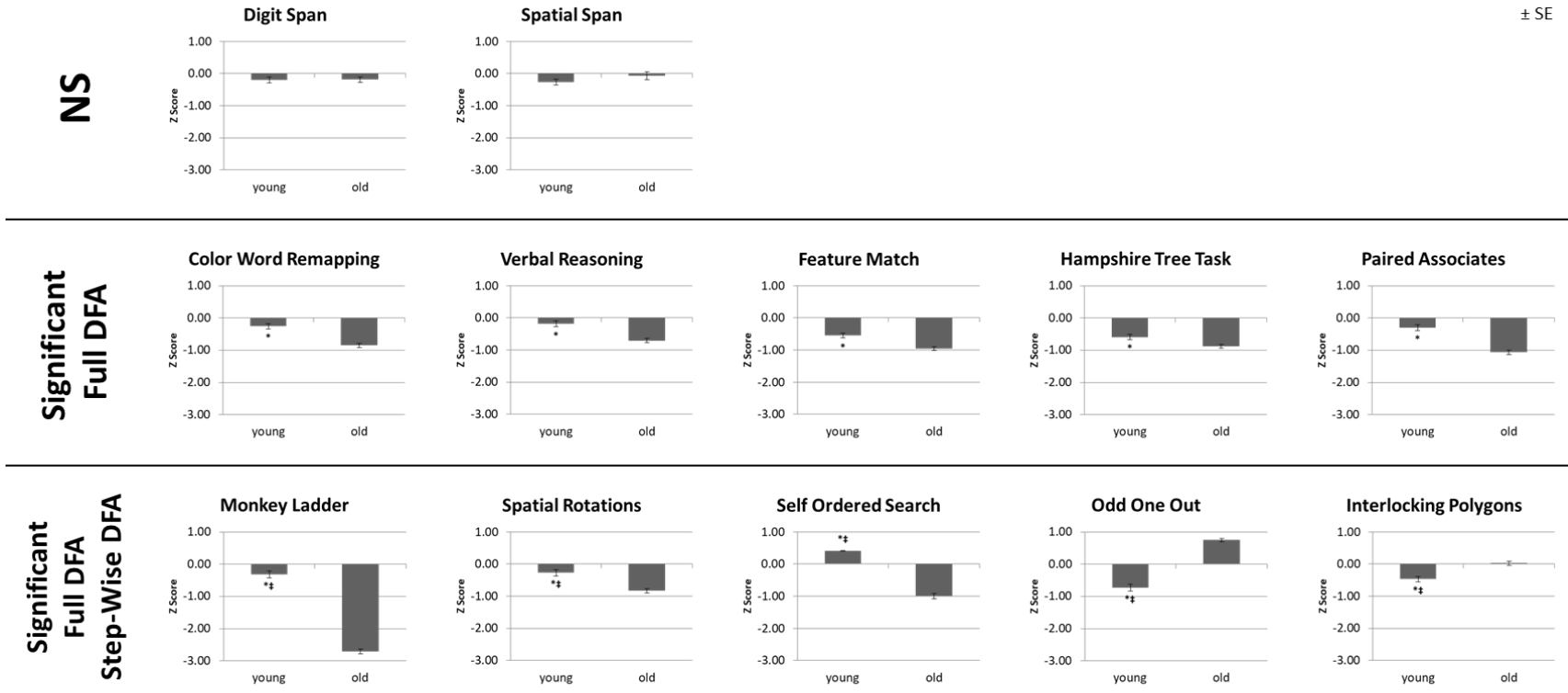

Figure 4.6: Standardized and Structure Coefficients for the Full- and Five-Factor Discriminant Functions
Tests are divided into 3 categories: no significant differences (NS), significant tests included in the full factor DFA, and significant tests included in both the full and step-wise DFAs.

4.10 Discussion

Based on their univariate significance and inclusion in the step-wise DFA, each CBS test was classified into one of three categories: 1) non-significant group differences (NS), 2) significant group differences on full factor DFA and 3) significant group differences on both full and step-wise DFAs (see Figure 4.6 and Table 4.6). These divisions will be further explored below and underscore where major age-based difference lie, which is an important consideration for clinicians and scientists looking to assess age-related cognitive changes.

4.10.1 Non-Significant Findings

There were no significant differences between groups for either the Digit Span or Spatial Span tasks. Preservation of select cognitive abilities in aging is well established and these results align well with the current understanding of age-related cognitive change. Specifically, digit span relies primarily upon short term memory which involves the simple maintenance of information over a short period of time.[21] Spatial span represents the spatial equivalent to the digit span task. Overall, this is an important finding as it specifies two tests on which scores are not expected to change with healthy normal aging, and could thereby represent an option for discriminating between individuals experiencing normal and pathological age-related cognitive decline.

4.10.2 Full vs Step-Wise DFA Significant Findings

Significant univariate differences between groups were noted on the remaining ten cognitive tasks, two of which (Interlocking Polygons and Odd One Out) demonstrated significantly better performance in the older group. The most interesting finding, however, was that five (Monkey Ladder, Self Ordered Search, Spatial Rotations, Interlocking Polygons, Odd One Out) out of these 10 significant tests were more salient in discriminating between groups as demonstrated by the preserved membership in the stepwise DFA . The results of the step-wise DFA further suggest that these 5 tests can discriminate between younger and older individuals nearly as well as all 12 together,

maintaining over 98% of the original variability accounted for in the full model, and that these 5 tests are also most strongly associated with aging.

As expected, the five tests that had the highest standardized coefficients in the full DFA model and demonstrated univariate statistical significance also demonstrated preserved membership in the step-wise DFA. While this is logical, why the distinction between the five significant and the five significant and salient tests occurred is not immediately apparent. In an effort to further explore this distinction, we examined two primary options; namely, the magnitude of the group-based univariate differences and the variability associated with each test (see Figure 4.7). More specifically, larger group-based differences may have better supported a test's inclusion in the step-wise DFA; however, of the five significant and salient tests, only three ranked in the five largest differences (Self Ordered Search, Odd One Out, Monkey Ladder). Similarly, more stable measures of cognition with reduced variability may offer greater discriminatory power, though of the five significant and salient tests, only one ranked in the five smallest variances, as measured by standard error (Self Ordered Search). These forays are inconclusive, and thus suggest that there could be an underlying age-related construct that is not overtly apparent driving this dissociation. Determining what this construct may represent, however, is a challenging task as cognitive aging is driven by complex interactions of several factors (health status, sex, disease, etc.) which cannot be causally linked to cognitive test performance alone. In fact, it is for this reason that we chose data-driven empirical methods for the data reduction. The best the literature can offer is a prediction of how we might expect younger and older people to perform on this battery of tests.

Our structure coefficient results suggest that this step-wise model represents performance on executive function and active working memory tasks. This is significant as it aligns with the well-established understanding that older individuals demonstrate preserved function in crystalized intelligence, yet are generally worse at tests of fluid intelligence,[22] typically demonstrate compromised executive function[21] and poorer performance in divided attention tasks.[23] Further, previous work by Hampshire et al noted that the CBS battery loads on three distinct cortical networks supporting short term memory, reasoning

and verbal abilities.[3] In applying our data to their model, we noted that two tests (Self Ordered Search, Monkey Ladder) load most heavily upon the short term memory component while three tests (Interlocking Polygons, Spatial Rotations and Odd One Out) load most heavily upon the reasoning component. Together these conclusions suggest that the five significant and salient CBS tests are broad enough to capture the age-based differences we would expect, and thus represent a group of tests that may be informative in age-related studies. The conclusions though do not explain why some tests were more salient in discriminating between these groups than others. In reframing our focus, however, determining why some tests were more salient than others was not the goal of this study. This idea, while interesting, is thus secondary to recognizing that this division between the CBS tests was empirically derived, which has the greatest value in informing test selection in future studies.

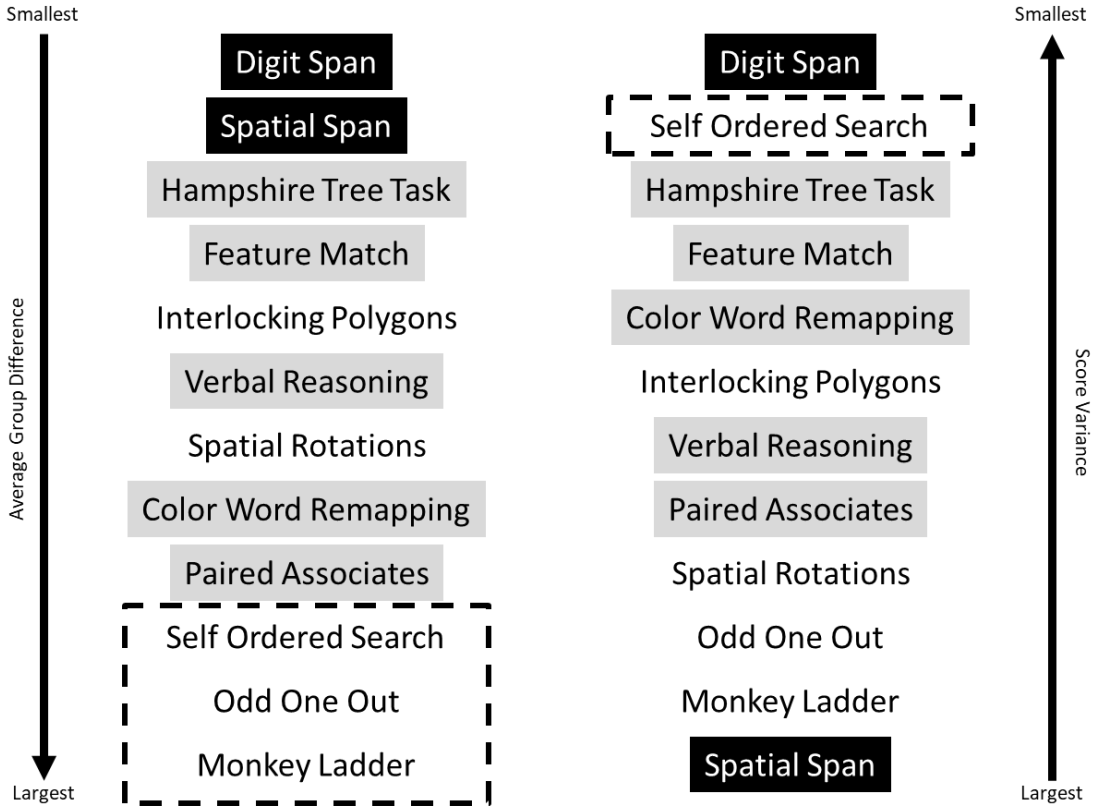

Figure 4.7: Test Rankings in Terms of Average Group-Based Differences and Score Variance. Black filled boxes denote NS tests, Grey filled boxes denote significant tests (full DFA only) and While filled boxes outlined with broken lines denote significant and salient tests. Dashed boxes highlight top ranking significant and salient tests.

4.10.3 Limitations

Since the DFA model is built to discriminate between two or more groups included in the analysis, the results are specific to that comparison. In other words, while we were able to identify the five most salient tests for age-based discrimination, our findings are specific to healthy normal aging, and it may not be the case that the same five tests are important for detecting other changes associated with other aspects of health and disease. Further, since our data only included healthy male participants, extending or replicating this study to include females, as well as clinical populations could offer insight into how overt cognitive behaviours may change based on sex and disease status.

Finally, there is some concern over the use of the step-wise procedure in DFA for two primary reasons. First, it is biased towards the order of variable entry as it considers variables added to the model one-at-a-time (based on correlation sizes) and thus does not analyze the variance jointly accounted for by each possible combination of tests.[24] Secondly, and as a consequence of the first limitation, the selected subset of variables may not be the "best" subset.[17] Overall, this overfitting, or sample specificity means that the resultant subset included in the step-wise DFA is highly sample dependent. Specifically, if participants are added or removed, such that variable correlations with the discriminant scores change, variable entry order will as well, which may change which variables are ultimately included in the final DFA. While definitely worth consideration, the goal of this study was to generate a subset of cognitive tests which preserved the variability accounted for in the full model. This goal was certainly accomplished and while it is possible that a "better" solution remains, the value added in its discovery is minimal. Further, we felt that this step-wise approach offered the best solution given that we had no a priori rationale for variable ordering yet wanted a more parsimonious model. Overall, our study offers researchers additional information on CBS tests which may be used in selecting tests for a given comparison. The "best" subset is somewhat subjective as it can refer to accounting for the most variance, providing the most stable results, or including tests which are short and easy to administer. These considerations must be taken into account by researchers selecting a given metric, thus, this limitation need not be addressed at this stage.

4.11 Conclusions

In summary, our results identify the five significant and salient CBS tests that are most strongly associated with aging and contribute most to discriminating between younger and older people. Further, they underscore areas in which age-based differences should and should not be expected which may offer valuable opportunities for detecting cognitive change in aging, and potentially disease. Overall, this additional information may support researchers in selecting a reduced test battery in age-related studies.

4.12 Acknowledgements

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Chapter 5

5. Concluding Summary

Throughout this dissertation, I have been mainly concerned with describing cognitive function in terms of cumulative head injury and aging. While these appear to be two separate conditions for study, as I alluded to earlier, they are inextricably linked. Cognitive changes in head injury and aging strongly parallel each other. Specifically, in the ways that they begin; slow and subtle, how they influence cognitive systems; selectively, and variably across domains and individuals, how they might be mitigated; through exercise and cognitive reserve, and in their end result; compromised function and quality of life. Determining how head injury and aging influence each other is paramount, and was the major motivation behind this dissertation. From the literature, we know that with head trauma exposure, expected age-related decline can present earlier, and that age-related pathologies tend to be more common. We also know that age of injury seems to matter, with a more plastic adolescent brain being either more protective or vulnerable depending on injury timing, location, and severity.

Although our studies did not reach the point of assessing head injury concurrently with aging, they provide foundations for future studies to better understand how aging and head injury might coexist. More specifically, our studies brought forth the following findings, which support future studies in specific ways.

Chapter 2: A Comparison of SCAT3 and CBS Tests to Assess Cognitive Dysfunction in Non-Concussed American Footballers

Chapter 2 described limitations in how current concussion tests assess cognition, underscoring issues of its limited scope. We compared CBS and SCAT3 - SAC test results using Pearson's Bi-variate correlations to determine which aspects of cognitive function are assessed by the SAC. The results demonstrated that the SCAT3 concussion test assesses parts of cognition but it is focused narrowly on verbal abilities and may miss important components of cognition that may be equally vulnerable to brain injury. These results suggest shortcomings with its use in detecting cognitive change in concussion. Findings thus clarify current international consensus statements which suggest that

SCAT3 assesses attention and memory, as well as demonstrate that executive function and speed of information processing, which are known to be impaired in concussion, are not assessed by the SCAT3.

Ideally, this study would have included a direct comparison including both baseline and concussive injury time points. This was not, however, possible. The frequency of concussion within the last year in our sample was less than 5% (n = 4) and, injury-specific SCAT3 data was unavailable for these participants. Considering the use of SCAT3 testing as a baseline and rehabilitative measure, that neuropsychological test scores may show no differences after recent concussion, and our goal of using CBS in assessing subconcussion, making a baseline comparison was adequate. Essentially, the premise is that if either test was incapable of comprehensively assessing cognition at baseline, their use in an injured or rehabilitative state would be fundamentally flawed.

Future work should 1) determine which aspects of the SAC are most important clinically to streamline the test, and 2) determine which comprehensive neuropsychological test batteries pair best with the SCAT3 for subsequent follow up.

Chapter 3: Slowed and Variable RT in Collegiate Footballers

Chapter 3 compared cognitive function, as assessed by neuropsychological test scores and response times, between football athletes (high cumulative head impact burden) and matched healthy controls (low cumulative head impact burden). The results exposed a response time impairment (slowed and more variable) linked to chronic head impact exposure. This finding supports reaction time measures as an index offering pre-clinical detection for when cognitive impairment may exist, but is not yet clinically relevant. Through earlier detection, this work may have identified a window for which intervention is most ideally timed. Additionally, increased response times in the absence of deficits in accuracy may represent compensatory mechanisms mitigating an increased cognitive demand in comparison to matched controls. Together, cognitive compensation and cognitive reserve are two themes explored through both aging and head injury literature which may mitigate age- and/or injury-related decline. Both are based on the idea that when an individual's cognitive capacity exceeds that which is required for task

performance, it is performed adequately (bar A in Figure 5.1), and when it is not, as in the case of head impacts and/or aging, compromised cognitive function ensues (bar B in Figure 5.1).

Cognitive Compensation

More specifically, cognitive compensation refers to the ability to recruit additional brain regions to perform a given task (see bar C of Figure 5.1). Although unavailable for study through behavioural data, several neuroimaging studies have demonstrated weaker, bilateral or atypical activation patterns in aging[1,2] and head injury.[3,4] Some evidence suggests that generalized cognitive deficits as a result of head injury is due to diffuse white matter damage (eg. axonal shearing)[5] which would produce a loss in processing efficiency requiring recruitment across domains or of similar processes to attain a behavioural goal.[6] This recruitment of additional neurons enables access to increased cortical resources and thus improved performance. Using neuroimaging techniques, and specifically pairing head injury/aging studies with controls studies will better support understanding the synergistic effects of aging and head injury in compensatory neural recruitment.

Cognitive Reserve

Cognitive reserve can be thought of as excess cortical capabilities beyond what is required to perform a given task, and may provide a buffer against small age- or injury-related declines.[7] Specifically, high cognitive reserve may allow for more flexible strategy usage, greater neural efficiency and capacity.[8] Together both genetic pre-disposition as well as an active (cognitive and physical) lifestyle promote an increased cognitive reserve (Bar D in Figure 5.1) which can better buffer any declines in cognitive function (Bar E in Figure 5.1).[7]

More specifically, exercise is a positive modifier of cognition, especially in age-related cognitive decline. In general, increased cardiovascular fitness is shown to be structurally and functionally neuroprotective in healthy older adults,[9,10] and "published longitudinal and cross-sectional studies have consistently shown a small but positive relationship between greater physical activity and lower risk of cognitive decline in older adults."[11] In

young healthy adults, however, the potential for exercise to improve cognitive function is less understood as in many cases where older adults gain benefits, young adults do not.[11,12] This lack of improvement may be due to several factors including: "an absence of a loss of function, leaving no room for improvement, or similarly the use of tasks that were too easy, yielding no cognitive deficit upon which to improve."[13,14] Most studies on exercise and cognition have focused on adults over the age of 55 with only a few investigating younger people; however, together many studies suggest that being physically active earlier in life is associated with preserved cognitive abilities later in life.[15] Additionally, one study found that exercised mice undergoing cortical impact injury showed improved cognitive recovery, reduced lesion size and attenuated neuronal loss in comparison to controls.[16] Together these studies suggest that physical activity may afford cognitive improvements or even protection in the event of injury. Given that in most cases where aging and head injury intersect, individuals are highly physically active, more work comparing highly trained athletes experiencing both high and low levels of chronic head trauma will be necessary to further explore this concept.

Overall, the difficulty in analyzing behavioural data is that those experiencing various mitigating factors will appear similar to each other (eg. Bars C and E in Figure 5.1) as well as to those who are unimpaired (Bar A in Figure 5.1) which limits the conclusions drawn. As such, future studies should employ fMRI techniques to determine if cortical activation patterns can account for the measured response time differences in this study (e.g. through demonstrating increased cortical recruitment or efficient function). Results of this future study could better explain why response time differences were present and support the use of behavioural response time measures as a low-cost, easily accessible way to look for pre-clinical increased cognitive demand.

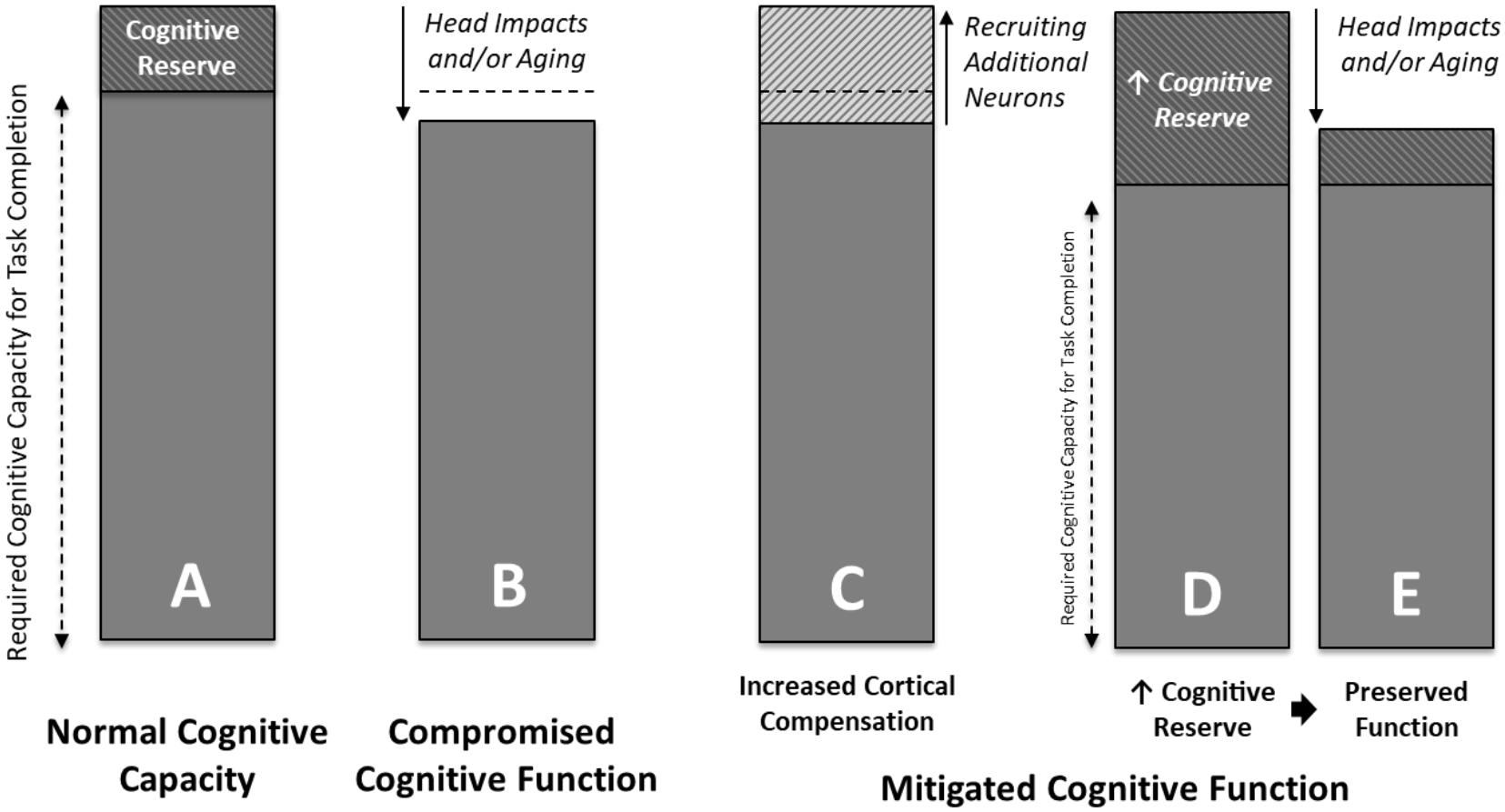

Figure 5.1: Theoretical Description of Cognitive Decline in Head Injury and/or Aging, and Mitigated Function through Improved Cognitive Reserve or Cortical Compensation

Bar A depicts normal cognitive capacity in young adulthood noting that capacity exceeding task requirements is termed cognitive reserve. Bar B demonstrates a decreased cognitive capacity below task requirements resulting in compromised function. Bar C demonstrates how recruiting additional cortical areas can increase the available resources to exceed the required capacity and mitigate cognitive decline. Bars D and E show how an individual with better cognitive reserve can perform adequately even with capacity decline.

Chapter 4: Optimizing the CBS Battery for use in Aging

Finally, Chapter 4 encompassed two statistical approaches to reduce the CBS cognitive battery. Initial work (chapter 4A) focused on employing principal component analysis to preserve known components in the data. Unfortunately, the planned data reduction could not be completed with these methods as the desired factor structure was not replicated in the data sample. This was attributed to differences between the populations used in this study (males, ages 18-24; 68-74, n = 236), and that used in previous work (males and females, ages 13-70, n > 44 000). The results, however, demonstrated that Older and Younger people employ differing cognitive strategies demonstrated through differential loading on cognitive networks when completing the same tests. The methodology for reducing the full battery while maintaining the three cognitive components of interest developed in **Chapter 4A** can be applied in future studies once a larger, broad sample is available.

Through our second approach, we employed discriminant function analysis methods to refine the CBS test battery to be more appropriate for age-related studies. More specifically, **Chapter 4B** classified CBS tests as demonstrating no significant age-related changes, significant changes and significant and salient changes. These results support test selection by researchers interested in reducing the time required to complete the battery, test for pathological change, or focus on age-sensitive tests. An important consideration moving forward is that since the DFA model is built to discriminate between two or more groups included in the analysis, the results are specific to that comparison (in this case, age). Future studies should replicate this methodology in other populations (eg. females, clinical groups) to ensure wide applicability of these test classifications.

The estimated prevalence of cognitive complaints (including trouble remembering recent events/conversations, the location of belongings, or upcoming appointments) in older adults ranges between 11 % and 56 %.[17–19] Given that those exposed to head trauma tend demonstrate an earlier presentation and higher incidence of age-related pathologies, ensuring the clinical applicability of these tests is an important next step. Unfortunately,

like normal aging, pathologies including Chronic Traumatic Encephalopathy (CTE),[20] Mild Cognitive Impairment (MCI – a transitional stage between normal aging and Alzheimer's dementia[21]), Alzheimer's disease (AD), and Parkinson's disease (PD), are characterized by a long preclinical stage in which subtle cognitive changes occur making it difficult to disentangle pathological from normal change.[22] As noted in Table 5.1, patterns of cortical and functional deficits vary between these states, which may be important for targeting specific cognitive tests.

Table 5.1: Cortical and Functional Deficits in Healthy Normal Aging, Alzheimer's Disease, Parkinson's Disease and Chronic Traumatic Encephalopathy

	Cortical Deficits	Functional Deficits
Healthy Normal Aging	Frontalstriatal System - decreases in dopamine, noradrenaline, serotonin and prefrontal cortex volume and function[23]	Long-term linear decline in executive function,[24,25] late life decline in vocabulary & semantic knowledge[25,26]
Alzheimer's Disease	Limbic System (hippocampus, amygdala, diencephalon, entorhinal and parahippocampal cortices), frontal, parietal and temporal association cortices [27]	early and severe deficit in declarative memory, deficits in attention, language, reasoning and other domains.[27]
Parkinson's Disease	Pars Compacta of the substantia nigra - progressive dopamine depletion[27]	Resting tremor, cogwheel rigidity, bradykinesia and postural reflex impairment. reduced processing speed, influences working memory and causes deficits in strategic memory [27]
Chronic Traumatic Encephalopathy	Commence in white matter, progressing deeper into sulci and then spreads into entorhinal cortex, amygdala, nucleus basalis of Meynert and locus coeruleus followed by the rest of the cortex[28]	irritability, impulsivity, aggression, depression, short-term memory loss and heightened suicidality,[20] in advanced stages dementia, gait and speech abnormalities and parkinsonism.[29]

Next Steps – Structural Neuroimaging

While primarily a research tool, neuroimaging offers an opportunity to better detect cortical changes responsible for cognitive changes. Beyond the previous mention of imaging as a tool to assess for neuronal recruitment, several researchers have begun to interrogate brain structure using diffuse tensor imaging (DTI), anatomical scans and resting state connectivity to better understand changes that occur in concussion.

DTI

Though not yet a direct measure of mTBI, functional and DTI based MRI shows promise in identifying impairments associated with concussion.[30,31] DTI offers some advantages over conventional methods as it is sensitive to imaging the movement of water molecules through nervous tissues expressed through measures of fractional anisotropy (FA) and mean diffusivity (MD). The premise is that when confined by surrounding myelin, flow and dispersion are perpendicular to the confining membrane wall,[32] while in injury, this restriction is lifted, and the relative dispersion changes – which is what DTI detects. With these properties, "DTI methods can uncover white matter abnormalities not visible on conventional clinical scans,[33–35] though no consistent spatial pattern of injury seems to emerge[36] and both increases and decreases in FA have been observed in concussion.[37–42] Overall, this suggests that there are likely to be more significant structural changes following TBI than previously assumed"[32] which may influence ongoing vulnerability. Future DTI work would benefit from establishing normative data sets for comparison of observed changes.[43]

Anatomical Scans

While many anatomical imaging studies fail to recognize immediate changes as the result of an acute concussive event, they remain evidence of long-term change and somewhat contrast previous work suggesting that concussion is primarily a functional rather than a structural injury.[44] For example, one study in collegiate football athletes found decreased bi-lateral hippocampal volume in comparison to controls for athletes both with and without a concussion history (control < no history < concussion history).[45] This evidence of prolonged/long-term cortical change suggests that more than both function and structure are compromised in head injury, of which the latter may serve as a marker for recovery or future impairments once more control studies are completed.

Resting State Connectivity

TBI can disrupt the brain's functional connectivity.[43] Evidence from a study on adolescent hockey players demonstrated hyperconnectivity patterns 3 months post-concussion in 4 resting-state networks (default mode, occipital pole visual, cerebellar and sensorimotor), specifically in those who sustained a less severe injury as indicated by

acute clinical measures.[42] This long-term increased connectivity between both correlated and inhibitory regions may be evidence of neural compensation in recovery[42] which may provide evidence of sustained impairments.

Conclusions

Overall, concerns in the spotlight today regarding the risks associated with long term head impact exposure have come to light before, and several attempts to mitigate concern and risk have been made. In my opinion, however, the biggest ongoing challenge is that we don't yet know enough to make educated decisions about what types and amounts of head impact exposure are safe. Research stands to make an enormous impact in targeting areas where perceived risk is not yet quantified (like subconcussion) to provide clarity. Unfortunately, without feasible and meaningful changes, we stand the risk of future generations sustaining otherwise preventable impairments which is why continued efforts to better understand the risks associated with contact sport are so important.

Through the studies within this dissertation we've learned that adequate cognitive tests are necessary to assess change, response time identified subclinical changes in footballers suggesting neural compensation for increased cognitive demand, and the full CBS battery can be reduced to support age-related studies. These studies lay a foundation for future studies on aging, injury and cognition. Based on our findings, future work should employ neuroimaging techniques, cognitive testing response times, and a reduced yet sensitive cognitive battery to better explore cognitive changes as a result of aging and cumulative head impact exposure.

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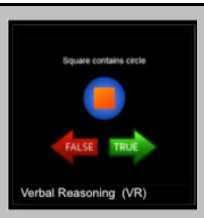
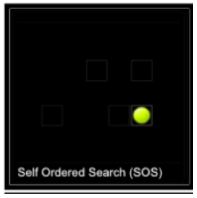
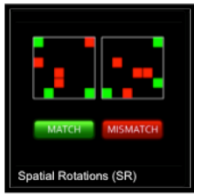
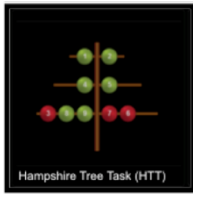
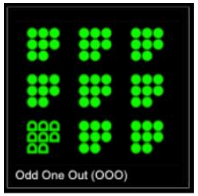
6. **Appendices**

Appendix 1: Brief Description of CBS Tasks

Test		Description	End Test After	Response Time	Cut Offs
Verbal Reasoning		**Reference**: Baddeley's 3min Grammatical Reasoning Test [1] **Task Type**: Grammatical Reasoning **Procedure**: Statements are displayed on screen with corresponding image. Determine if statement is true or false. **Primary CBS Composite Contribution**: Verbal	3 min	✓	> 0
Self Ordered Search		**Reference**: Search strategy task [2] **Task Type**: Working memory, inhibitory control, sequence planning. **Procedure**: Find hidden token in boxes within an invisible 5X5 grid without re-searching known locations. **Primary CBS Composite Contribution**: Short Term Memory	3 errors		> 0
Colour Word Remapping		**Reference**: Variant of Stroop Test [3] **Task Type**: Processing speed, cognitive flexibility, and inhibition or disinhibition **Procedure**: Indicate the color of the ink that the top word is written in. **Primary CBS Composite Contribution**: Verbal	90 s	✓	> 0
Interlocking Polygons		**Reference**: Adapted Mini-Mental State Interlocking Pentagons [4] **Task Type**: Age-related disorders, perceptual acuity **Procedure**: Pair of overlapping polygons displayed on screen. Determine if right-side single polygon matches either of the interlocking polygons **Primary CBS Composite Contribution**: Reasoning	90 s	✓	> -10

Paired Associates		**Reference**: Paradigm commonly used to assess memory impairments in aging clinical populations. [5] **Task Type**: Recognition and retrieval processing. **Procedure**: Boxes open one at a time on a 5X5 grid displaying objects. Target then displayed in the center, must click corresponding box pair **Primary CBS Composite Contribution**: Short Term Memory	3 errors		> 0
Spatial Rotations		**Reference**: 2D assessment based on Vandenberg and Kuse Mental Rotations Test [6] **Task Type**: Mental Rotation Ability test – maintain a mental image of a 2- or 3D object turning in space **Procedure**: Two grids of colored squares presented. When rotated by a multiple of 90 degrees, squares either match or mismatch. Identify if match or mismatch. **Primary CBS Composite Contribution**: Reasoning	90 s	✓	> 0
Spatial Span		**Reference**: Corsi Block Tapping Task [7] **Task Type:** measures short term memory capacity. Requires sequence reproduction **Procedure**: 15 squares aligned on a 4X4 grid flash in a random sequence. Repeat sequence. **Primary CBS Composite Contribution**: Short Term Memory	3 errors		> 0
Monkey Ladder		**Reference**: Non-human primate literature [8] **Task Type**: Visuospatial working memory task. **Procedure**: Shown numbers within an invisible 5X5 grid, which then disappear. Click boxes in ascending numerical order **Primary CBS Composite Contribution**: Short Term Memory	3 errors		0 - 14

Digit Span		**Reference:** Variant of verbal working memory component of WAIS-R intelligence test. Assesses immediate memory span [9] **Task Type:** Verbal Working Memory **Procedure**: View sequence of single digits. Repeat sequence using number pad. **Primary CBS Composite Contribution**: Verbal	3 errors		1 - 12
Hampshire Tree Task		**Reference:** Tower of London task [10] **Task Type:** Exec Function: spatial working memory, short term memory for sequence production and execution. **Procedure**: Reposition beads in ascending numerical order from left to right, top to bottom in as few moves as possible. **Primary CBS Composite Contribution**: Short Term Memory/Reasoning	3 min		> 0
Feature Match		**Reference**: Classical feature search tasks [11] **Task Type**: Attentional processing and simultaneous synthesis (capacity to pull together relevant elements into coherent unity) **Procedure**: Two grids displayed with set of abstract shapes. Determine if grids match or mismatch. **Primary CBS Composite Contribution**: Reasoning	90 s	✓	0 - 250
Odd One Out		**Reference**: Classification problems from Cattell Culture Fair Intelligence Test [12] **Task Type**: Deductive reasoning **Procedure**: 3X3 grid of cells displayed, each containing a variable number of copies of a colored shape. Features of 8/9 cells (number, color, shape) relate to each other based on unstated rule. Find odd cell. **Primary CBS Composite Contribution**: Reasoning	90 s		> -10

Appendix 2: Demographic, Sport and Health Questionnaire

Demographics
What year were you born in?
What is your sex (male or female – females are excluded)
What is your current profession

Education
Please describe your completed post-secondary education (degree completed, field, GPA, year graduated, length of studies in years)
Are you currently attending University or College? (list field of study, degree, years completed)

Health History
Please list any health conditions that affect your cognition (MCI, Stroke, Alzheimer's Dementia, Learning Disabilities)
How many concussions have you sustained in your lifetime
In what year did you sustain your most recent concussion

Physical Activity History
How many years have you been physically active?
How many hours per week do you engage in physical activity?
Please indicate the number of seasons you have played of all organized sports listed: (Baseball, Hockey, Football, Rugby, Golf, Figure Skating, Skiing, Swimming/Diving, Wrestling, Racket Sports, Sailing, Volleyball, Basketball, Gymnastics/Cheerleading, Cross Country Running/Track & Field, Power-Lifting/Olympic Lifting, Lacrosse, Rowing, Soccer, Weight Training*, Running* -- * indicate quantity of training in years)
What is the highest level of competition you've competed at (indicate sport and level)

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Western Research

Research Ethics

Western University Health Science Research Ethics Board
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Principal Investigator: Dr. Adrian Owen
Department & Institution: Social Science\Psychology, Western University

HSREB File Number: 105510
Study Title: Cognitive Assessment of Athletes and Sedentary young Adults experiencing sub-clinical and clinical mTBI Throughout an athletic season.
Sponsor: Canadian Excellence Research Chair

HSREB Initial Approval Date: August 14, 2014
HSREB Expiry Date: August 31, 2015

Documents Approved and/or Received for Information:

Document Name	Comments	Version Date
Instruments	Outline of 12 CBS trials tasks (Received 02Jun2014)	
Recruitment Items	Poster	2014/07/30
Recruitment Items	Script	2014/07/30
Instruments	Participant enrollment Survey	2014/07/30
Instruments	Concussion History Weekly Survey	2014/07/30
Other	Bi-weekly participant reminder emails	2014/07/30
Letter of Information & Consent		2014/08/11
Western University Protocol		2014/08/11

The Western University Health Science Research Ethics Board (HSREB) has reviewed and approved the above named study, as of the HSREB Initial Approval Date noted above.

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The Western University HSREB operates in compliance with the Tri-Council Policy Statement Ethical Conduct for Research Involving Humans (TCPS2), the International Conference on Harmonization of Technical Requirements for Registration of Pharmaceuticals for Human Use Guideline for Good Clinical Practice Practices (ICH E6 R1), the Ontario Personal Health Information Protection Act (PHIPA, 2004), Part 4 of the Natural Health Product Regulations, Health Canada Medical Device Regulations and Part C, Division 5, of the Food and Drug Regulations of Health Canada.

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The HSREB is registered with the U.S. Department of Health & Human Services under the IRB registration number IRB 00000940.

Ethics Officer, on behalf of Dr. Joseph Gilbert, HSREB Chair

Ethics Officer to Contact for Further Information

___ Erika Basile	___ Grace Kelly	✓ Nina Mekhail	___ Vikki Tran

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Western Research

Research Ethics

Western University Health Science Research Ethics Board
HSREB Delegated Initial Approval Notice

Principal Investigator: Dr. Adrian Owen
Department & Institution: Social Science\Psychology, Western University

Review Type: Delegated
HSREB File Number: 108257
Study Title: Examination of Cognitive Function in North American Sport Alumni and Healthy Controls.

HSREB Initial Approval Date: September 06, 2016
HSREB Expiry Date: September 06, 2017

Documents Approved and/or Received for Information:

Document Name	Comments	Version Date
Advertisement	Twitter Advertisement	2016/08/15
Instruments	Revised History Survey	2016/08/15
Advertisement	Poster Advertisement	2016/08/15
Instruments	History Survey - July 2016	
Advertisement	Social Media Advertisement	2016/08/15
Advertisement	Email Advertisement (Received 21Aug16)	
Letter of Information & Consent		2016/08/15
Western University Protocol	Revised Protocol (Received 21Aug16)	

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Ethics Officer: Erika Basile __ Nicole Kaniki __ Grace Kelly __ Katelyn Harris __ Vikki Tran __ Karen Gopaul __

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Western Research

Research Ethics

Use of Human Participants - Ethics Approval Notice

Principal Investigator: Dr. Adrian Owen
File Number:103472
Review Level: Delegated
Approved Local Adult Participants:11430
Approved Local Minor Participants:0
Protocol Title:A web-based study of cognitive training in healthy controls
Department & Institution: Social Science/Psychology,Western University
Sponsor:
Ethics Approval Date: May 28, 2013 **Expiry Date:**January 31, 2018
Documents Reviewed & Approved & Documents Received for Information:

Document Name	Comments	Version Date
Other	Example feedback page from Cambridge Brain Sciences	2013/01/19
Instruments	Cognitive task descriptions	2013/01/19
Western University Protocol		2013/01/28
Addition of Co-investigator	Addition of Co-Investigator	2013/05/28
Response to Board Recommendations	Response to Board Recommendations RE May 24	2013/05/28
Amendment	Amended Letter of Information for Piloting RE May 24	2013/05/28
Advertisement	Resubmission of poster for behavioural pilot according to ethics board recommendations. Compensation will be financial according to time invested.	2013/02/21
Board Recommendations	Response to board recommendations regarding participant compensation	2013/03/25

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Appendix 5: Multivariate Statistics Primer

Multivariate Statistical Methods Overview

The bulk of the data contained within this dissertation is multivariate in nature. This means that multiple measures of cognition, as assessed by independent cognitive tests, are often considered simultaneously in a statistical test. For most between-group comparisons a MANOVA is sufficient (chapter 2). In answering questions of variable selection (studies 3A and 3B), however, more sophisticated methods, including Discriminant Function Analysis (DFA) and Principal Components Analysis (PCA), are necessary.

The goal of this section is to first provide a brief primer on MANOVA general linear model (GLM) statistics, and then build understanding towards the more sophisticated yet related Discriminant Function Analysis (DFA), Principal Component Analysis (PCA).

6.1 Multivariate Analysis of Variance (MANOVA)

MANOVA is a powerful statistical tool that allows several dependent measures to be analyzed simultaneously,[13] taking into account correlations between related variables. It's not only particularly useful when assessing an ability or function that cannot be easily represented/described by a single dependent variable, but should be used for correlated dependent variables as experimentwise error rates are unpredictable and tend to increase with more variables and more covariance amongst them.[14] In effect, a synthetic or latent variable comprised of all relevant dependent variables is created and then used for comparison. In this case, synthetic/latent refers to the fact that the variable was not directly observed in an experiment but rather constructed through a statistical procedure.[15]

In practice, MANOVA is a two-step process in which a multivariate hypothesis is tested for main effects and interactions, and if it is significant, it is then followed by another analysis to determine which of the dependent variables account for the effects.[13] There are, however, a few different options for researchers to explore for this secondary step

depending upon their research question, and how they intend to interpret the data. In the literature, three main tests stand out as most common: ANOVA, discriminant analysis and step-down analysis, which I will outline here.

6.1.1 Analysis of Variance (ANOVA) as a post hoc

In 1971, Hummel and Sligo published a Monte Carlo study suggesting that following a significant multivariate test, experimentwise error rates are reasonably consistent,[14] and thus no correction (eg. Bonferroni) for multiple-comparison bias and type-1 error is required for subsequent ANOVAs – a feature widely known as a "protected F". Since their report, however, many have found this to be true in only 3 cases:[16–19]

1. When a MANOVA null hypothesis is completely true (no post hocs should be conducted in this case as the result is non-significant, or should only be carried out 5% of the time),
2. When a MANOVA null hypothesis is completely false, meaning there is no chance of a type 1 error because the result is significant (in which case there is no possibility of a type 1 error),
3. When a MANOVA is false for all but one outcome variable (because it is possible to make a Type 1 error for only a single variable while maintaining the error rate at α).

Still, many researchers will exploit MANOVA for this benefit. One of the major qualms against the use of univariate tests after a significant multivariate test is that the question answered is empirically different.[19] Many would argue that completing a multivariate test in the first place should be based on wanting to draw multivariate conclusions when dependent variables are related to each other. Thus, it may be counterintuitive to switch to a univariate paradigm which isolates dependent variables for analysis. That being said, univariate results are generally more simple to interpret and can offer understanding of how a specific variable functions across groups (albeit in the absence of the influence of other potentially related variables). If that indeed is the goal of an analysis, it seems appropriate to use ANOVAs, though many still suggest exercising a correction which challenges why a MANOVA might be useful in the first place.

6.2 Discriminant Analysis

Discriminant function analysis is an alternative way to view MANOVA, and is generally focused on a different outcome. As previously described, MANOVA is focused on differences between groups, while in discriminant function analysis, the focus is on how the different weighted linear combinations of the dependent variables predict group membership or explain difference between groups.[15] It's also useful in choosing subsets of the original *p* variables for future studies through its combined use with step-down analysis,[13] a key method in this dissertation. Additionally, since discriminant analysis can indicate both that group differences exist and where they are when there is only one grouping variable, it can be used in lieu of MANOVA altogether,[16] though it remains useful as a post hoc in multi-factor MANOVA designs.[20]

6.2.1 Discriminant Function Mathematics

Mathematically, discriminant analysis is based on comparing discriminant scores (*DS*). This value is calculated for each quantitative measure (predictor variable) using the Discriminant function as the sum of each predictor multiplied by its discriminant coefficient with a constant. The discriminant score is a latent factor and generally takes the form of the following equation[15]:

Equation 2: General Discriminant Function

$$DS = a + w_1X_1 + w_2X_2 + \cdots + w_vX_v$$

In this equation, *a* represents the constant (y-intercept), *w* represents the discriminant coefficients and X represents individual quantitative measures (predictor). In all cases, discriminant scores maximally separate the groups.[15] For reference, the group mean discriminant score is known as the group centroid.[15] The overall sample centroid including all groups is zero, as the discriminant scores are centered on the sample as a whole.[15]

The maximum number of discriminant functions that may be generated is the smaller of *k* – 1, where *k* represents the number of groups in the analysis, or the number of predictor

variables in the analysis.[15] Each discriminant function is independent of (orthogonal to) each of the others. Thus variance between groups accounted for by each function is independent, and may be summed to represent the total amount of between-group variance that is explained.[15] Similar to factor analysis, the first function explains the largest amount of variance, and then subsequent functions are created to explain that which remains, in decreasing amounts.[20] The statistical significance and meaningfulness of each function can be assessed using Wilks' λ.[15] In terms of effect size, Wilks' λ can be directly interpreted as the amount of variance not explained by the set of functions, thus 1- Wilks' λ represents the amount of variance explained.[15]

6.2.2 Assumptions and Sample Size in Discriminant Analysis

As a GLM statistic, discriminant analysis conforms to the same assumptions as other members like multiple regression and MANOVA including: multivariate normality, independence of predictors, homoscedasticity, absence of multicollinearity, and the presumption that outliers are not adversely affecting the results of the analysis.[15] It also is fairly robust to minor violations of these assumptions, but is highly sensitive to outliers which can make the test prone to type 1 error.[15]

Groups assessed via discriminant analysis can be of different sizes, though the "sample sizes of the smallest group should exceed the number of predictor (quantitative measures) variables."[15] The maximum number of predictor variables should be taken as *N*-2, where *N* is the sample size of the smallest group; however, the recommended sample size for the smallest group should be at least 20 times the number of predictors.[15]

6.2.3 Discriminant Function Coefficients

Four main values are available to researchers conducting a discriminant function analysis:

Raw Discriminant Coefficient[15]

- weights linked to predictor variables when the predictors are in raw score form
- analogous to beta weights in ordinary least squares regression

- "*w*" in the general discriminant function
- used in applying the discriminant model to a new sample

Standardized Function Coefficients:

- weights linked to predictor variables when the predictors are standardized or in z-score form[15]
- amount of relative credit an observed dependent variable received when creating the composite[15,20]
- analogous to standardized beta weights in regression. If several dependent variables are highly correlated, then one standardized coefficient may arbitrarily receive more credit for shared variance than the others[21,22]
- specific to this sample – will change if variables are added or deleted from the equation[15] as they are influenced by intercorrelations among predictor variables [23–25]

Structure Coefficients/Canonical Correlations:

- represents the correlation between each predictor variable and the discriminant score.[15,21]
    - denotes how strongly a variable indicates what the discriminant function represents (higher correlation = more relevant variable)[15]
    - determining which variables most strongly correlate with the discriminant score can allow researchers to better describe what the discriminant function actually represents, and thus interpret what was being measured
- squaring these correlations determines how much variance in the composite is explained by each predictor variable.[15,22] This is analogous to the R^2 value obtained in regression.[15]
- particularly useful as the correlations among dependent variables increases[20] as these coefficients are independent of these correlations[15]

Classification Function Coefficients

- cases are classified on the basis of these coefficients – each predictor is associated with a classification coefficient for each group as well as a constant for each group[15]
- for each individual case, variables are multiplied by their classification coefficient, and then summed together with the constant for each potential group. The group with the highest total score at the end denotes that case's classification[15]

6.2.4 Methods for Building the Discriminant Function

In general, there are two methods used to build the discriminant function[15]:

1. **Standard Method**: enter all quantitative measures (predictors) into the equation at once
    - also known as: simultaneous or direct method
    - provides a full-model solution that all predictors are a part of
    - weight of each variable is determined with all other variables statistically controlled

2. **Stepwise Method**: build the equation one predictor at a time only allowing predictors to be included if they significantly contribute to the equation, and removing those that don't.[15] Offers a data-driven avenue for variable selection.
    - alternative to the standard method
    - requires specified criterion for variable entry and removal – entry is more stringent than removal
        - can set particular F ratio or probabilities as criteria
        - usually use p=0.05 for entry, p=0.10 for removal
    - five variations offered in SPSS differing in the type of criterion used to evaluate contributions made to the discriminant function by predictors
        i. *Wilks' Lambda:* lower Wilks' λ

ii. *Unexplained Variance:* reduce unexplained variance (similar to Wilks' λ)
iii. *Mahalanobis Distance:* built function maximizes Mahalanobis distances or separation between groups and overall centroid (0)
iv. *Smallest F Ratio:* maximize F ratio
v. *Rao's V:* variation of Mahalanobis distance, increase Rao's V

In a comparison of six variable selection methods (reviewed by Huberty[26]), stepwise discriminant analysis yielded the best subsets and most accurate classification.[27]

6.2.5 Interpreting the Discriminant Function

Discriminant function analysis can be used both to predict group membership (Predictive Discriminant Analysis - PDA) or explain differences between groups[15] (Descriptive Discriminant Analysis - DDA). Regardless, there isn't a major difference in how the analysis is conducted, but rather in how it is interpreted with each predictive and descriptive analyses reflecting an approach to specific set of questions. "In most research studies, both the classification and explanatory aspects of the analysis are of interest and the results pertaining to both aspects are reported."[15]

In Predictive Discriminant Analysis (PDA), predictors (equivalent to measured dependent variables in a MANOVA) are used to predict group membership[20] which can be compared to what would be expected to happen by chance. This performance is evaluated by examining rates of correction classifications ("hits") and misclassifications ("misses").[15] A classification table or prediction matrix displays these results such that the rows indicate observed group membership and the columns are the predicted group membership (Table 6.1). The percentage of correct classifications, cases seen on the "hit" diagonal is called the hit ratio, and are compared with the percentage of cases that would have been correctly classified by chance, not zero.[15] "Chance in this application, is the expectation that we would be correct 1 of *k* times, where *k* is the number of groups" (ie. for 2 groups, ½ = 50%, for 3 groups, 1/3 = 33%...).[15] In determining whether or not classification is better than chance, Press' Q Statistic may be used.[28] This statistic is unavailable in SPSS but can be calculated by hand using the following equation:

Equation 3: Press' Q Statistic

$$Press'Q = \frac{[N - (n * k)]^2}{N(k - 1)}$$

where *N* = total number of cases in sample, *n* = number of cases correctly identified, and *k* = number of groups in the analysis.[15] "Press' Q can be described as a chi-square distribution with 1 degree of freedom (the critical value for chi-square with 1 degree of freedom and thus Q, using an alpha level of .05, is 3.841)."[15] If Press'Q is greater than the chi-square critical value of 3.841, the value is statistically significant ($p<0.05$) and the conclusion can be drawn that cases were correctly classified better than chance level.[15] Hit proportion (n/N) can provide an idea of the practicality significance of this finding.[15] Press' Q is, however, sensitive to sample size such that large samples increase the power of the test[15], and unequal sample sizes can render the statistical outcome ambiguous.[29]

Table 6.1: Discriminant Analysis Classification Table

		Predicted Group		
		Group 1	Group 2	Group 3
Actual (observed) group	Group 1	**Hit**	Miss	Miss
	Group 2	Miss	**Hit**	Miss
	Group 3	Miss	Miss	**Hit**

When evaluating the classification power of the developed DFA model three primary options exist:

1. Applying the model to the current data set although it biases the results to be more favorable.[15] Still, the model will not function perfectly, thus how far the prediction is from perfection is one way to evaluate the quality of the solution.[15]
2. An alternative is to perform a jackknife or leave-one-out classification wherein a single case is omitted in deriving the discriminant function. A prediction of that case's membership is made based on the model developed from all other cases in the sample. The outcome is noted, and then the procedure repeated for each case after replacing the previously removed case into the sample. The jackknife or

leave-one-out procedure offers a form of cross-validation and a less biased result.[15]

3. Finally, the model can also be applied to a different sample altogether.[15]

Descriptive Discriminant Analysis (DDA) looks to determine what variables contribute to group separation. It is particularly useful for understanding differences between groups and identifying which variables best capture group differences.[16] Both the standardized function coefficients and structure coefficients are particularly important here. Where DDA has power is in determining which variables/predictors most strongly represent what the discriminant score is in fact measuring. With this knowledge, researchers can begin to assign value to the discriminant score and better appreciate on which factors separate the groups.

6.2.6 Challenges with Discriminant Analysis

While a useful method for describing/classifying data, or selecting variables for future use, DFA has some limitations to consider as described below:

1. Multicollinearity: if two variables are highly correlated, the relative importance of the variables must be divided between the two, which can be relatively arbitrary.[23,24] This means that standardized function coefficient weights are highly sample dependent,[30] and may not truly reflect a variable's association with the discriminant function. To ameliorate this, structure coefficients should be considered alongside standardized function coefficients to determine if some variables are suppressor variables (which increase the relationship between another independent variable and the outcome[16]) which could influence conclusions drawn.
2. Caution should be exercised in interpreting results of tests with small sample sizes.[13]
3. Since the DFA model is built to discriminate between two or more groups included in the analysis, the results are specific to that comparison.
4. In general, stepwise DFA is biased towards the order of variable entry as it considers variables added to the model one-at-a-time and thus does not analyze

the variance jointly accounted for by each possible combination of tests.[31] as a consequence the selected subset of variables may not be the "best" subset[26] in terms of variability accounted for.

6.3 Step-Down Analysis (after MANOVA)

Step-down analysis is similar and can even be identical to the step-wise methods described in discriminant analysis but it is conceptually different.[24] While step-wise discriminant analysis adds or deletes variables based on predetermined mathematical criteria, step-down analysis requires an a priori ordering of variables to test how a specific set of variables contribute to group separation.[24] According to Roy[32], it is typically used for three purposes: selection or deletion of variables, assessing relative variable importance and both variable selection and ordering.[33]

This methodology was not employed in this dissertation.

6.4 Principal Components Analysis (PCA)

Exploratory analysis methods focus on data exploration and aim to describe and simplify relationships among variables. This means that they are not testing a null hypothesis, although hypotheses regarding the factor structure that emerges from the analysis can still be made.[15] These methods are particularly useful when the data exists on a continuous scale and comes from a single population as arbitrarily dividing the group into two would eliminate valuable information.

The general purpose of PCA is to identify a relatively small number of components underlying a relatively large set of variables by distinguishing sets of variables that have more in common with each other than with other variables in the analysis.[15] "What the subsets of variables have in common are the underlying components."[15] In psychological research, principal components analysis is most commonly used in test development and scoring, as well as in organizing or conceptualizing a set of measures by determining which ones might be measuring the same thing.[15] In the second case, further analyses can be conducted based on components rather than individual dependent variables including

examining group differences through MANOVA and predicting group membership through DFA or logistic regression.[15] This reduces the data dimensionality and can sometimes make the data easier to work with (e.g. 2-3 components instead of 10-20 variables). Additionally, what is often most important in interpreting what an inventory of tests/variables is measuring is number of factors that underlie the items rather than the individual items themselves.[15]

6.4.1 PCA Methods

PCA is typically performed in two successive phases – the extraction, followed by the rotation. Each phase can be accomplished with different analytic methods depending on a researcher's preference.[15]

6.4.2 Extraction

In extraction, components are extracted one at a time to explain more and more variance such that they are all orthogonal to each other (thus uncorrelated with/independent of each other), and the independent amount of variance accounted for by each component is less with each extraction. The maximum number of extracted components always equals the number of variables included in the analysis. Naturally, not every extracted component will account for a meaningful amount of variance. Researchers must examine extracted components to decide when to stop the process when "enough" components have been extracted.[15]

6.4.3 Rotation

By virtue of the extraction process, components are mathematically placed such that the first placed component accounts for the greatest portion of variance, the second component accounts for the next largest portion, and so on. While mathematically sound, many argue that this does not optimize the interpretability of the solution as it is impossible for a component to show a strong association with some variables without being unassociated with other (which inflates their least-squares value).[15] Thus, after the number of components to be analyzed has been decided, the factors are rotated around

their point of intersection to achieve a simpler structure, which is then interpreted.[15] Rotating an extracted factor doesn't change the amount of variance explained but rather redistributes it across factors such that correlations between variables and the component become either very great (almost 1) or very small (almost 0) which makes for easier interpretation. Since multiple factors are in play, the sum of least squares principal matters less, as while a variable may be further from one component, it will inevitably be closer to another, thus balancing out the change.

In general there are two approaches to factor rotation: orthogonal and oblique.

Orthogonal: maintains the 90˚ angle between components and thus keeps them independent. There are three forms of orthogonal rotation[15]:

- *Varimax*: simplifies variable correlations within each factor, striving towards values of 1 or 0 for each factor, most frequently used orthogonal rotation strategy
- *Quartimax*: simplifies the variables to correlate more strongly to one factor and more weakly to all other factors. This strategy tends to drive the rotated solution toward a single general factor
- *Equimax*: combination of varimax and quartimax methods, though unpopular

Oblique: does not require factors to remain uncorrelated. There are two forms of oblique rotation:

- *Direct Oblimin*: amount of correlation between factors is controlled by researcher
- *Promax*: involves 3 steps – varimax rotation, coefficients raised to a power called kappa which drives their correlations towards 0 and 1, then simplified coefficients are obliquely rotated

6.4.4 Interpreting a PCA

The interpreted solution should account for at least 50% of the variance[34], and is cumulative in that it assess the first *n* number of components.[15] However, deciding which components to include is an important task for researchers. As aforementioned, a component's eigenvalue indicates the amount of variance that it accounts for. Generally,

components whose eigenvalues do not achieve a value of 1 or greater are not included in the final interpreted solution as they do not account for enough variance.

Eigenvalues

Eigenvalues mathematically describe the distance of variables to a component, noting how related each variable is to that component. They are based on adding r^2 values acquired from Pearson's correlations for each variable for a given component. In a perfect circumstance, where each variable correlated perfectly with the component, the overall eigenvalue would equal the number of variables in the analysis (as each would have a correlation of 1 which is then summed). Thus, eigenvalues are a direct measure of the amount of explained variance of a component.[15]

The final interpretation of a PCA solution is made using a factor matrix which displays weights (loadings) of variables, organized by factor. Examining the factor matrix allows for an interpretation of how each variable behaves across factors/components (rows), and also, how to interpret the factors/components based on how strongly each variable is represented (columns). The magnitude of these variable loadings is important in determining whether or not it relates to a given factor. "Comrey and Lee (1992)[35] have characterized coefficients of 0.7 as excellent, 0.63 as very good, 0.55 as good, 0.45 as fair and 0.32 as close to minimal."[15] Whether or not the value is positive or negative makes no difference in terms of strength, but merely notes the direction of the relationship with the component. However, determining what a factor represents is up to the researcher and understanding what underlying themes or constructs that variables related to a component share.

6.4.5 PCA Sample Size

Sample size is an important consideration when completing a PCA. Based on several sources, Meyers et al suggest the following evaluations of the adequacy of various sample sizes for PCA: "50 is very poor, 100 is poor, 200 is fair, 300 is good, 500 is very good, 1000 is excellent".[15] They also suggest a target ratio of 20 participants to every variable.[15]

6.5 Measures of Internal Reliability

As a follow up to PCA, researchers interested in variable selection may choose to analyze sub-scale scores with a measure of internal reliability to determine if all included variables are necessary for sub-scale consistency. One such test is the "α if item deleted procedure" which exploits Chronbach's α, to determine how reliability would change with the removal of a single variable from the subscale.

6.5.1 α if Item Deleted

α if item deleted methods are routinely used in behavioural and social sciences for the purposes of instrument revision[36] and employs Chronbach's α as a measure of internal consistency for a group of variables. Combined with PCA, it helps researchers determine which variables are more associated with a given component, and thus eliminate those which are not. The analysis itself provides Chronbach's α values for each variable submitted which denotes what the α for the whole group, excluding that variable would be. Researchers should aim to eliminate those variables which either increase α, or minimally decrease α as higher values suggest that variables within the set are associated with the same construct (which is what a component aims to measure).

Typically, to ensure that the construct measured by a given component is adequately measured, a minimum of 3 variables must be measured.

Limitations of α if item deleted methods

Since "α in general incorrectly evaluates scale reliability at the population level", removing a variable associated with a maximal increase in α may lead to a scale with lower criterion validity and reliability.[36] The solution is to employ an additional measure of reliability and validity following the removal of a single variable[36] so that they might be considered alongside α values in choosing which variables to eliminate.

6.6 The Premise of Variable Selection

In the above sections, two methods for variable selection, were outlined: DFA step-wise methods, and α if item deleted methods for PCA. While each method has merits, the theory and requirements of each also differ.

If a researcher has a set of continuous data, and is looking to maintain PCA components, α if item deleted methods are most valuable as they allow for variables to be selected while maintaining those factors. By extension, however, in cases such as our chapter 4, where we failed to replicate a known factor structure with an independent sample, these methods won't work.

An alternative approach is stepwise DFA methods which as explained above, exploits differences between groups to build a statistical model. It is useful as it offers a data-driven approach to ordering and selecting variables, but may be limited in that it requires a group-based division, and it may not offer the "best" subset as all possible solutions are not examined.

Regardless, in both circumstances, variable selection is a valuable effort and it may be considered before or after a significant multivariate test. Selecting variables beforehand requires that variables are chosen judiciously,[37] and then are subject to univariate analysis.[27] Those yielding significant results are carried forward to a multivariate analysis, and those yielding non-significant results are deleted.[27] In cases where a significant multivariate analysis has already been found, the question regarding which variables are necessary and which might be discarded is also valid, particularly if the researcher wishes to:[27]

1. Obtain fundamental and generally applicable variables
2. Avoid prohibitive labor
3. Increase the sampling stability of discriminant functions (as the ratio of the number of discriminators to the number of individuals increases, the accuracy of the discrimination tends to decrease when applied to subsequent samples[38])

As expected, the objective is "to include as many variables as possible so that reliable results may be obtained, and yet as few as possible so as to keep the costs of acquiring data at a minimum."[27] Reducing the number of variables to include only those relevant to the construct of interest is also important as the presence of items "not germane to the topic can adversely affect the assessment process by substantially lowering the validity and reliability of the instrument".[15]

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1. **Brewer-Deluce D,** Gibson CJ. "Teaching Matters: Developing Teaching Dossiers to Showcase Teaching Success and Competency". Teaching Innovation Projects. Vol. 7: Iss. 1, Article 1. May 2017

2. Zubin Maslov P, Breskovic T, **Brewer DN,** Shoemaker JK, Dujic Z. "Recruitment pattern of sympathetic muscle neurons during premature ventricular contractions in heart failure patients and controls". Am J Physiol - Regulatory, Integrative and Comparative Physiology. Volume 303, p. R1157-64, 2012.

3. **Brewer DN,** Wilson TD, Eagleson R, de Ribaupierre S. "Evaluation of Neuroanatomical Training using a 3D Visual Reality Model". Studies in Health Tech and Infor, IOS Press, Amsterdam. Volume 173, p. 85-91, 2012.

Abstracts & Presentations:

1. **D Brewer-Deluce,** TD Wilson, AM Owen. Investigating the Relationship between Chronic Elite Exercise, Cognitive Performance and Exposure to Subconcussive Impacts. Exercise is Medicine Canada National Student Research Conference. London ON. (Platform, June 2017)

2. **D Brewer-Deluce**, TD Wilson, AM Owen. Cognitive Function in Varsity Football Athletes is Maintained in the Absence of Concussion. Canadian Association of Neuroscience 2017. Montreal QC. (Poster, May 2017)

3. **D Brewer-Deluce**, TD Wilson, AM Owen. Cognitive Function in Varsity Football Athletes is Maintained in the Absence of Concussion. SONA Annual Meeting 2017. St. Catherines ON. (Poster, May 2017)

4. **D Brewer-Deluce**, TD Wilson, AM Owen. Cognitive Function in Varsity Football Athletes is Maintained in the Absence of Concussion. American Association of Anatomists – EB 2017. Chicago IL. (***Poster Award,*** April 2017)

5. **D Brewer-Deluce**, TD Wilson, AM Owen. Cognitive Function in Varsity Football Athletes is Maintained in the Absence of Concussion. LHRD 2017. London ON. (Poster, March 2017)

6. **D Brewer-Deluce,** TD Wilson, AM Owen. Cognitive Function as Related to Head Impact Exposure in Football: Effects of Position. Canadian Association of Neuroscience 2016. Toronto ON. (Poster, May 2016)

7. **D Brewer-Deluce,** TD Wilson, AM Owen. Cognitive Function as Related to Head Impact Exposure in Football: Effects of Position. SONA Annual Meeting 2016. Waterloo ON. (Poster, May 2016)

8. **D Brewer-Deluce,** TD Wilson, AM Owen. Cognitive Function as Related to Head Impact Exposure in Football: Effects of Position. American Association of Anatomists – EB 2016. San Diego CA. (Poster, April 2016)

9. **D Brewer-Deluce,** TD Wilson, AM Owen. Cognitive Function as Related to Head Impact Exposure in Football: Effects of Position. LHRD 2016. London ON. (Poster, April 2016)

10. **D Brewer-Deluce**, TD Wilson, AM Owen. Cognitive Function Changes in Long-Term and Seasonal Contact Sport Participation. Anatomy and Cell Biology Murray Barr Research Day. London ON. (Platform, October 2015)

11. **DN Brewer,** TD Wilson, AM Owen. The Effects of Long-Term and Acute Contact Sport Participation on Cognitive Function in Varsity Athletes. International Conference on Paediatric Acquired Brain Injury. Liverpool UK. (**Top Abstract Platform,** September 2015)

12. **DN Brewer**, TD Wilson, AM Owen. The Effects of Long-Term and Acute Contact Sport Participation and mTBI on Cognitive Function in Varsity Athletes. SONA Annual Meeting. Hamilton ON. (Poster, May 2015)

13. **DN Brewer**, TD Wilson, AM Owen. The Effects of Clinical, and Sub-Clinical mTBI on Cognitive Function in Varsity Athletes. American Association of Anatomists – EB 2015. Boston MA. (Poster Presentation, March 2015)

14. **DN Brewer**, P Zubin Maslov, Z Dujic, JK Shoemaker. Do multi-unit sympathetic discharge patterns change with age and cardiovascular disease? 23rd International Symposium on the Autonomic Nervous System. Paradise Island, Bahamas. (Poster, November 2012)

15. P Zubin Maslov, T Breskovic, **DN Brewer**, JK Shoemaker, Z Dujic. Recruitment pattern of muscle sympathetic neurons during premature ventricular contractions in heart failure patients and controls. 23rd International Symposium on the Autonomic Nervous System. Atlantis, Paradise Island, Bahamas. (Poster, November 2012)

16. P Zubin Maslov, T Breskovic, **DN Brewer**, JK Shoemaker, Z Dujic. Recruitment pattern of sympathetic muscle neurons during premature ventricular contractions in heart failure patients and healthy controls. Croatian Physiology Society Annual Symposium. Zagreb, Croatia. (Platform, September 2012)

17. **DN Brewer,** T Wilson, R Eagleson, S de Ribaupierre. Teaching Neuroanatomy using a 3D VR Model. Medicine Meets Virtual Reality (MMVR 2012). Newport Beach, CA. (Platform, February 2012)

18. S de Ribaupierre, **D Brewer**, R Eagleson, and T Wilson. The role of spatial abilities in learning neurosurgical procedures. International Symposium on Pediatric Neurosurgery. Goa, India. (Platform, October 2011)

19. **DN Brewer**, S de Ribaupierre, TD Wilson. Use of a Digital 3D Brain Model as an Intermediate Step in Learning Spatial Anatomy. EB 2011. Washington D.C. (Poster, April 2011)

20. **DN Brewer**, S de Ribaupierre, TD Wilson. Use of a 3D Brain Model in Teaching Neuroanatomy. Western Undergraduate Research Journal Conference 2011. London ON. (Platform, March 2011)

21. S de Ribaupierre, R Eagleson, **D Brewer**, T Wilson. Ubiquitous Learning for Neuroanatomy. Ubiquitous Learning International Conference 2010, Vancouver BC. (Platform, December 2010)

Scholarships & Awards:

2018	**American Association of Anatomists Symposium Travel Bursary**
2017, 2016, 2015	**American Association of Anatomists Student Travel Scholarship**
2017	**American Association of Anatomists Graduate Student Poster Presentation Award, 2nd place**
2017	**Canadian Association of Neuroscience Travel Award**
2016, 2015, 2014, 2013, 2012	**Western University Ontario Graduate Scholarship**
2016, 2015, 2014, 2013, 2012, 2011	**Western Graduate Research Scholarship**
2015	**ACB Graduate Student and Post-Doctoral Travel Prize**
2015	**Drs. Madge and Charles Macklin Fellowship for Teaching & Research**
2015	**International Conference on Pediatric Acquired Brain Injury Top Abstract**
2012	**Kinesiology Graduate Student Travel Award**
2013	**Great Ideas for Teaching Award**
2012	**Graduate Student Teaching Award Nominee**