# COMPARISON OF RELIABLE CHANGE INDICES OF CNS VITAL SIGNS FOR DIFFERENT RANGES OF BASELINE SCORES

By

Michelle M. Ikoma

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Department of Exercise and Sport Science
University of North Carolina

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Approved:

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## ABSTRACT

MICHELLE IKOMA: Comparison of Reliable Change Indices of CNS Vital Signs for Different Ranges of Baseline Scores
(Under the direction of Jason P. Mihalik)

Computerized neurocognitive tests are widely used in the management of sport-related concussion. Many of these assessments use reliable change confidence intervals—computed as *baseline score* ± *reliable change index (RCI)*—to classify an individual as impaired or unimpaired at a follow-up test point. If an individual's retest score falls outside of the reliable change confidence interval on a given domain, he or she is classified as impaired on that domain. The purpose of this study was to compare RCIs for three different ranges of CNS Vital Signs baseline scores: the lowest quintile (0-20$^{th}$ percentile), middle quintile (40-60$^{th}$ percentile), and highest quintile (80-100$^{th}$ percentile). One-hundred seven Division I student-athletes completed baseline and follow-up computerized neurocognitive testing on CNS Vital Signs and were divided into quintile groups based on their baseline score for each clinical domain. RCIs were computed for the lowest, middle, and highest quintiles for each domain. Overall group RCIs were also computed. The RCIs varied considerably across the quintile groups, with average and high baseline performers tending to have smaller RCIs than low baseline performers and the full group in each domain. In addition, significant interaction effects of time and quintile group were found for several domains as well as for Neurocognition Index. These results suggest that it is important for clinicians to consider an individual's baseline performance level when interpreting CNS Vital Signs neurocognitive test results using a baseline/post-injury comparison model.

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# CHAPTER I

## INTRODUCTION

In the United States alone, an estimated 1.6 to 3.8 million sport-related concussions occur each year (Langlois, Rutland-Brown et al. 2006). Concussion is defined as "a traumatically induced transient disturbance of brain function…[involving] a complex pathophysiological process," and can have numerous adverse short-term effects including, but not limited to, headaches, balance deficits, sensitivity to light and noise, and difficulty concentrating (Harmon, Drezner et al. 2013). While symptoms generally resolve within 7 to 10 days in college athletes, in some cases they may persist for weeks, months, or even years (Frommer, Gurka, et al. 2011; Makdissi, Darby et al. 2010; Marar, McIlvain et al. 2012; Meehan, d'Hemecourt et al. 2010). Objective measures are important for concussion evaluation, because cognitive recovery can lag behind clinical concussion symptom resolution (Lovell, Collins et al. 2004; McCrea, Barr et al. 2005). This has prompted the widespread adoption of neurocognitive testing in managing sport-related concussion over the past 15 years (Echemendia, Iverson et al. 2013). Currently, several organizations recommend using neurocognitive testing as part of a comprehensive, multidimensional concussion management program (Harmon, Drezner et al. 2013; McCrory, Meeuwisse et al. 2013). In addition, many high schools and other institutions with limited resources may rely heavily on the results of computerized neurocognitive testing in making return-to-play decisions for athletes who have sustained concussions (Resch, Driscoll et al. 2013).

An athlete's neurocognition is generally evaluated during a baseline test prior to sports participation to establish his or her "normal" level of neurocognitive functioning. Then following a concussive incident, the athlete takes a similar neurocognitive test, and the results of this post-injury test are compared to the athlete's baseline performance to provide some level of objective information with respect to the level of injury severity or state of recovery. While this baseline/post-injury comparison protocol helps control for inherent inter-individual differences in cognitive abilities, it depends on an athlete's baseline neurocognitive scores' being truly representative of his or her "normal" cognitive functioning level. However, at present, evidence that athletes' preseason test scores serve as reliable baselines for comparison to post-injury test results weeks, months, or even years later is insufficient to recommend widespread baseline testing for all athletes (Harmon, Drezner et al. 2013; McCrory, Meeuwisse et al. 2013).

As with any test, random variability plays a role in determining an individual's performance level on a neurocognitive assessment. Exceptionally low neurocognitive test performance likely results from the interaction of below average cognitive abilities and unfavorable random variability. Symmetrically, exceptionally high neurocognitive test performance likely results from the interaction of above average cognitive abilities and favorable random variability. Thus, regression to the mean theory suggests that, due to chance alone, exceptionally low performers at baseline will score higher the second time they take a neurocognitive test, and vice versa for exceptionally high performers at baseline. Consequently, the reliable change indices (RCIs) for a neurocognitive assessment may be different for these extreme score ranges as compared to "average" performers at baseline. Thus, the purpose of this thesis was to compare RCIs for one

commonly used neurocognitive assessment tool, CNS Vital Signs, for three different ranges of baseline test scores—(1) the lowest quintile (0-20$^{th}$ percentile), (2) the middle quintile (40$^{th}$-60$^{th}$ percentile), and (3) the highest quintile (80$^{th}$-100$^{th}$ percentile)—in a large sample of college student-athletes. Different RCIs across these groups would imply different utility levels of NC testing in helping clinicians and other healthcare providers make the most prudent return-to-play decisions for their athletes. Additionally, we were interested in whether test-retest scores differed based on group (quintile) assignment.

**Research Question and Hypothesis**

What are the RCIs for CNS Vital Signs for the lowest quintile, middle quintile, and highest quintile of baseline scores for each clinical domain and Neurocognition Index (NCI)?

We hypothesize the RCIs for CNS Vital Signs will be larger for the lowest quintile and highest quintile of baseline scores than for the middle quintile of baseline scores for each clinical domain and NCI.

**Significance of the Study**

If the research hypothesis is accepted, the results would suggest that baseline/post-injury comparisons of performance on neurocognitive assessments may be less sensitive to changes in cognitive functioning for those scoring in the extreme ranges at baseline when a baseline/post-injury comparison interpretation method is used. This would suggest that larger score variations from baseline may be normal for these individuals, and therefore less conservative RCIs may need to be applied in interpreting

these athletes post-injury neurocognitive test results. Moreover, if these quintile RCIs are found to be too large to be clinically meaningful for certain domains, the results would suggest that these domains may contribute limited value in informing clinicians' return-to-play decisions for very low and very high baseline performers in these domains. In addition, the results may prompt similar studies investigating variability in test-retest reliability across different baseline score ranges using other commonly used NC test batteries, such as ImPACT, Headminder, and Axon.

# CHAPTER II

# LITERATURE REVIEW

## Introduction

Sport-related concussion has drawn a great deal of attention from medical practitioners, researchers, and the general public alike. Consequently, increasing attention has been paid to best practices in the prevention, management, and treatment of sport-related concussions. One area in concussion management that has grown exceptionally over the past two decades is using NC assessment tools to aid return-to-play decisions. Over the past 15 years, there has been an exponential increase in the use of NC testing in managing sport-related concussion (Echemendia, Iverson et al. 2013).

However, evidence has recently suggested that the pre-injury/post-injury comparison model which has been widely adopted for NC testing in concussion management may frequently result in false positives, raising concerns about relying on such information in making return-to-play decisions (Randolph 2011; Resch, Driscoll et al. 2013). Nonetheless, computerized NC assessment continues to be a key component of sport-related concussion management programs in high schools and universities across the country since neurocognitive deficits are commonly the last adverse effects of a concussion to resolve (Bleiberg, Cernich et al. 2004; Bleiberg, Warden 2005; Ellemberg, Henry et al. 2009; Fazio, Lovell et al. 2007; Johnson, Kegel et al. 2011; Makdissi, Darby et al. 2010; Resch, Driscoll et al. 2013). Moreover, authorities on concussion in sport continue to endorse NC testing as a clinically valuable tool, which “contributes

significant information in concussion evaluation" (McCrory, Meeuwisse et al. 2013). Therefore, this study aims to better understand how the test-retest reliability of such computerized NC tests may be impacted by an individual's baseline performance on these assessments.

This literature review will provide a thorough description of sport-related concussion, including its epidemiology, pathophysiology, symptomology, and potential consequences of repeat concussions; briefly describe current recommendations regarding proper management of sport-related concussion; and describe how NC assessment tools are currently used in the management of sport-related concussion.

## Sport-Related Concussion

### *Definition & Epidemiology*

Concussion is a form of mild traumatic brain injury (TBI). As defined by the AMSSM, a concussion is "a traumatically induced transient disturbance of brain function…caused by a complex pathophysiological process" (Harmon, Drezner et al. 2013). Although concussion may involve a loss of consciousness, in 80.8% to 92% of all instances of sport-related concussion, athletes remain fully conscious (Collins, Iverson et al. 2003; Schulz, Marshall et al. 2004). Based on data collected by the Centers for Disease Control and Prevention, it is estimated that as many as 3.8 million sport-related concussions occur each year (Langlois, Rutland-Brown et al. 2006). Moreover, because many mild TBIs may go unrecognized and thus unreported, the true number of sport-related concussions occurring annually may be even higher (Langlois, Rutland-Brown et al. 2006).

Approximately 5% to 9% of all injuries that occur in high school and collegiate sports are concussions (Gessel, Fields et al. 2007; Hootman, Dick et al. 2007; Powell and Barber-Foss 1999). Although concussions occur in a wide array of sports, they are most prevalent in football, wrestling, women's soccer, men's soccer, and women's basketball (Gessel, Fields et al. 2007; Lincoln, Caswell et al. 2011; Powell and Barber-Foss 1999; Schulz, Marshall et al. 2004). Concussion rates tend to be higher in competition than in practice, especially for contact sports (Gessel, Fields et al. 2007; Marar, McIlvain et al. 2012). Recent studies have also shown systematically higher concussion rates for women's soccer and basketball as compared to their men's equivalents, suggesting a possible gender difference in concussion risk (Covassin, Swanik et al. 2003; Dick 2009; Gessel, Fields et al. 2007; Lincoln, Caswell et al. 2011; Marar, McIlvain et al. 2012).

*Pathophysiology*

Concussion is caused by the transmission of rotational and/or linear forces to the brain (Harmon, Drezner et al. 2013). These forces "initiate a complex cascade of neurochemical and neurometabolic events" known commonly as the 'neurometabolic cascade' which manifest themselves outwardly as NC deficits and concussion symptoms (Barkhoudarian, Hovda et al. 2011). This neurometabolic cascade begins with a non-discriminant flux of ions across neuronal membranes resulting in membrane depolarization and action potential (AP) generation in turn causes excitatory neurotransmitters to be released (Barkhoudarian, Hovda et al. 2011). This results in a massive efflux of potassium, leading to a widespread suppression of neurons, temporarily impairing normal NC function (Barkhoudarian, Hovda et al. 2011). To restore resting

membrane potential, sodium-potassium pumps must operate at maximal capacity, quickly depleting adenosine-triphosphate (ATP) stores, resulting in hyperglycolysis immediately following injury (Barkhoudarian, Hovda et al. 2011). Glucose, which has been shown to contribute to both learning and memory, is thus diminished, potentially explaining acute memory deficits resulting from concussion (Gold 2001; Korol and Gold 1998).

Concurrently, large influxes of calcium cause oxidative dysfunction in mitochondria, resulting in impaired oxidative glucose metabolism for up to 10 days following a mild concussive injury (Barkhoudarian, Hovda et al. 2011). Because glucose metabolism is vital to proper brain function—particularly for learning and memory tasks—this impairment may result in temporary attention and memory deficits associated with concussion (Gold 2001; Korol and Gold 1998). Likewise, axonal injury resulting from concussive forces has been associated with diminished cognitive performance in both children and adults (Niogi, Mukherjee et al. 2008; Wozniak, Krach et al. 2007).

*Symptomatology*

The most common symptoms associated with concussion are headaches, dizziness, and difficulty concentrating, all of which may interfere with normal cognitive functioning (Marar, McIlvain et al. 2012; Meehan, d'Hemecourt et al. 2010). Over 90% of high school athletes diagnosed with a concussion reported headaches, 75% reported dizziness, and over half reported having difficulty concentrating (Marar, McIlvain et al. 2012; Meehan, d'Hemecourt et al. 2010). Other commonly reported symptoms include confusion/disorientation, nausea, drowsiness, and sensitivity to light (Marar, McIlvain et al. 2012; Meehan, d'Hemecourt et al. 2010). The non-specific nature of these symptoms

and their overlap with those of other neurocognitive disorders such as ADHD and depression can make concussions difficult to identify and diagnose (Harmon, Drezner et al. 2013). Moreover, athletes may underreport (or simply *not* report) their symptoms and/or the severity of their symptoms to avoid losing playing time, further complicating the diagnosis and management of sport-related concussion (McCrea, Hammeke et al. 2004; Register-Mihalik, Guskiewicz et al. 2013). Thus, authorities on concussion in sport more strongly recommend the use of NC testing for athletes who may deny their symptoms in hopes of returning to play sooner (Harmon, Drezner et al. 2013).

Short-term balance and neurocognitive deficits also commonly result from concussion (Harmon, Drezner et al. 2013; McCrory, Meeuwisse et al. 2013). Approximately 30% of athletes diagnosed with concussion experience balance deficits which generally resolve within 3 to 7 days (Guskiewicz 2011; Harmon, Drezner et al. 2013). Neurocognitive deficits often coincide with self-reported concussion symptoms (such as difficulty concentrating and feeling mentally 'foggy'), and NC recovery generally overlaps with symptom resolution (McCrory, Meeuwisse et al. 2013). In some instances, however, cognitive deficits may persist beyond clinical symptom recovery, prompting many organizations to adopt baseline NC testing as a key component of their concussion management programs (Bleiberg, Cernich et al. 2004; Bleiberg and Warden 2005; Broglio, Macciocchi et al. 2007; Fazio, Lovell et al. 2007).

**Proper Management of Sport-Related Concussion**

Proper management of sport-related concussion is critical to ensure that athletes return to play in the fastest but safest way possible. Premature return to play can

predispose athletes to sustaining a subsequent, more severe concussion and lead to prolonged symptom duration (Harmon, Drezner et al. 2013). Currently, authorities in this area recommend a multifaceted, multimodal approach to managing sports-related concussion, which includes consideration of an athlete's concussion history, comorbidities and complicating factors (such as LD or ADHD), symptoms, balance/postural stability, and cognitive function (Echemendia, Iverson et al. 2013; Harmon, Drezner et al. 2013; McCrory, Meeuwisse et al. 2013).

Thus, 'best practices' in sport-related concussion management encompass the following components:

- A pre-participation exam (PPE), including:
    - Questions about concussion history,
    - Questions about learning, mood, attention, and/or migraine disorders,
    - Baseline symptom evaluation,
    - Baseline balance evaluation, and
    - Baseline sideline assessment using a well-validated sideline assessment tool (which may itself include symptom and balance evaluation) and/or baseline computerized NC testing;
- Immediate post-injury evaluation, including:
    - Symptom evaluation,
    - Balance evaluation, and
    - Cognitive evaluation;
- And ongoing evaluation of an athlete's:
    - Self-reported symptoms and

- Neurocognitive function, once the athlete is symptom-free.

(Guskiewicz, Bruce et al. 2004; Harmon, Drezner et al. 2013)

*Early Return-to-Play and Repeat Concussions*

Even with proper management, those with a previous concussion are over twice as likely to have a concussive injury in the future (Colvin, Mullen et al. 2009; Guskiewicz, Marshall et al. 2007; Guskiewicz, McCrea et al. 2003; Schulz, Marshall et al. 2004). Allowing an athlete with unresolved symptoms or NC deficits to return to play can further increase his/her risk of sustaining a subsequent concussion by diminishing his/her ability to meet the physical and mental demands of his/her sport (Longhi, Saatman et al. 2005; Lovell and Collins 1998; McCrea, Guskiewicz et al. 2003; Slobounov, Slobounov et al. 2007).

Repeat concussions predispose athletes to developing both clinical depression and mild cognitive impairment (MCI) and may lead to persistent neurocognitive deficits (Guskiewicz, Marshall et al. 2005; Guskiewicz, Marshall et al. 2007; Iverson, Echemendia et al. 2012). Among retired professional football players, those who sustained three or more concussions were three times more likely to be diagnosed with depression and five times as likely to be diagnosed with MCI as compared with those with no history of concussion (Guskiewicz, Marshall et al. 2005; Guskiewicz, Marshall et al. 2007). In addition, studies have suggested that lingering cognitive deficits may result from sustaining three or more concussions (Collins, Grindel et al. 1999; Iverson, Echemendia et al. 2012). Notably however, evidence on this outcome is mixed, and

further investigation is needed to understand how NC function is impacted by repeat concussions (Broglio, Ferrara, et al. 2006; De Beaumont, Brisson et al. 2007).

*Neurocognitive Testing in Sport-Related Concussion Management*

Evaluation of an athlete's neurocognitive functioning can be particularly beneficial in helping clinicians make return-to-play decisions (Harmon, Drezner et al. 2013; McCrory, Meeuwisse et al. 2013). NC testing "can identify occult cognitive impairment" in athletes, providing clinicians with more complete information to use in their decision-making process (Harmon, Drezner et al. 2013). Either paper-and-pencil tests or computerized NC assessment tools such as Immediate Postconcussion Assessment and Cognitive Testing (ImPACT), CNS Vital Signs, and Headminder can be used for NC testing. Computerized NC tests are used far more commonly than their paper-and-pencil counterparts by schools and professional sports organizations because they are much more efficient and cost-effective to administer (Echemendia, Iverson et al. 2013; Harmon, Drezner et al. 2013; Johnson, Kegel et al. 2011). ImPACT alone is used by over 7,000 high schools, more than 1,000 universities, and numerous MLB, NFL, and NHL teams (*About ImPACT*). Other possible advantages of computerized NC assessment tools over traditional paper-and-pencil tests include reduced practice effects, improved reliability across multiple test administrators, increased accuracy in reaction time measurement, and greater validity in identifying subtle changes in cognitive speed (Johnson, Kegel et al. 2011). One key disadvantage of computerized NC testing, however, is the test administrator's inability to directly observe an individual as he/she completes each test (Johnson, Kegel et al. 2011).

*Interpretation of Neurocognitive Test Scores*

Baseline/Post-Injury Comparison

The notion behind baseline testing is intuitive. In theory, baseline testing provides an individualized benchmark of what is "normal" for a particular athlete which can be used as a basis of comparison for that person following a concussion (Guskiewicz, Bruce et al. 2004). However, in reality, numerous intrinsic and extrinsic factors other than an athlete's cognitive functioning impact his/her performance on an NC test (Johnson, Kegel et al. 2011; Mulligan, Boland et al. 2012). Both physiological variables such as fatigue (Mulligan, Boland et al. 2012), as well as environmental variables like the presence/absence of distractions (Echemendia, Herring et al. 2009; Johnson, Kegel et al. 2011), can impact an athlete's performance on a NC assessment. Likewise, motivation and effort on the part of the athlete can also significantly impact his/her NC test scores (Erdal 2012). High false positive rates exceeding 35% on computerized NC assessments, pointing to this inherent variability in NC test scores (Resch, Driscoll et al. 2013).

Normative Comparisons

Thus, some investigations have looked at normative comparisons as an alternative method for interpreting NC test scores. In two recent studies, impaired/not impaired classifications made using normative benchmarks differed minimally from classifications made using baseline comparisons (Echemendia, Bruce et al. 2012; Schmidt, Register-Mihalik et al. 2012). Thus, preliminary evidence suggests that, for the college-age population, normative comparison may be a viable alternative to the time- and resource-

intensive process of obtaining individual baseline NC scores for all athletes (Echemendia, Bruce et al. 2012; Schmidt, Register-Mihalik et al. 2012).

However, Schmidt and colleagues' results also point to potential limitations of normative comparison methods for identifying cognitive impairment. On a test of mathematical processing ability, normative comparisons classified individuals as impaired 7.6 times more often than baseline comparisons. This discrepancy likely resulted due to inherent differences in people's cognitive abilities which limit some individuals from performing at a "normal" level (Schmidt, Register-Mihalik et al. 2012). Thus, it is possible that normative comparison could result in systematically lower or higher rates of impairment for individuals with above or below average cognitive abilities, respectively.

Therefore, additional research is needed to understand the most effective method of interpreting NC test results in sport-related concussion management. Limitations of normative comparisons may make baseline comparisons the preferred interpretation method, particularly for certain subgroups. Authorities in sport-related concussion management have already identified those with a history of concussion and those with learning disabilities or attention disorders as specific subpopulations for whom baseline NC testing may be more valuable since these groups demonstrate overall lower performance on NC tests (Harmon, Drezner et al. 2013). However, evidence on the reliability of an athlete's preseason baseline score as a dependable benchmark of his/her normal cognitive functioning level against which to compare post-injury data is currently inconclusive (Harmon, Drezner et al. 2013). Thus, further investigation in this area is

warranted to ensure that return-to-play decisions are made in the most prudent way possible for all athletes affected by sport-related concussions.

# CHAPTER III

# METHODOLOGY

## Participants

This study included 107 (67 male, 40 female; at testing session 1, age = 18.7 ± 1.1 yrs; height = 177.6 ± 12.2 cm; mass = 77.7 ± 19.6 kg) NCAA Division I college student-athletes who completed the CNS Vital Signs neurocognitive test battery at two different time points (median time between sessions = 10 weeks; range = 7 to 81 weeks). Participation by sport for these athletes is listed in **Table 3.1**. Athletes who sustained a concussion between these two testing sessions or with diagnosed depression, anxiety disorders, learning disabilities or attention disorders were excluded from the analysis. Individuals who had sustained a concussion in the six months preceding initial testing or reported having vestibular, visual, or balance disorders at either time point were also excluded.

## Instrumentation

CNS Vital Signs is a comprehensive neurocognitive test battery that takes about 30 minutes to complete which has been shown to be both reliable and valid (Gualtieri and Johnson 2006). The CNS Vital Signs consists of eight different tests. These tests include visual memory, verbal memory, finger tapping, symbol digit coding, the Stroop Test, the shifting attention test, the non-verbal reasoning test, and the continuous performance test.

Brief descriptions of these tests can be found in Table 3.2, and more detailed descriptions are provided in Appendix A.

Based on these eight subtests, scores were calculated for 9 different clinical domains. These clinical domains were: (1) verbal memory, (2) visual memory, (3) psychomotor speed, (4) reaction time, (5) complex attention, (6) cognitive flexibility, (7) processing speed, (8) executive function, and (9) reasoning ("CNS Vital Signs Interpretation Guide"). Neurocognition Index (NCI), an aggregate metric of overall neurocognitive function was also calculated. Automatic reports generated by CNS Vital Signs include both raw scores and standardized scores with a mean of 100 and standard deviation of 15 for each of these domains.

**Procedures**

Athletes reported to the Matthew Gfeller Sport-Related Traumatic Brain Injury Research Center at the University of North Carolina at Chapel Hill on the day of their team's pre-participation examination (baseline time point). Prior to participation, each athlete signed an informed consent form approved by the university institutional review board. Pre-season testing occurred at different times based on when an athlete's competitive season began. As part of their school's standard baseline testing program, athletes completed the CNS Vital Signs test battery on a desktop computer. Athletes were tested in groups of approximately three people. In order to ensure that the testing environment was as quiet and distraction-free as possible, dividers were placed between the computers, the athletes were given ear plugs and they were instructed to turn off and store

all electronic devices and to remain silent throughout the test. For 56 participants, follow up testing (retest time point) was conducted 10 weeks following the initial baseline (±1 week). For the remaining participants, follow up testing was conducted at the conclusion of an athlete's competitive season, ranging between 19 to 40 weeks following the initial baseline. For six participants, follow up testing occurred one year following baseline, and for five participants, follow up testing was approximately 18 months following initial baseline. The same testing procedures were repeated in that session.

**Data Reduction**

Invalid scores were considered to be any score that fell outside of two standard deviations from the mean on that clinical domain. If an individual had an invalid score at either time point on a given domain, his or her score for that domain was excluded from analysis. In addition, if an athlete had an invalid score on any of the clinical domains (except reasoning) contributing to the NCI, that athlete was removed from the NCI analysis.

**Statistical Analysis**

The remaining observations were rank-ordered and grouped into quintiles in each of the nine CNS Vital Signs clinical domains based on athletes' raw baseline scores. For each domain, the participants were categorized into 1 of 5 quintiles based on baseline scores as follows: 0-20$^{th}$ percentile (lowest 20%), 20-40$^{th}$ percentile, 40-60$^{th}$ percentile ('average' category), 60-80$^{th}$ percentile, and 80-100$^{th}$ percentile (highest 20%). The number of observations per quintile (excluding NCI) varied between 19 and 34. Pearson

correlation coefficients and standard deviations for both time points (baseline and retest) were computed for the lowest quintile, middle quintile, and highest quintile of baseline scores for each of the nine CNS Vital Signs domains and NCI. From these values, the RCI outcomes were computed using an identical and systematic approach employed for each outcome measure and quintile of interest as follows:

(1) Correlation (r) between the two test sessions was determined.

(2) Descriptive statistics included standard deviations (SD) for each outcome measure derived for each test session.

(3) Standard error of the measurements (SEM) were computed:

$$SEM = SD\sqrt{1 - r}$$

(4) Standard error of the difference ($SE_{diff}$) was computed:

$$SE_{diff} = \sqrt{{SEM_1}^2 + {SEM_2}^2}$$

(5) The $SE_{diff}$ was multiplied by the *z* scores associated with 80% (z = 1.282), 90% (z = 1.684), and 95% (z = 1.96) confidence intervals to compute the RCI values for each of the measures as follows (Iverson, Lovell et al. 2003; Register-Mihalik, Guskiewicz et al. 2013):

$$RCI = SE_{diff} \times z \text{ score}$$

Additionally, we performed 3 (quintile group assignment) x 2 (test session) mixed model ANOVA to identify whether test-retest scores differed based on group (quintile) assignment. Data were analyzed using SPSS 19 (SPSS Inc.; Chicago, IL). An a priori α level of significance was set at 0.05 for all analyses.

**Table 3.1.** Participants by sport

| **Sport** | **Number of Subjects** |
|---|---|
| Men's basketball | 6 |
| Women's basketball | 2 |
| Men's cheerleading | 4 |
| Women's cheerleading | 5 |
| Men's diving | 1 |
| Women's diving | 1 |
| Field hockey | 1 |
| Football | 20 |
| Gymnastics | 2 |
| Men's lacrosse | 13 |
| Women's lacrosse | 8 |
| Men's soccer | 16 |
| Women's soccer | 13 |
| Softball | 5 |
| Men's track and field | 2 |
| Women's track and field | 3 |
| Wrestling | 5 |

**Table 3.2.** Descriptions of CNS Vital Signs subtests

| **Subtest** | **Cognitive Tasks Assessed** |
|---|---|
| Verbal Memory | • Verbal learning<br>• Memory for words<br>• Word recognition<br>• Immediate and delayed recall |
| Visual Memory | • Visual learning<br>• Memory for geometric shapes<br>• Geometric shape recognition<br>• Immediate and delayed recall |
| Finger Tapping | • Motor speed<br>• Fine motor control |
| Symbol Digit Coding | • Information processing speed<br>• Complex attention<br>• Visual-perceptual speed |
| Stroop Test | • Simple reaction time<br>• Complex reaction time<br>• Inhibition/disinhibition<br>• Frontal/executive skills<br>• Processing speed |
| Shifting Attention | • Executive function<br>• Rapid decision making<br>• Reaction time |
| Continuous Performance | • Sustained attention<br>• Choice reaction time<br>• Impulsivity |
| Non-verbal Reasoning | • Reasoning<br>• Reasoning recognition speed |

# CHAPTER IV

# MANUSCRIPT

## Introduction

In the United States alone, an estimated 1.6 to 3.8 million sport-related concussions occur each year (Langlois, Rutland-Brown et al. 2006). Concussion is defined as "a traumatically induced transient disturbance of brain function…[involving] a complex pathophysiological process," and can have numerous adverse short-term effects including, but not limited to, headaches, balance deficits, sensitivity to light and noise, and difficulty concentrating (Harmon, Drezner et al. 2013). While symptoms generally resolve within 7 to 10 days in college athletes, in some cases they may persist for weeks, months, or even years (Frommer, Gurka, et al. 2011; Makdissi, Darby et al. 2010; Marar, McIlvain et al. 2012; Meehan, d'Hemecourt et al. 2010). Objective measures are important for concussion evaluation, because cognitive recovery can lag behind clinical concussion symptom resolution (Lovell, Collins et al. 2004; McCrea, Barr et al. 2005). This has prompted the widespread adoption of neurocognitive testing in managing sport-related concussion over the past 15 years (Echemendia, Iverson et al. 2013). Currently, several organizations recommend using neurocognitive testing as part of a comprehensive, multidimensional concussion management program (Harmon, Drezner et al. 2013; McCrory, Meeuwisse et al. 2013). Although the upfront costs associated with computerized neurocognitive assessment tools can be substantial, they confer a

significant overall cost-advantage to traditional paper-and-pencil tests because they are less time- and labor-intensive to administer (Collie, Maruff et al. 2004; Ellemberg, Henry et al. 2009). Therefore, under mounting medicolegal pressure to properly manage sport-related concussions (Frollo 2013), even under-resourced schools have increasingly adopted computerized neurocognitive tests. With few clinicians on staff, these tests often become stand-alone concussion diagnostic tools due to their ease and convenience of use.

An athlete's neurocognition is generally evaluated during a baseline test prior to sports participation to establish his or her "normal" level of neurocognitive functioning. Then following a concussive incident, the athlete takes the same neurocognitive test, and the results of this post-injury test are compared to the athlete's baseline performance to provide some level of objective information with respect to the level of injury severity or state of recovery. While this baseline/post-injury comparison protocol helps control for inherent inter-individual differences in cognitive abilities, it depends on an athlete's baseline neurocognitive scores' being truly representative of his or her "normal" cognitive functioning level.

As with any test, random variability plays a role in determining an individual's performance level on a neurocognitive assessment. Exceptionally low neurocognitive test performance likely results from the interaction of below average cognitive abilities and unfavorable random variability. Symmetrically, exceptionally high neurocognitive test performance likely results from the interaction of above average cognitive abilities and favorable random variability. Thus, regression to the mean theory suggests that, due to chance alone, exceptionally low performers at baseline will score higher the second time they take a neurocognitive test, and vice versa for exceptionally high performers at

baseline. Consequently, the reliable change indices (RCIs) for a neurocognitive assessment may be different for these extreme score ranges as compared to "average" performers at baseline. Thus, the purpose of this thesis was to compare RCIs for one commonly used neurocognitive assessment tool, CNS Vital Signs, for three different ranges of baseline test scores—(1) the lowest quintile (0-20$^{th}$ percentile), (2) the middle quintile (40$^{th}$-60$^{th}$ percentile), and (3) the highest quintile (80$^{th}$-100$^{th}$ percentile)—in a large sample of college student-athletes. Different RCIs across these groups would imply different utility levels of NC testing in helping clinicians and other healthcare providers make the most prudent return-to-play decisions for their athletes. Additionally, we were interested in whether test-retest scores differed based on group (quintile) assignment.

## Methods

### *Participants*

This study included 107 (67 male, 40 female; at testing session 1, age = 18.7 ± 1.1 yrs; height = 177.6 ± 12.2 cm; mass = 77.7 ± 19.6 kg) NCAA Division I college student-athletes who completed the CNS Vital Signs neurocognitive test battery at two different time points (median time between sessions = 10 weeks; range = 7 to 81 weeks). Participation by sport for these athletes is listed in **Table 3.1**. Athletes who sustained a concussion between these two testing sessions or with diagnosed depression, anxiety disorders, learning disabilities or attention disorders were excluded from the analysis. Individuals who had sustained a concussion in the six months preceding initial testing or reported having vestibular, visual, or balance disorders at either time point were also excluded.

### *Instrumentation*

CNS Vital Signs is a comprehensive neurocognitive test battery that takes about 30 minutes to complete which has been shown to be both reliable and valid (Gualtieri and Johnson 2006). The CNS Vital Signs consists of eight different tests. These tests include visual memory, verbal memory, finger tapping, symbol digit coding, the Stroop Test, the shifting attention test, the non-verbal reasoning test, and the continuous performance test. Brief descriptions of these tests can be found in Table 3.2, and more detailed descriptions are provided in Appendix A.

Based on these eight subtests, scores were calculated for 9 different clinical domains. These clinical domains were: (1) verbal memory, (2) visual memory, (3) psychomotor speed, (4) reaction time, (5) complex attention, (6) cognitive flexibility, (7) processing speed, (8) executive function, and (9) reasoning ("CNS Vital Signs Interpretation Guide"). Neurocognition Index (NCI), an aggregate metric of overall neurocognitive function was also calculated. Automatic reports generated by CNS Vital Signs include both raw scores and standardized scores with a mean of 100 and standard deviation of 15 for each of these domains.

### *Procedures*

Athletes reported to the Matthew Gfeller Sport-Related Traumatic Brain Injury Research Center at the University of North Carolina at Chapel Hill on the day of their team's pre-participation examination (baseline time point). Prior to participation, each athlete signed an informed consent form approved by the university institutional review board. Pre-season testing occurred at different times based on when an athlete's competitive season began. As part of their school's standard baseline testing program, athletes

completed the CNS Vital Signs test battery on a desktop computer. Athletes were tested in groups of approximately three people. In order to ensure that the testing environment was as quiet and distraction-free as possible, dividers were placed between the computers, the athletes were given ear plugs and they were instructed to turn off and store all electronic devices and to remain silent throughout the test. For 56 participants, follow up testing (retest time point) was conducted 10 weeks following the initial baseline (±1 week). For the remaining participants, follow up testing was conducted at the conclusion of an athlete's competitive season, ranging between 19 to 40 weeks following the initial baseline. For six participants, follow up testing occurred one year following baseline, and for five participants, follow up testing was approximately 18 months following initial baseline. The same testing procedures were repeated in that session.

### *Data Reduction*

Invalid scores were considered to be any score that fell outside of two standard deviations from the mean on that clinical domain. If an individual had an invalid score at either time point on a given domain, his or her score for that domain was excluded from data analysis. In addition, if an athlete had an invalid score on any of the clinical domains (except reasoning) contributing to the NCI, that athlete was removed from the NCI analysis.

### *Statistical Analysis*

The remaining observations were rank-ordered and grouped into quintiles in each of the nine CNS Vital Signs clinical domains based on athletes' raw baseline scores. For

each domain, the participants were categorized into 1 of 5 quintiles based on baseline scores as follows: 0-20$^{th}$ percentile (lowest 20%), 20-40$^{th}$ percentile, 40-60$^{th}$ percentile ('average' category), 60-80$^{th}$ percentile, and 80-100$^{th}$ percentile (highest 20%). The number of observations per quintile (excluding NCI) varied between 19 and 34. Pearson correlation coefficients and standard deviations for both time points (baseline and retest) were computed for the lowest quintile, middle quintile, and highest quintile of baseline scores for each of the nine CNS Vital Signs domains and NCI. From these values, the RCI outcomes were computed using an identical and systematic approach employed for each outcome measure and quintile of interest as follows:

(1) Correlation (r) between the two test sessions was determined.

(2) Descriptive statistics included standard deviations (SD) for each outcome measure derived for each test session.

(3) Standard error of the measurements (SEM) were computed:

$$SEM = SD\sqrt{1 - r}$$

(4) Standard error of the difference ($SE_{diff}$) was computed:

$$SE_{diff} = \sqrt{{SEM_1}^2 + {SEM_2}^2}$$

(5) The $SE_{diff}$ was multiplied by the *z* scores associated with 80% (z = 1.282), 90% (z = 1.684), and 95% (z = 1.96) confidence intervals to compute the RCI values for each of the measures as follows (Iverson, Lovell et al. 2003; Register-Mihalik, Guskiewicz et al. 2013):

$$RCI = SE_{diff} \times z \text{ score}$$

Additionally, we performed 3 (quintile group assignment) x 2 (test session) mixed model ANOVA to identify whether test-retest scores differed based on group (quintile)

assignment. Post hoc Tukey analyses were also performed to identify significant pairwise critical differences ($d_{crit}$) in baseline versus retest score in each quintile group. Data were analyzed using SPSS 19 (SPSS Inc.; Chicago, IL). An a priori α level of significance was set at 0.05 for all analyses.

**Results**

The overall RCIs and RCIs by quintile for each domain are reported in **Table 4.3**. Significant interaction effects were observed for verbal memory ($F_{2,65} = 22.03$, $P < 0.001$), psychomotor speed ($F_{2,56} = 10.48$, $P < 0.001$), reaction time ($F_{2,68} = 7.37$, $P = 0.001$), cognitive flexibility ($F_{2,71} = 8.45$, $P = 0.001$), processing speed ($F_{2,62} = 19.03$, $P < 0.001$), executive function ($F_{2,71} = 11.42$, $P < 0.001$), reasoning ($F_{2,82} = 3.29$, $P = 0.042$), and NCI ($F_{2,36} = 5.80$, $P = 0.007$). Specifically, the lowest quintile performed significantly better at retest than at baseline on psychomotor speed ($d_{crit}$=7.68), reaction time ($d_{crit}$=7.57), cognitive flexibility ($d_{crit}$=7.77), processing speed ($d_{crit}$=7.28), and executive function ($d_{crit}$=7.50). The highest quintile performed better at baseline than at retest on verbal memory ($d_{crit}$=11.87), processing speed, and reasoning ($d_{crit}$=22.40) ($P < 0.05$ for all). There were no differences between baseline and retest for the middle quintile group ($P > 0.05$). In the absence of a significant interaction effect, we observed a main effect of time for visual memory ($F_{1,69} = 11.78$, $P = 0.001$) and complex attention ($F_{1,76} = 7.33$, $P = 0.008$), with participants performing better at the first time point than the second time point. In addition, significant main effects of group were observed for all domains and NCI ($P < 0.05$ for all). **Table 4.4** includes all descriptive and statistical information for our outcome measures.

## Discussion

Our main finding was that RCIs varied considerably across the quintile groups for several CNS Vital Signs clinical domains as well as for NCI. Moreover, our results also showed that the RCI we determined for each overall domain deviated from the individual quintile RCI we identified across multiple domains in each quintile group. These results are significant because they show that the "one-size-fits-all" application of RCIs used by many computerized neurocognitive assessment tools may lead to higher false-positive and false-negative rates for subgroups of people who perform differently at baseline. Relying on the overall RCI for quintile groups where the overall RCI exceeds the quintile-specific RCI could lead to systematic misclassification of cognitively-impaired individuals as unimpaired (**Figure 4.1a**); symmetrically, relying on the overall RCI for groups where the quintile-specific RCI exceeds the overall RCI could lead to systematic misclassification of healthy individuals as impaired (**Figure 4.1b**). Thus, investigating the specificity of each CNS Vital Signs domain as well as the test battery as a whole may be an interesting avenue for further study.

Specifically, our results suggest that for individuals who score near the mean or exceptionally well at baseline, even relatively small deviations from baseline scores may denote clinically meaningful differences. This implies that clinicians should exercise particular caution in evaluating these athletes' neurocognitive recovery from a concussion since automated reports generated by computerized neurocognitive test batteries may not flag all significant changes from baseline performance. In contrast, our results suggest that for individuals who score poorly at baseline, reliance on impairment classifications

made by computer-generated reports may lead to overly-conservative management of concussions given the generally larger RCIs we determined for this group. These larger RCIs found in the low baseline performers likely resulted because of a number of factors. These may include the presence of distractions, fatigue, and lack of effort which can lead to poor neurocognitive test performance even in the absence of low cognitive abilities (Erdal 2011; Johnson, Kegel et al. 2011; Mulligan, Boland et al. 2012). Thus, for these low-scoring individuals, baseline/post-injury comparisons of neurocognitive test scores may have limited value since the "normal" (unimpaired) score range for these athletes may be too large to provide clinicians with meaningful information about an athlete's neurocognitive functioning level. Although using normative comparisons to interpret neurocognitive test results is one potential alternative, this method may also result in overly conservative concussion management for the subset of these low baseline performers with below average cognitive abilities (Echemendia, Iverson, et al. 2013; Schmidt, Register-Mihalik et al. 2012). While we did not directly measure this, we speculate that most of the low-performers were individuals with lower cognitive abilities, but acknowledge that many factors (described earlier) may adversely affect test performance such that lower-than-expected scores are measured. Therefore, while neurocognitive testing as a whole has been shown to add value in managing sport-related concussions and continues to be recommended as part of a multidimensional approach to concussion management, our results suggest that neurocognitive testing may have more limited application for those who score poorly at baseline (Harmon, Drezner et al. 2013; McCrory, Meeuwisse et al. 2013; Van Kampen, Lovell et al. 2006). That is, individuals who score poorly at baseline on several (more than half) of the clinical domains without

tripping any built-in validity checks the test battery may incorporate should be candidates for rebaselining so that more meaningful baseline/post-injury comparisons can be made. Alternatively, for individuals with only one or two very low baseline scores, it may suffice for clinicians to flag these low-performance domains and apply less conservative RCIs to these domain scores in interpreting post-injury test results. More broadly, our results highlight potential problems with indiscriminately drawing conclusions based on convenient end-user reports generated by computerized neurocognitive assessments and underscore the importance of having qualified clinicians to interpret neurocognitive test results.

More generally, it was also notable that the overall RCIs for the clinical domains found in this study appeared to be considerably larger than those reported by Littleton, Register-Mihalik, et al. in a forthcoming publication. While our 80% RCIs ranged from 14.86 to 51.41, the 80% RCIs found by Littleton, Register-Mihalik et al. ranged from 9.44 to 20.22. These large discrepancies in RCIs resulted in part due to the lower Pearson *r* correlations observed in this study (0.08 to 0.60) as compared to those observed in Littleton's study (0.11 to 0.87). Our correlations were also lower than those previously reported by Gualtieri and Johnson (0.31 to 0.88) and Cole, Arrieux, et al. (0.34 to 0.79). In addition, particularly large standard deviations at retest for visual memory, complex attention, and reasoning contributed to the wide RCIs we found for these domains. These large standard deviations resulted from very low retest scores which remained in the analysis despite removing scores with a $|z| > 2$. The persistence of these values underscores the importance of using neurocognitive testing as one tool in concussion management rather than a stand-alone diagnostic program.

These unusually low correlations and large standard deviations may have resulted from a number of different factors. Because baseline testing for the student-athletes in this study was mandatory and no incentives were provided to participants during follow-up testing, submaximal effort may be one factor contributing to the low correlations and large retest standard deviations we observed. In addition, the longer test-retest time interval as compared to Littleton et al. and Cole et al.'s studies may have also contributed to the lower correlations. Notably, the longer and more diverse range of test-retest time intervals used in this study as compared to the consistent 1-week and 1-month intervals used by Littleton and Cole, respectively, more closely approximates the true, uncertain length of time which may pass between baseline and post-injury testing for an athlete, and therefore may be more clinically relevant. Different study populations may explain some of the disparity in the correlations found as well; Littleton's study included recreationally active college students while Cole's study focused on active-duty members of the United States military in contrast to this study which included only NCAA Division I varsity student-athletes.

Furthermore, mixed-model ANOVA analysis and subsequent Tukey post hoc results provided evidence that low performers at baseline had systematically inflated scores at retest, and high performers at baseline had systematically deflated scores at retest for select domains (specifically verbal memory, processing speed, and reasoning). These results provide further evidence that baseline/post-injury comparisons may be an ineffective method of determining cognitive impairment following a concussion for those who scored poorly at baseline. These findings also suggest that for high baseline performers, particular caution should be exercised when using verbal memory, processing

speed, or reasoning to determine an athlete's impairment status post-injury since 8 to 10 point declines in these domain scores are expected for this group. Additionally, with the exception of processing speed, none of the domains which showed systematic improvement for low baseline performers overlapped with those that demonstrated a systematic decline among high baseline performers. For poor performers at baseline, the domains demonstrating systematic score inflation related to cognitive speed; whereas, domains showing consistent score deflation generally related to information recall for high performers at baseline.

Moreover, the two domains (visual memory and complex attention) where no significant interaction effect was found were both domains with very large RCIs, which resulted from large retest standard deviations. These same large standard deviations may explain why significant interactions were not found in these domains. Our ANOVA analyses also revealed that participants improved overall fromm baseline to retest on visual memory, psychomotor speed, and reaction time, which is consistent with previous findings on practice effects for computerized neurocognitive assessments. Littleton et al. similarly found significant practice effects on psychomotor speed, reasoning, and reaction time for CNS Vital Signs, and other researchers have demonstrated practice effects for analogous reaction time and motor processing speed domains on similar computerized neurocognitive assessment tools like ImPACT and Automated Neuropsychological Assessment Metrics (ANAM) (Elbin, Schatz et al 2011; Register-Mihalik, Kontos et al. 2012; Register-Mihalik, Guskiewicz et al. 2013). Our ANOVA analyses also revealed unique overall declines in performance from baseline to retest on visual memory and complex attention. These declines may suggest submaximal effort on the part of

participants at the retest time point or may have been unique to this study due to the longer and more variable test-retest timeframe.

Finally, while this study focused on computerized neurocognitive assessments in contrast to traditional paper-and-pencil neurocognitive tests, similar results may be found for such paper-and-pencil tests. Because factors other than an individual's neurocognitive functioning level like random variability, fatigue, and stress similarly influence these two variations of neurocognitive tests, the RCIs for paper-and-pencil tests will likely also vary considerably across different initial performance ranges on these tests. However, the pattern of variability observed may differ from that observed for CNS Vital Signs since paper-and-pencil neurocognitive tests are influenced by a unique set of factors, and this may be an interesting area for further study.

### *Limitations*

This study was limited to healthy, Division I NCAA student-athletes, and therefore the results may not be generalizable to other populations. Another limitation was the exclusive use of CNS Vital Signs—one of many different neurocognitive test batteries available to clinicians—in this study. Additionally, because baseline testing was mandatory for all student-athletes and no incentives were provided for completion of follow-up testing, lack of full effort being given by participants was another potential limitation of this study. Furthermore, the persistence of very low retest scores even after removing scores falling outside of two standard deviations from the mean was another limitation of this study; removing outliers based on the 1.5*[Interquartile range (IQR)] criterion rather than the $|z| > 2$ criterion may be one way to mitigate this limitation in

future investigations since IQR is more resistant to the effects of outliers than standard deviation.

### *Conclusions and Clinical Implications*

Our results demonstrate that RCIs vary considerably from one performance quintile to another for several CNS Vital Signs clinical domains, as well as for NCI. These results suggest that clinicians using CNS Vital Signs need to be aware of an athlete's baseline performance level when interpreting his or her results using the baseline/post-injury comparison model. Specifically, clinicians should recognize that for average and very high performers at baseline, even relatively small deviations from baseline performance (those smaller than the overall RCIs for that domain) may be clinically-meaningful. In contrast, clinicians should expect greater deviations from baseline performance for those who initially scored poorly on a particular domain, and they may need to apply less conservative RCIs in interpreting post-injury test scores for these individuals. In addition, clinicians who currently use the 95% of baseline method in determining impairment should exercise particular caution in clearing low baseline performers on psychomotor speed, reaction time, cognitive flexibility, processing speed and/or executive function to return to play since above-average gains in performance on these domains are expected for these individuals. Conversely, clinicians who use the 95% of baseline approach should expect 8 to 10 point declines in performance on verbal memory, processing speed, and reasoning, in the absence of lingering cognitive deficits, and therefore should be cautious about holding athletes out of participation based on score deficiencies on these domains. Moreover, our results may prompt similar

investigations of the consistency of RCIs and test-retest score differences across different baseline score ranges for other commonly used computerized neurocognitive test batteries such as ImPACT and ANAM.

**Table 4.1.** Participation by sport

| **Sport** | **Number of Subjects** |
|---|---|
| Men's basketball | 6 |
| Women's basketball | 2 |
| Men's cheerleading | 4 |
| Women's cheerleading | 5 |
| Men's diving | 1 |
| Women's diving | 1 |
| Field hockey | 1 |
| Football | 20 |
| Gymnastics | 2 |
| Men's lacrosse | 13 |
| Women's lacrosse | 8 |
| Men's soccer | 16 |
| Women's soccer | 13 |
| Softball | 5 |
| Men's track and field | 2 |
| Women's track and field | 3 |
| Wrestling | 5 |

**Table 4.2.** Description of CNS Vital Signs subtests

| Subtest | Cognitive Tasks Assessed |
|---|---|
| Verbal Memory | • Verbal learning<br>• Memory for words<br>• Word recognition<br>• Immediate and delayed recall |
| Visual Memory | • Visual learning<br>• Memory for geometric shapes<br>• Geometric shape recognition<br>• Immediate and delayed recall |
| Finger Tapping | • Motor speed<br>• Fine motor control |
| Symbol Digit Coding | • Information processing speed<br>• Complex attention<br>• Visual-perceptual speed |
| Stroop Test | • Simple reaction time<br>• Complex reaction time<br>• Inhibition/disinhibition<br>• Frontal/executive skills<br>• Processing speed |
| Shifting Attention | • Executive function<br>• Rapid decision making<br>• Reaction time |
| Continuous Performance | • Sustained attention<br>• Choice reaction time<br>• Impulsivity |
| Non-verbal Reasoning | • Reasoning<br>• Reasoning recognition speed |

**Table 4.3.** Overall domain reliable change indices (RCIs) and RCIs for each quintile

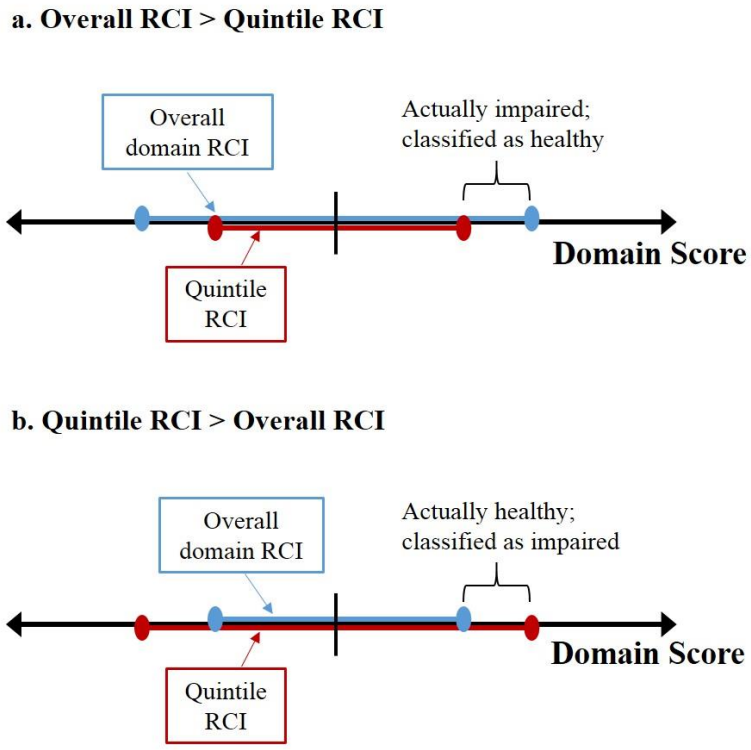
| CNS Vital Signs Domain | Reliable Change Indices | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | 80% | | | | 90% | | | | 95% | | | |
| | Entire Sample | Lowest | Middle | Highest | Entire Sample | Lowest | Middle | Highest | Entire Sample | Lowest | Middle | Highest |
| Verbal Memory | 25.80 | 25.52 | 23.93 | 22.58 | 33.10 | 32.75 | 30.70 | 28.98 | 39.44 | 39.02 | 36.58 | 34.53 |
| Visual Memory | 50.28 | 57.86 | 35.99 | 45.67 | 64.52 | 74.24 | 46.18 | 58.61 | 76.88 | 88.46 | 55.03 | 69.83 |
| Psychomotor Speed | 14.98 | 19.90 | 12.50 | 9.67 | 19.23 | 25.54 | 16.04 | 12.41 | 22.91 | 30.43 | 19.11 | 14.79 |
| Reaction Time | 14.86 | 17.77 | 13.78 | 11.38 | 19.06 | 22.80 | 17.68 | 14.61 | 22.71 | 27.17 | 21.06 | 17.40 |
| Cognitive Flexibility | 15.75 | 16.40 | 15.75 | 17.46 | 20.21 | 21.05 | 20.21 | 22.40 | 24.08 | 25.08 | 24.08 | 26.69 |
| Complex Attention | 29.76 | 29.97 | 36.01 | 18.42 | 38.19 | 38.46 | 46.21 | 23.64 | 45.50 | 45.82 | 55.06 | 28.16 |
| Processing Speed | 17.25 | 16.70 | 11.44 | 13.81 | 22.14 | 21.43 | 14.69 | 17.72 | 26.38 | 25.54 | 17.50 | 21.12 |
| Executive Functioning | 15.88 | 18.93 | 9.23 | 16.79 | 20.38 | 24.29 | 11.84 | 21.55 | 24.28 | 28.94 | 14.11 | 25.67 |
| Reasoning | 51.41 | 48.27 | 50.21 | 52.99 | 65.97 | 61.93 | 64.43 | 67.99 | 78.60 | 73.79 | 76.77 | 81.01 |
| NCI | 8.62 | 8.96 | 4.32 | 7.80 | 11.06 | 11.49 | 5.54 | 10.01 | 13.18 | 13.70 | 6.60 | 11.92 |

**Table 4.4.** Effect of time and quintile on CNS Vital Signs domain scores

| CNS Vital Signs Domain | | Mean (95% CI) Baseline | | Mean (95% CI) Retest | | N | F-value (P-value) Time main effect | F-value (P-value) Group main effect | F-value (P-value) Time* Group Interaction |
|---|---|---|---|---|---|---|---|---|---|
| Verbal Memory | Lowest | 78.90 | (76.64, 81.15) | 99.84 | (92.27, 107.42) | 20 | $F_{1, 65} = 0.00$ P= 0.949 | $F_{2,65} = 50.61^{a,b,c}$ [P< 0.001] | $F_{2, 65} = 22.03^{e}$ [P< 0.001] |
| | Middle | 105.71 | (103.70, 107.71) | 97.46 | (90.72, 104.20) | 24 | | | |
| | Highest | 121.24 | (119.28, 123.21) | 108.12 | (101.52, 114.72) | 26 | | | |
| Visual Memory | Lowest | 81.86 | (79.95, 83.76) | 75.76 | (59.47, 92.06) | 21 | $F_{1, 69} = 11.78$ [P= 0.001] | $F_{2, 69} = 14.30^{a,b,c}$ [P< 0.001] | $F_{2, 69} = 1.02$ [P= 0.367] |
| | Middle | 103.90 | (102.28, 105.52) | 85.03 | (71.17, 98.90) | 29 | | | |
| | Highest | 120.18 | (118.32, 122.04) | 99.05 | (83.12, 114.97) | 23 | | | |
| Psychomotor Speed | Lowest | 90.60 | (88.31, 92.89) | 104.45 | (99.97, 108.93) | 20 | $F_{1, 56} = 9.96$ [P= 0.003] | $F_{2, 56} = 91.73^{a,b,c}$ [P< 0.001] | $F_{2, 56} = 10.48^{d}$ [P< 0.001] |
| | Middle | 105.60 | (103.31, 107.89) | 108.15 | (103.67, 112.63) | 22 | | | |
| | Highest | 122.58 | (120.23, 124.93) | 120.21 | (115.62, 124.80) | 19 | | | |
| Reaction Time | Lowest | 85.46 | (83.23, 87.68) | 96.73 | (92.36, 101.09) | 23 | $F_{1, 68} = 7.46$ [P= 0.008] | $F_{2, 68} = 128.98^{a,b,c}$ [P< 0.001] | $F_{2, 68} = 7.37^{d}$ [P= 0.001] |
| | Middle | 104.59 | (102.65, 106.53) | 103.66 | (99.86, 107.43) | 23 | | | |
| | Highest | 118.70 | (116.36, 121.04) | 119.85 | (115.27, 124.43) | 21 | | | |
| Complex Attention | Lowest | 75.71 | (71.86, 79.57) | 77.95 | (66.41, 89.49) | 21 | $F_{1, 76} = 7.33$ [P= 0.008] | $F_{2, 76} = 33.28^{a,b,c}$ [P< 0.001] | $F_{2, 76} = 2.86$ [P= 0.063] |
| | Middle | 106.59 | (103.56, 109.62) | 93.38 | (84.31, 102.45) | 36 | | | |
| | Highest | 120.42 | (116.81, 124.02) | 108.46 | (97.66, 119.25) | 24 | | | |
| Cognitive Flexibility | Lowest | 81.71 | (79.53, 83.90) | 89.62 | (83.98, 95.26) | 22 | $F_{1, 71} = 0.45$ [P= 0.505] | $F_{2, 71} = 69.93^{a,b,c}$ [P< 0.001] | $F_{2, 71} = 8.45^{d}$ [P= 0.001] |
| | Middle | 102.93 | (101.04, 104.82) | 104.75 | (99.86, 109.64) | 24 | | | |
| | Highest | 115.56 | (113.56, 117.56) | 108.72 | (103.55, 113.89) | 25 | | | |
| Processing Speed | Lowest | 86.50 | (84.22, 88.78) | 99.32 | (95.27, 103.37) | 23 | $F_{1, 62} = 1.28$ [P= 0.262] | $F_{2, 62} = 105.34^{a,b,c}$ [P< 0.001] | $F_{2, 62} = 19.03^{d,e}$ [P< 0.001] |
| | Middle | 102.50 | (100.31, 104.69) | 102.21 | (98.33, 106.09) | 19 | | | |
| | Highest | 121.47 | (119.02, 123.93) | 113.58 | (109.22, 117.94) | 19 | | | |
| Executive Function | Lowest | 79.82 | (76.43, 83.21) | 89.77 | (84.55, 94.99) | 23 | $F_{1, 71} = 1.02$ [P= 0.317] | $F_{2, 71} = 58.90^{a,b,c}$ [P< 0.001] | $F_{2, 71} = 11.42^{d}$ [P< 0.001] |
| | Middle | 102.13 | (99.27, 104.99) | 103.74 | (99.34, 108.14) | 27 | | | |
| | Highest | 115.91 | (112.43, 119.38) | 108.57 | (103.23, 113.92) | 21 | | | |
| Reasoning | Lowest | 78.74 | (77.11, 80.37) | 75.07 | (59.76, 90.39) | 27 | $F_{1, 82} = 17.93$ [P< 0.001] | $F_{2, 82} = 8.46^{b}$ [P< 0.001] | $F_{2, 82} = 3.29^{e}$ [P= 0.042] |
| | Middle | 98.83 | (97.26, 100.40) | 78.17 | (63.40, 92.95) | 31 | | | |
| | Highest | 114.59 | (113.01, 116.16) | 83.55 | (68.78, 98.33) | 30 | | | |
| NCI | Lowest | 90.20 | (88.08, 92.32) | 103.9 | (94.74, 113.06) | 11 | $F_{1, 36} = 0.31$ [P= 0.581] | $F_{2, 36} = 10.60^{b,c}$ [P< 0.001] | $F_{2, 36} = 5.80$ [P= 0.007] |
| | Middle | 105.07 | (103.33, 106.80) | 101.2 | (93.72, 108.68) | 16 | | | |
| | Highest | 113.50 | (111.71, 115.29) | 107.714 | (99.97, 115.46) | 14 | | | |

Group main effects: [a] Middle quintile superior to lowest quintile; [b] Highest quintile superior to lowest quintile; [c] Highest quintile superior to middle quintile;
Interaction effects: [d] Retest superior to baseline for lowest quintile; [e] Baseline superior to retest for highest quintile

**Figure 4.1.** Misclassifications from different overall and quintile RCIs



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## Appendix A. Detailed Descriptions of CNS Vital Signs Subtests

*Visual Memory*

The verbal memory test assesses recognition memory for words. A total of 15 words are flashed on the screen, one at a time, for two seconds each. Those 15 words as well as 15 other words are then flashed on the screen in the same fashion in a random order, and the subject is tasked with identifying which words were part of the original 15 presented to him/her. This recall task is repeated a second time approximately 30 minutes later once the following seven other tests have been completed.

*Verbal Memory*

This test is identical to the verbal memory test except geometric figures are used in place of words. In addition, the delayed recall trial for this test occurs after *six* subsequent tests have been completed.

*Finger Tapping*

The finger tapping test measures motor speed. A subject is instructed to press the space bar with their right index finger as many times as possible in ten seconds, and the test is repeated two additional times for a total of three trials. The subject then completes the same three trials using his/her left index finger.

*Symbol Digit Coding*

The symbol digit coding test measures an individual's complex attention and information processing speed. A "key" showing the numbers 2 through 9 matched up

with different symbols is presented at the top of the screen, and a matrix of 8 symbols (identical to those in the key) with empty boxes beneath them is presented at the bottom of the screen. The subject is instructed to enter the number associated with each symbol in the matrix in a serial fashion, moving from left to right, as quickly but as accurately as possible. Once the subject has correctly matched up numbers to the first 8 symbols, a new matrix with empty boxes appears, and he/she continues to match numbers with the symbols in the same manner until 120 seconds has expired.

*Stroop Test*

The Stroop Test is a measure of reaction time, complex attention, and cognitive flexibility which is composed of the different parts. In the first part of the test, the words *red*, *yellow*, *blue*, and *green* are presented randomly on the screen in black text, and the subject is instructed to press the space bar as soon as they see a word. In the second part of the test, the words *red*, *yellow*, *blue*, and *green* are again presented randomly on the screen, but this time in a random text color (chosen from those four options); the subject is instructed to press the space bar only when the text color matches the word. The third part of the test is set up identically to the second part, however, this time the subject is instructed to press the space bar only when the text color does *not* match the word.

*Shifting Attention Test*

The shifting attention test measures both reaction time and executive function. In this test, three figures appear on the screen, one at the top, and two on the bottom of the screen. The figure at the top is either a square or circle that is red or blue in color. The

figures on the bottom of the screen are a circle and a square, one of which is red and the other of which is blue, decided at random. The subject must match one of the bottom figures to the top figure by either shape or color.

*Non-Verbal Reasoning Test*

The non-verbal reasoning test measures an individual's ability to understand visual-abstract relationships. Fifteen visual analogies are presented to the subject one at a time, and the subject must choose the figure that best completes the analogy.

*Continuous Performance Test*

The continuous performance test measures sustained attention. Different letters are randomly flashed on the screen for five minutes, and the subject must press the space bar each time the letter "B" appears.