QUANTIFYING COGNITIVE DEFICITS IN THE HUMAN IMMUNODEFICIENCY VIRUS: A RASCH ANALYSIS

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ABSTRACT

With a prevalence rate of 30-60%, cognitive deficits are one of the most predominant comorbidities in people with the Human Immunodeficiency Virus\(^1\). As a result it is common for patients to present themselves at the clinic reporting problems with their cognition, however these perceived deficits don’t always agree with what their screening and neuropsychological tests are reporting\(^2\). Patient reported outcomes are poorly understood, and the literature is inconclusive about their clinical significance\(^3\),\(^4\). Some studies conclude they are simply a reflection of a patient’s affective state instead of a true reflection of a cognitive deficit.\(^3\) Understanding this source of information is crucial in a clinical setting where there are an increasing number of patients reporting problems, and neuropsychological testing is costly and time consuming. Therefore the objective of this study was to contribute evidence that the latent construct of cognitive ability does include items from both the patient perspective and neuropsychological test results. More specifically, the goal was to estimate the extent to which items of patient reported cognitive difficulties and items from direct measures of cognition form a unidimensional construct.

Using Rasch Measurement Theory, a measure was created containing a total of 26-items, which incorporate both sources of information; that from the patient and that from neuropsychological testing. The measure covers a reasonable spectrum of difficulty, with an excess of items too easy for this sample, and the easiest and hardest items of the measure being items of perceived deficit. This provides preliminary evidence that combining these two sources of information is possible, and with further validation, could allow clinicians to better understand the meaning of perceived deficits.
ABRÉGÉ

Avec un prévalence de 30 à 60 %, des déficits cognitifs sont parmi les comorbidités les plus importantes chez les personnes atteintes du Virus de l'immunodéficience humaine (VIH)\(^1\). En clinique, il est fréquent que les patients se plaignent des problèmes cognitifs, bien que les résultats de leurs examens neuropsychologiques ne confirment pas toujours ces plaintes\(^2\). Les déterminants de ces plaintes sont mal comprises, et la littérature quant à leur importance clinique n'est pas concluante\(^3,4\); certaines études concluent qu'elles sont le reflet d'un état affectif et non pas un vrai reflet d'un déficit cognitif\(^5\). Une meilleure compréhension de cette source d'information est essentielle dans un environnement clinique où ces plaintes sont de plus en plus fréquentes et les examens neuropsychologiques sont coûteux et long à administrer. L'objectif de cette étude était donc de démontrer qu’un concept latent de capacités cognitives peut inclure à la fois des éléments de la perspective du patient en plus des tests neuropsychologiques. Plus précisément, l'objectif était d’estimer dans quelle mesure les plaintes cognitives et les mesures directes de la cognition forment un concept unidimensionnel.

En utilisant la théorie de mesure Rasch, une mesure a été créée contenant un total de 26 questions intégrant les deux sources d'information (plaintes du patient et tests cognitifs). La mesure couvre un spectre de difficulté raisonnable, avec un excès d'items trop faciles pour cet échantillon ; et les questions plus faciles et les plus difficiles de la mesure sont des questions du patient. Ceci constitue une preuve préliminaire qu'il est possible de combiner ces deux sources d'information et, avec une validation additionnelle, cette méthode pourrait permettre aux cliniciens de mieux comprendre ce que signifie les déficits rapportés par le patient.
ACKNOWLEDGMENTS

First and foremost I would like to thank my supervisor, Dr. Nancy Mayo. Without her patience, support, and genuine interest in research, I would have never pursued a Master’s degree. She has provided me with so much guidance on my path to becoming a clinician, and I will remember the invaluable lessons she taught me as I go on to pursue my career. A special thank you is also required for my committee members, Dr. Lesley Fellows, and Dr. Marie-Josee Brouillette, who have contributed much intelligence and expertise to my thesis work, as well as allow me to understand the importance of putting the patient first.

I would also like to thank Dr. Lois Finch, who has counseled me since my first days at the Division. Without her encouragement, I would have never learned the complicated world of Rasch.

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PREFACE

Author’s contributions
The project began in Dr. Lesley Fellows laboratory, in which she prepared the protocol, which was then approved by the McGill University Health Center’s Research Institute Ethics Committee. Data was collected and entered by the research assistants in Dr. Fellow’s laboratory. Additional data entry was completed by Lisa Palladini. A thesis protocol was then prepared by Lisa Palladini and approved by the thesis supervisor Dr. Nancy Mayo. Data extraction and analyses were completed by Lisa Palladini and under the supervision of Dr. Nancy Mayo and Dr. Lesley Fellows, with additional assistance given by Dr. Marie Josee Brouillette. Assistance with statistical analyses and interpretation was provided by Dr. Lois Finch and Dr. Nancy Mayo. The thesis was written by Lisa Palladini. With regards to the manuscript, it was written by Lisa Palladini, with the help of Dr. Lois Finch and Dr. Nancy Mayo. We admit to duplications within this thesis, and that they are inevitable.

Organization of thesis
The objective of this thesis is to estimate the extent to which items of patient and care partner reported cognitive difficulties and items from direct measures of cognition form a unidimensional construct. The hypothesis is that a latent construct, labeled in this thesis as “cognitive ability” will emerge from these items and will include items from all three sources.

Chapter 1 provides an overview of the Human Immunodeficiency Virus (HIV), including information on aetiology, course of disease, epidemiological features of the disease and disease severity.

Chapter 2 provides a description of one of the most prevalent comorbidities found in HIV, that of cognitive deficits.
Chapter 3 provides an overview on the measurement strategies chosen by the field of HIV to measure these cognitive deficits. A table outlining all the screening tests in current use is provided.

Chapter 4 is an introduction to Modern Psychometric Methods, and Rasch Measurement Theory (RMT). It explains the differences between Classical Test Theory and Modern Test Theory, and how using RMT can help solve some of the issues in measurement seen in the field of HIV.

Chapter 5 is an introductory chapter to the first manuscript and provides the rationale and objective.

Chapter 6 is the manuscript. The study’s objective is to estimate the extent to which items of patient and care partner reported cognitive difficulties and items from direct measures of cognition form a unidimensional construct.

Chapter 7 is the concluding chapter. The appendices also include additional information pertaining to item selection, and a construct map.
CHAPTER 1
An Overview of Human Immunodeficiency Virus

1.1 Human Immunodeficiency Virus
The Human Immunodeficiency Virus (HIV) is a retrovirus that incorporates itself into the host cell and causes a systemic infection in the body\(^5\). The continual replication of the virus leads to a gradual depletion of the immune system. When the virus was first discovered, the immune system depletion lead to Acquired Immunodeficiency Syndrome (AIDS) and death by opportunistic infections in 1-3 years\(^6,7\). However due to the new drug regimens, disease severity has decreased and patients now live 13 years longer on average than without medications \(^8\). There are currently 1-2 million people living with the virus in North America\(^9\), with new cases being upwards of 40,000 per year\(^10\). The most common subtype of HIV in North America is HIV-1 clade B, which in the United States of America represents 98% of infections \(^5\).

1.2 Aetiology
The most common mode of transmission of HIV is through sexual intercourse, which accounts for over two thirds of HIV infections worldwide\(^11\). Infected vaginal or penile secretions make contact with a mucous membrane where the virus enters the body and selectively infect CD4 expressing lymphocytes, monocytes and macrophages cells. The virus inserts its viral RNA into the host cell DNA \(^5\), and directs the host cell to produce the viruses’ own enzymes. The virus then buds from the host cell, ready to continuously and preferentially infect CD4 expressing cells, leading to an eventual deterioration of the body’s white blood cell count and consequently the immune system\(^12\).

Other common modes of transmission are through contact with infected blood and through the reuse of stained syringes by intravenous drug users\(^13\). As HIV can survive for up to two hours outside of the body, it is possible for a small amount of blood to remain on the syringe once used, ready to infect\(^12\).
A third mode of transmission, though not common to North America due to the use of antiretroviral medication\textsuperscript{14}, is known as “vertical transmission” or mother-to-child transmission. A mother can pass the virus onto her newborn child through pregnancy, during delivery or through breastfeeding\textsuperscript{12}. 90\% of children currently living with HIV are from Sub Saharan Africa and have been infected this way\textsuperscript{12}.

1.3 Course of HIV

The course of HIV occurs in 3 stages, with variation as to how long a person spends in each stage (see Figure 1.1)\textsuperscript{15}. \textit{Acute infection} occurs after primary infection, in which the person does not know they have been infected, and would still test negatively for anti-HIV antibodies. This stage lasts from 6-12 weeks in which people typically experience flu-like symptoms but are otherwise asymptomatic, and large amounts of the virus are being replicated throughout the body. \textit{Chronic asymptomatic infection} is when the body makes the initial immune response. The virus continues to replicate in the body at low levels. This period could last a couple of months to several years. The immune system tries to prevent the infection, which leads to a high turnover of immune cells (CD4+ and CD8+ T cells), and a gradual decrease in the body’s ability to fight off infection. The final stage is \textit{clinical AIDS}, which is defined as a T-cell count below 200 cells/uL, and/or the presentation of an AIDS-defining illness (Figure 1.2)\textsuperscript{16}. The immune system at this stage is very impaired, and patients are prone to contracting opportunistic infections. Without treatment, a patient with AIDS can live up to 3 years, with the life expectancy dropping to 1 year once diagnosed with an opportunistic infection\textsuperscript{6, 7}.

1.4 Disease severity

The best predictor of progression to AIDS is CD4 cell count, as it is a direct indication of immune functioning\textsuperscript{17}. It is also the benchmark used by clinicians to measure when a patient should start treatment\textsuperscript{17}. It correlates with the risk to develop opportunistic infections\textsuperscript{5}, and gives an indication to how much the disease has progressed. Patients should begin treatment when their CD4 cell count is <350/mm\textsuperscript{3}, and a T cell count lower than 200 cells/uL indicates entry into the clinical AIDS stage.

Plasma viral load, which is defined as “…the number of HIV RNA copies per millimeter of blood plasma”, is the most important gauge of treatment effectiveness\textsuperscript{17, 18}. Patients should be
tested for their viral load before the start of treatment, and shortly after initiation of a treatment\textsuperscript{17}. Viral load is a test that indicates the amount of viral replication in the body, and is suitable for measuring the progression of the disease\textsuperscript{17}.

With the advent of combination antiretroviral therapies (cART) in the late 1990’s\textsuperscript{19}, the disease is now termed a “chronic illness”, as the prognosis of these patients is excellent. Patients who adhere properly to their medications maintain plasma viral loads of HIV at an undetectable level. Consequently this reduces the amount of CD4 cell loss, extends life, reduces the severity of opportunistic infections, and most importantly decreases transmission. When the virus was first discovered, the immune system depletion lead to Acquired Immunodeficiency Syndrome (AIDS) and death by opportunistic infections in 1-3 years\textsuperscript{6,7}, however due to the new drug regimens disease severity has decreased, and patients now live 13 years longer\textsuperscript{8}.

1.5 Epidemiologic Features of HIV
HIV is an epidemic that affects approximately 34 million people worldwide\textsuperscript{12}. The area most affected by the disease is Sub Sahara Africa; less than 10% of the world lives in this region, yet it houses up to 67% of all those affected by HIV in the world\textsuperscript{5,14}. This area has an annual incidence of 1.9 million and prevalence in adults of approximately 5%. Other areas of the world which are most affected are Latin America, Eastern Europe and Central Asia, where the prevalence is 0.9%.

North America has an incidence of approximately 58 000 people, and a prevalence at 0.6%. The populations most affected by HIV in North America are men who have sex with men, and intravenous drug users\textsuperscript{14}. Ethnic minorities are also at an incredibly high risk for infection due to poverty and lack of education\textsuperscript{20}, and studies have shown that they are not benefiting as much as others from antiretroviral therapies\textsuperscript{14}. Women represent half of all people infected with HIV worldwide, however this varies by region, with the rate of infection for women being higher than that for men only in Sub Saharan Africa at 61%\textsuperscript{5,14}.

The rate of incidence and death due to AIDS-related illnesses has decreased by 21% since 2005 in developed countries\textsuperscript{5}. The latter is due to access to antiretroviral treatments.
HIV is also classified into subtypes, which help at identifying genetic variants of the disease. Western countries are affected primarily by HIV-1 clade B, which represents 10% of the infections worldwide (see Figure 1.3)\(^9\). The association between disease progression and HIV subtype remains unclear \(^9\).

**1.6 Medical Treatment**

As previously mentioned, since the advent of cART, HIV is now deemed a chronic illness. In addition to extending life expectancy, these medications also reduce the likelihood of transmission of the virus; either through vertical transmission or person-person transmission\(^21\). The rates of infection have been decreasing since 2009 \(^9\).

A full discussion on the classes of antiretroviral therapies is beyond the scope of this thesis, but refer to Figure 1.4 for an overview on the life cycle of HIV and potential areas for drug targeting. There are 6 potential classes of antiretroviral medication, each with the capability to intercept the replication of the virus at different points of the life cycle. cART treatments consists of 3 medications, with at least 2 medications originating from different classes. The latter is to prevent drug resistance, as this is a common problem \(^9\).

The US Department of Health and Human Services recommends that patients begin treatment when their CD4 count is \(<350/mm^3\).

A disadvantage to the drug regimens is that they are very complicated to maintain\(^22\). Adherence is further complicated by the prevalence of psychosocial problems typically seen with HIV populations, such as drug abuse. Treatment non-adherence reduces effectiveness \(^10\), and can lead to drug resistance\(^6\). When starting new medications, surveillance needs to be maintained for adherence and with careful consideration to drug toxicity and side effects (i.e. hyperlipidemia, insulin resistance and glucose intolerance, to name a few)\(^6\).
1.7 Rehabilitation
HIV is new to the field of rehabilitation. However with a longer life span due to the drug regimens, patients are at a higher risk for disability.\textsuperscript{23} Formation of the \textit{Canadian Working Group on HIV and Rehabilitation} in 1998 is proof that HIV research in rehabilitation is becoming essential. From the outset, this group acknowledged the lack of information for rehabilitative professionals in treating patients with HIV. Now, the field of rehabilitation is targeting a range of disabilities such as pain and function of the cardiovascular systems, to self care and interpersonal relationships.\textsuperscript{24} The focus is now aimed at developing a multidisciplinary approach to chronic illness patient management, and maintenance of high health-related quality of life throughout their disease course.\textsuperscript{10,23}

1.8 cART era
Despite these promising results from cART, comorbidities in this population has increased. People with HIV are at twice the risk of myocardial infarction, and 3 times the risk of osteoporosis.\textsuperscript{25,26} Another common comorbidity is neurocognitive deficits, with a prevalence rate ranging from 30-60\%.\textsuperscript{1} Of note is that patients still have symptoms of cognitive deficit despite being controlled on their medication, and the presence of a neurological disorder is a significant predictor of AIDS mortality.\textsuperscript{27}

The material presented in this chapter provides a brief overview of HIV, and the complexity of treatment. In the next chapter an overview of one of the most predominant comorbidities found in patients with HIV will be presented.
Figure 1.1 Disease Course of HIV

![Disease Course of HIV](image)

Taken from *Accelerated immune senescence and HIV-1 infection*\(^{28}\)

Figure 1.2 AIDS Defining Illnesses

**Box 1. Definition of AIDS**

AIDS is defined as a CD4\(^+\) T-lymphocyte count below 200 cells/\(\mu\)L of blood with or without the presence of an AIDS-defining illness, including the following:

- HIV-associated dementia
- Opportunistic infections such as *Pneumocystis jiroveci* pneumonia, Kaposi sarcoma, *Mycobacterium avium*, and tuberculosis; and neurologic disorders including cryptococcal meningitis, toxoplasmic encephalitis, progressive multifocal leukoencephalopathy, primary CNS lymphoma, and cytomegalovirus encephalitis.
- HIV wasting syndrome

Taken from *HIV Infection of the Central Nervous System: Clinical Features and Neuropathogenesis*\(^{16}\)
Figure 1.3 Worldwide Distribution of HIV by clade.

Taken from HIV InSite®
Figure 1.4 HIV Life Cycle and Potential Targets for Antiretroviral Therapies.

Taken from: Human Immunodeficiency Virus-associated Neurocognitive Disorders: Mind the Gap
CHAPTER 2
Cognitive Disorders Found in HIV

2.1 Defining HIV-Associated Neurocognitive Disorders

In 2008, an expert panel convened in Frascotti, Italy and created a new definition of HIV-Associated Neurocognitive Disorder (HAND) (Figure 2.1). This new definition, known as the Frascotti definition, includes 3 categories: HIV-associated asymptomatic neurocognitive impairment (AND), HIV-1 associated mild neurocognitive disorder (MND), and HIV-1-associated dementia. \(^{29,30}\) **HIV-Associated Dementia** is defined by performance of at least 2.0 standard deviations below the norm on two cognitive ability domains, with marked interference in work and social function. **HIV-associated mild neurocognitive disorder** is defined by performance of at least 1.0 standard deviation below the norm in at least two cognitive ability domains with “...mild interference in work and social function as indicated by self-report or observation.” Lastly **HIV-associated asymptomatic neurocognitive impairment**, a new disease category created in the 2008 definition, is also defined by performance of 1 standard deviation below the norm on two ability domains, with no interference on daily functioning.

In comparison to the previous definitions published by the American Academy of Neurology in 1991, the new classification unambiguously defines deficits required for each of the categories. Since the advent of cART, the number of patients developing dementia has decreased significantly (fallen from approximately 20% to 5% of patients), however epidemiological data has shown that several individuals show impairment in neuropsychological testing without experiencing functioning decline; a new diagnostic category was therefore created to identify this group of interest, asymptomatic neurocognitive impairment. \(^{29}\)

Currently 30-60% of patients with neurological disorders are being classified in the mild neurocognitive disorder or asymptomatic categories. \(^{1,19}\) Moreover many studies are reporting a high frequency of self-reported complaints. Using memory loss as an example, in a population based study of HIV patients, self-reported complaints ranged from 20-70% \(^{19}\).
2.2 Aetiology
The exact mechanism of pathophysiology leading to mild neurological deficits is widely debated in the literature, however several theories have been suggested\textsuperscript{5, 19}.

During the time of HIV infection, the blood brain barrier is structurally altered and cellular uptake is not as highly regulated. The virus preferentially infects, or stimulates through the immune system, CD4 expressing macrophages and microglia. The latter then are able to cross the blood brain barrier\textsuperscript{27}, otherwise known as the “Trojan Horse” hypothesis\textsuperscript{19, 31}, where the virus enters the central nervous system “hidden” in these specific cells. The virus does not infect neurons, but is it thought that non-specific neuronal cell death occurs indirectly through the synthesis and exposure of molecules produced by these HIV-infected cells\textsuperscript{16, 32}. Ongoing replication in the central nervous system is then believed to occur due to poor penetration of several antiretroviral agents\textsuperscript{19}.

There are other factors that contribute to neurological deficits. Comorbid conditions such as substance abuse and Hepatitis C contribute to the extensive inflammatory processes in the body\textsuperscript{16}. Additionally, it is currently debated in the literature whether the cART regimens have an additional neurotoxic effect on the brain, as different medications have varying levels of central nervous system penetration. Some studies report that initiating the regimen improves neuropsychological functioning\textsuperscript{1}, while others have demonstrated that even after 5 years on the regimens, no reversal of neuropsychological deficit was observed\textsuperscript{19}.

Hence neuronal cell injury results from a complex process involving both direct and indirect pathways, such as virus factors and inflammatory host factors, as well as probable drug effects on the brain\textsuperscript{33}. These factors all contribute to non-specific neuronal cell death.

2.3 Clinical Characteristics of HAND
HIV causes neuronal injury in both the sub-cortical areas and cortex. More specifically this includes the pre-frontal and frontal cortex, the hippocampus, the basal ganglia, the brainstem, and their respective white matter tracts\textsuperscript{19, 34}. The common problems seen with such generalized brain lesions include executive dysfunction problems, working memory difficulties, motor
problems (e.g. bradykinesia and hand agility), memory impairment, attention problems, and gait disturbances. The medications have changed the temporal progression of neurocognitive disorders, as patients now have a slowly progressing form of neurocognitive deficit instead of a rapidly progressing dementia. Moreover, the HIV populations in the developed world is aging and therefore more susceptible to neurological illnesses.

Imaging is often used to rule out other central nervous system opportunistic infections. These studies have demonstrated white matter abnormalities, volume loss, and brain atrophy. Currently there are no biomarkers or tests that are being used in clinical practice to diagnose HAND.

Of particular importance is the fact that once diagnosed with a neurological disorder, patients have a diminished chance of survival regardless of whether or not they are receiving cART. Even a slight decline in cognitive capacity has been shown to affect important aspects of daily life, such as medication adherence. In patients with decline, medication regimens are 2.3 times less likely to not be properly adhered to. Poor adherence puts patients at risk for decreasing their positive clinical outcomes with the disease, increase their chances of co-infection, and increase their chance of drug resistance. Decline in cognitive capacity has also been shown to decrease health related quality of life, as patients have a hard time participating in basic activities of daily living, such as grocery shopping and cooking. Patients are also less capable of using effective coping strategies due to their decline, making efforts to deal with their illness very burdensome. Finally, decline in cognitive capacity has been shown to affect patient employment. In a study by Gorman et al., it was reported that after being diagnosed with a cognitive deficit, 40% of patients became continuously unemployed.

2.4 Our definition
As HIV is such a complex disease, multidisciplinary research is necessary. Unfortunately the terminology used to describe cognition varies across disciplines, and is used inconsistently in the literature. The first issue leading to the complication in vocabulary is negative vs. positive wording. An example is in the field of psychology, which takes a very negative approach towards cognition and commonly refers to “impairments” and “deficits”. In contrast, the field of
mathematics, education, and rehabilitation all take a positive approach, and the word “ability” or “function” is used. The second issue, as demonstrated by the Frascotti definition of HAND, is that clinically there are multiple sources of information on cognition i.e. information obtained from the patient, caregiver, or through neuropsychological testing.

Therefore, for the remainder of the thesis we have created a definition that follows the Frascotti guidelines, and allows for consistent vocabulary usage across several disciplines (See Figure 2.2). A patient’s cognitive “deficit or ability” is comprised of two parts: what can be measured through neuropsychological testing, which will be labeled “measured deficits or ability”, and what is reported by the patient, which will be labeled “perceived deficit or ability”. To put the latter in context, what is reported by the patient is commonly referred to by the Federal Drug Administration as “patient-reported outcomes” (PROs), and are deemed an indicator of a “patient’s quality of life”.

In this chapter we have tried to provide a brief overview of one of the most common comorbidities found in patients with HIV, that of cognitive deficits. In the next chapter we will provide an overview of how these deficits are measured in the literature.
Figure 2.1 Current HIV-Associated Neurocognitive Disorders Definition

<table>
<thead>
<tr>
<th>Table</th>
<th>Revised research criteria for HIV-associated neurocognitive disorders (HAND) modified from HIV Neurobehavioral Research Center criteria34</th>
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</table>
| HIV-associated asymptomatic neurocognitive impairment (ANI)* | 1. Acquired impairment in cognitive functioning, involving at least two ability domains, documented by performance of at least 1.0 SD below the mean for age-education-appropriate norms on standardized neuropsychological tests. The neuropsychological assessment must survey at least the following abilities: verbal/language, attention/working memory, abstraction/executive, memory (learning, recall), speed of information processing, sensory-perceptual, motor skills.  
2. The cognitive impairment does not interfere with everyday functioning.  
3. The cognitive impairment does not meet criteria for delirium or dementia.  
4. There is no evidence of another preexisting cause for the ANI.* |

*If there is a prior diagnosis of ANI, but currently the individual does not meet criteria, the diagnosis of ANI in remission can be made.

HIV-1-associated mild neurocognitive disorder (MND)*

1. Acquired impairment in cognitive functioning, involving at least two ability domains, documented by performance of at least 1.0 SD below the mean for age-education-appropriate norms on standardized neuropsychological tests. The neuropsychological assessment must survey at least the following abilities: verbal/language, attention/working memory, abstraction/executive, memory (learning, recall), speed of information processing, sensory-perceptual, motor skills.  
Typically, this would correspond to an MSK scale stage of 0.5 to 1.0.  
2. The cognitive impairment produces at least mild interference in daily functioning (at least one of the following):  
   a) Self-report of reduced mental acuity, inefficiency in work, homemaking, or social functioning  
   b) Observation by knowledgeable others that the individual has undergone at least mild decline in mental acuity with resultant inefficiency in work, homemaking, or social functioning.  
3. The cognitive impairment does not meet criteria for delirium or dementia.  
4. There is no evidence of another preexisting cause for the MND.*

*If there is a prior diagnosis of MND, but currently the individual does not meet criteria, the diagnosis of MND in remission can be made.

HIV-1-associated dementia (HAD)*

1. Marked acquired impairment in cognitive functioning, involving at least two ability domains; typically the impairment is in multiple domains, especially in learning of new information, slowed information processing, and defective attention/concentration. The cognitive impairment must be ascertained by neuropsychological testing with at least two domains 2 SD or greater than demographically corrected means. (Note that where neuropsychological testing is not available, standard neurological evaluation and simple bedside testing may be used, but this should be done as indicated in algorithm, see below).  
Typically, this would correspond to an MSK scale stage of 2.0 or greater.  
2. The cognitive impairment produces marked interference with day-to-day functioning (work, home life, social activities)  
3. The pattern of cognitive impairment does not meet criteria for delirium (e.g., clouding of consciousness is not a prominent feature), or, if delirium is present, criteria for dementia need to have been met on a prior examination when delirium was not present.  
4. There is no evidence of another preexisting cause for the dementia (e.g., other CNS infections, CNS neoplasm, cerebrovascular disease, preexisting neurologic disease, or severe substance abuse compatible with CNS disorder)*

*If there is a prior diagnosis of HAD, but currently the individual does not meet criteria, the diagnosis of HAD in remission can be made.

If the individual with suspected HAD also satisfies criteria for a severe episode of major depression with significant functional limitations or psychotic features, or substance dependence, the diagnosis of HAD should be deferred to a subsequent examination conducted at a time when the major depression has remitted or at least 1 month after cessation of substance use. Note that the consensus was that even when major depression and HAD occurred together, there is little evidence that pseudodementia exists and the cognitive deficits do not generally improve with treatment of depression.

Taken from *Updated Research Nosology for HIV-associated Neurocognitive Disorders*30
Figure 2.2 Our Definition of Cognitive Ability/Deficit

Cognitive Ability/Deficit

- Directly Measured using Neuropsychological Tests
  - Measured Deficits
- Patient Reported
  - Perceived Deficits
CHAPTER 3

Overview of Neuropsychological Measures and Cognitive Assessment in HIV

3.1 The Gold Standard
In accordance with the definitions in section 2.1, a proper research diagnosis of HAND has 2 requirements: a decline in cognitive ability, and a decline in daily function\(^{30}\). To satisfy the first requirement, regardless of the category (*HIV-Dementia, Mild Neurocognitive Impairment*, or *Asymptomatic Neurocognitive Impairment*) patients must be tested using a “…performance based neurocognitive battery…” in 5 areas of cognition that are commonly affected by HIV (memory, attention, executive functioning, visuo-perception, speed of processing, speech and language)\(^{33}\). There are many standardized neuropsychological tests that fulfill these requirements\(^{33}\). However, a decline in daily activities and functional impact of this decline, is more difficult to quantify. As a result, there is no agreed upon measure to estimate functional deficit in the literature.

3.2 Screening Measures for Measured Deficits
As several domains of cognition need to be assessed, a full neuropsychological battery can take 2-4 hours to administer. The length of the battery can also be frustrating and discouraging for patients if they are continuously asked to do tasks that they do not understand, or are beyond their level of capacity\(^{40}\). Additionally, patients experiencing fatigue and pain find it hard to sit through long tests, creating test anxiety\(^{40}\). These tests also require trained professionals to administer and interpret them, which may not be feasible in all clinical settings.

As a result of the growing number of patients experiencing difficulties, and the lack of resources to perform a full battery of tests on every patient, screening measures were created to alert clinicians as to which patients are at a high risk for cognitive deficit. There are several generic as well as HIV specific cognitive screening tests available (see Table 3.1), but should all be used with caution. An example of one such measure is the HIV-dementia scale, which was created in the pre-cART era. While being sensitive to detecting HIV related dementia, it has demonstrated insensitivity to detecting minor cognitive deficits\(^{41-43}\). Additionally, the well-known and widely
used Mini Mental State Examination does not adequately measure sub-cortical deficits as it is more suitable for cortical deficits; of which HIV patients have both types. Table 3.1 summarizes the current screening tests used in the literature.

There is currently no consensus in the literature for how often asymptomatic patients should be screened, albeit the evidence that these patients develop more severe cognitive deficits. The only known group to properly define their screening methods is the European AIDS Clinical Society. Their most recent guidelines suggest asking the following 3 questions:

“1. Do you experience frequent memory loss (e.g. do you forget the occurrence of special events even the more recent ones, appointments, etc.)?

2. Do you feel that you are slower when reasoning, planning activities, or solving problems?

3. Do you have difficulties paying attention (e.g. to a conversation, a book, or a movie)?

with the following response options: “a) never, b) hardly ever, or c)yes, definitely.” If a patient is to answer “yes, definitely” to any of the questions, it is considered “abnormal”. A repetition of the questions is required, either after 2 years, or every 6 months depending on their neuropsychological test results.

3.3 Measures for Perceived Deficits

Including perceived deficits in the definition of HAND implies that it is measurable, yet many clinicians do not trust the reliability of self-reported complaints as there are so many factors involved when completing a questionnaire such as mood, and education. There are also many types of patient reporters, an example being patients who are in denial about their disease, and may under report actual deficits, or simply having un-reliable memories or recollections. Many patients also have a tendency to distort self-reports in order to appear more favorably, a phenomenon known as ‘social desirability’. Also, due to the cortical damage typically seen in HIV, there are patients who have a lack of awareness of their cognitive deficit labeled “anosognosics”. Finally, studies have shown that HIV can lead to mood disturbances such as
depression, as a direct and indirect result of the disease. Depression is well-known to be associated with cognitive decline and a depressed mood can increase the number of cognitive complaints, otherwise known as “over-reporters.” A review of the literature shows that there is a lack of agreement in the scientific community as to which indices are optimal for measuring patient reported outcomes, especially in light of all the patient factors involved in answering these sorts of questions.

Including perceived deficits in the HANDs definitions would also imply that they have clinical significance, yet the effort made by researchers to bridge the gap between perceived deficits and measured deficits is confusing and lacks consensus. Two points of view have emerged in the literature. The first is illustrated in a study by Moore et al. Neuropsychological tests were administered to 92 symptomatic HIV patients to see the association of these tests to perceived deficits. They concluded that complaints were highly associated to endorsement of negative affect items on the Beck Depression Inventory and Hamilton Depression and anxiety scales, but were not associated with neuropsychological testing. These results, where poor affect is seen to be directly associated with cognitive complaints, have been replicated many times in the literature using different measures of cognitive capacity and patient reported outcomes. These researchers believe that there is little validity in a patient’s self-report they have no clinical significance in terms of measured cognitive ability.

The second point of view is demonstrated in a study by Carter et al. Researchers were able to show, using structural equation modeling, that cognitive complaints were the best predictor of cognitive ability, independently of mood and medical symptoms. Although causality cannot be inferred from the latter study, it demonstrates that a relationship may exist between ability and complaints. Similar findings have been demonstrated elsewhere. As with other patient reported outcomes such as fatigue, mood, and pain, there may be no better method of symptom estimation than to ask the patient directly. The differing points of view on this matter leads to confusion as to the relevance of complaints in measuring cognitive ability. Additionally, studies have used different patient reported outcomes, and have had heterogeneous samples making comparison and generalizability between studies difficult. Table 3.2 summarizes the measures of perceived deficit being used in the literature.
Hence, though quick and inexpensive, PROs for cognitive deficits are not commonly used. The latter is due to lack of normative data, the unknown clinical relevance of this information, and the complexity of reporting a deficit.

3.4 The need for a proper screening method
That there are no measures that aim to estimate change in both measured and perceived deficits over time, however it would be logical to combine the two as both are undoubtedly important in measuring the construct of cognitive ability. In order to do this, a measure must be created in which both sources of information are considered. This measure must also include a wide spectrum of item difficulties, but remain sensitive enough to detecting minor declines in cognitive functioning \(^{41}\), especially in high functioning individuals as this group may benefit the most from intervention. Additionally, due to the complex nature of measurement in this population owing to a wide range of clinical manifestations (e.g. over-reporters, anosognosics) the necessity of an individual approach to cognitive testing is evident \(^{29,51}\).

This chapter has provided a brief overview of the method by which cognition is measured in the field of HIV. The problems encountered with generic and HIV specific screening tests was summarized, as well as the appreciation of the potential importance of patient reported deficits. It can be concluded from the literature that there is a need for a screening test that includes multiple sources of information with a wide range of item difficulties, and methods that would provide a solution for this complex challenge. In the next chapter we provide an overview of measurement.
Table 3.1 - Summary of Measures for Measured Deficits used in HIV

<table>
<thead>
<tr>
<th>Type of Measure</th>
<th>Screening test</th>
<th>Time needed to complete</th>
<th>Strengths</th>
<th>Limitations</th>
<th>References</th>
</tr>
</thead>
<tbody>
<tr>
<td>Generic, for mild cognitive impairment</td>
<td>Mini Mental State Examination</td>
<td>10 minutes</td>
<td>Most widely used test to screen for cognitive impairment</td>
<td>Detects cortical impairments (such as those found in Alzheimer’s disease), therefore not appropriate in HIV</td>
<td>(Schouten, 2011) 52</td>
</tr>
<tr>
<td>HIV Specific</td>
<td>HIV dementia scale</td>
<td>10 minutes</td>
<td>Created to assess dementia specific to HIV populations</td>
<td>The ability to detect mild cognitive impairment questionable, certain level of literacy and language comprehension required therefore limiting its’ use.</td>
<td>(Schouten, 2011) 52</td>
</tr>
<tr>
<td>HIV specific</td>
<td>Mental alteration test</td>
<td>1 min</td>
<td>Can be used in the visually impaired, and those with trouble holding a pen and paper</td>
<td>Psychometric properties based on MMSE scores</td>
<td>(Salib, 2002) 53, (Jones et al, 1993) 54</td>
</tr>
<tr>
<td>HIV Specific</td>
<td>International HIV Dementia Scale</td>
<td>5 minutes</td>
<td>Validated to be used internationally</td>
<td>The ability to detect mild cognitive impairment questionable</td>
<td>(Valcour, 2011) 55, (Sacktor et al., 2005) 56</td>
</tr>
<tr>
<td>Generic, but made HIV specific</td>
<td>CogState</td>
<td>Not known</td>
<td>Created in post-cART era, computerized</td>
<td>Commercial, software is expensive</td>
<td>(Cysique et al., 2006) 57</td>
</tr>
<tr>
<td>HIV Specific</td>
<td>Algorithm (no name)</td>
<td>Not known</td>
<td>Created using computer algorithm, identifies those at risk</td>
<td>Created in very advanced disease population, no aspects of cognition involved in algorithm (just based on factors such CD4 cell count, treatment duration etc…)</td>
<td>(Cysique et al., 2006)</td>
</tr>
<tr>
<td>--------------</td>
<td>---------------------</td>
<td>-----------</td>
<td>----------------------------------------------------------</td>
<td>-------------------------------------------------------------------------------------------------</td>
<td>------------------------</td>
</tr>
<tr>
<td>Generic</td>
<td>Sequential and Choice Reaction Time Program (CALCAP)</td>
<td>Not known</td>
<td>Computer based measure</td>
<td>The ability to detect mild cognitive impairment questionable, software is expensive</td>
<td>(Valcour, 2011)</td>
</tr>
<tr>
<td>Generic</td>
<td>Computer Assessment of Mild Cognitive Impairment (CAMCI)</td>
<td>15-20 minutes</td>
<td>Computer based measure, measures a range of deficits seen in HIV</td>
<td>Small study sample, software is expensive</td>
<td>(Becker, 2011)</td>
</tr>
<tr>
<td>Generic</td>
<td>Cambridge Neuropsychological Test Automated Battery (CANTAB)</td>
<td>Not known</td>
<td>Computer based software</td>
<td>software is expensive</td>
<td>(Sahakian, 1992)</td>
</tr>
</tbody>
</table>
### Figure 3.2- Summary of Measures for Perceived Deficits used in HIV

<table>
<thead>
<tr>
<th>Type of Measure</th>
<th>Screening test</th>
<th>Time needed to complete</th>
<th>Strengths</th>
<th>Limitations</th>
<th>References</th>
</tr>
</thead>
<tbody>
<tr>
<td>Generic</td>
<td>Patient Assessment of Own Functioning</td>
<td>33 questions, 6 ordinal response options</td>
<td>Commonly used in the HIV literature</td>
<td>Long to administer</td>
<td>(Rourke et al, 1999) , Cheluene et al., 1986)</td>
</tr>
<tr>
<td>Generic</td>
<td>Cognitive failures questionnaire</td>
<td>25 questions, 5 ordinal response options</td>
<td>Measured in many psychiatric populations</td>
<td>Only measures some of the problem domains found in HIV,</td>
<td>(Vance et al., 2008) , Larson et al, 1997) , (Broadbent et al, 1982)</td>
</tr>
</tbody>
</table>
CHAPTER 4
Measurement in the Human Sciences

4.1 Problems with Current Screening Measures
The goal of a screening measure is simply to provide information on whether a patient meets a certain cutoff, signifying whether or not s/he possesses a certain condition of interest; for the purposes of this thesis this condition would be “cognitive ability”. In other words, the total score informs the clinician how a patient performed, i.e. better or worse, with respect to a sample of people, usually from the same population under study. However, the total score does not inform the clinician about the amount of knowledge that a patient has in comparison to this sample. What clinicians often forget is “the number of correct responses on an assessment of a particular ability does not necessarily quantify an individual’s level or amount of that ability” 63. Hence, testing whether a patient has a certain condition of interest, and quantifying the amount of that quality they possess, are two separate goals in measurement.

4.2 Measuring a Construct
In the natural sciences, temperature and height could be quantified simply by using a thermometer or a ruler 64. There is a general understanding of how big or small a centimeter is, for example, and no matter what object is being measured, the units of the ruler used to measure an object do not change. However when trying to measure constructs such as depression and cognitive ability in the human and social sciences is challenging. There is no precise way to quantify these constructs as no true measuring instrument in the natural sciences is available 64. Thus responses to a series of questions or items are used as the measuring method, under the assumption that the items operationalize the construct of interest. Typically an ordinal scale is used as the unit of measurement for each response option 65.

The problem arises when trying to interpret the total score on these questionnaires. Consider a questionnaire where the total score is obtained from adding the ordinal scores from each individual item. This implies that each item contributes equally to measuring the construct when they may or may not be of equal value. Second, the ordinal response options do not provide an interval scale as the distance between the categories may not be equal. Interval scales are needed
in order to provide an interpretable total score and allow for mathematical manipulations such as addition and subtraction. Measuring change over time also cannot be accurately determined.  

How then, does one properly measure a deficit in cognition, and more importantly change? A patient’s cognitive ability must be placed on a linear continuum with a continuous unit of measurement of uniform magnitude. Peoples’ cognitive ability can then be quantified by their place on the continuum. Change over time can also be measured, as the distance between the units is meaningful, and interval in nature. To develop a measure such as this we must consider Modern Test Theory.

**4.3 Classical Test Theory vs. Modern Test Theory**

Classical Test Theory (CCT) is the most commonly used theory in the development of measurement scales. A score derived from a measure of this kind is based on the following formula:

\[ T = O + E \]

Where “T” is the true score and is a theoretical quantity, “O” is the observed score of a patient, and “E” is the error. The measurement error in this formula is assumed to be random, and the relationship between these variables is assumed to be linear.

The problem with the formula is that the focus is on a patient’s total score, and the relationships between the variables of “T”, “O” and “E” can never be tested due to the theoretical value “T”. What results when trying to perform mathematical manipulations on a patient’s total score was described in section 4.2; i.e. items contributing equally to the total, and ordinal response options being treated as interval.

In contrast, modern methods such as Item Response Theory, and Rasch Measurement Theory (RMT) focus on “…a person’s unobservable measurement on the underlying trait and the probability of responding to one of the response categories of a scale item.” Additionally, mathematical models of these two theories exist which allow for formal testing of the theory. Though both are very similar and categorized under “Modern Test Theory”, these theories are in fact very different.
Item Response Theory is based on the work carried out by Lord. It began by trying to develop models for CCT in an effort to “formalize” it as a theory, then it became a means to try and “establish the function that underlies the data”\textsuperscript{66} in which models are tested to best fit the data.

In the mean time, the Rasch model was proposed by George Rasch. This model is an “invariant” model with which, “…the relative locations [on the continuum of your latent trait] of any two people does not depend on the items they take, and that the relative locations of any two items does not depend on the people from whom the estimates are made.”\textsuperscript{66} In other words, person location estimation can occur independently of the items chosen to measure them, and item location can be estimated independently of the people chosen\textsuperscript{66}. The latter is the fundamental difference in the two modern theories, whereby in using RMT, the data is tested against strict criteria of the model. Once the data fits the Rasch Measurement Model, the data is said to measure only one construct, otherwise known as unidimensionality, and creates a measure that is invariant\textsuperscript{66}.

There exists a strong conceptual model of cognition in HIV, yet many flaws exist in the way it is operationalized into a measure. Hence for the purposes of this study, RMT was chosen as the statistical technique to aid in developing a set of items measuring cognitive ability, as this theory strongly prioritizes the model over prioritizing the data\textsuperscript{66}.

Refer to Appendix A1.0 for a justification of all measures included in the analysis in this thesis, as well as a construct map in Appendix A2.0 outlining the cognitive domain for each item.

### 4.4 Rasch Measurement Theory

RMT is a probabilistic model that looks at the interaction between person ability and item difficulty to arrive at a score which represents a trait level on a variable of interest \textsuperscript{67} (This is illustrated in Figure 4.1). Item difficulty and person ability are calculated based on the proportion of people that succeeded on each item, and the proportion of items that each person successfully completed\textsuperscript{68}. The calculations are based on the following formulas, with a “logit” being the unit of measurement used in RMT:

\textsuperscript{\textcopyright University of North Carolina at Greensboro}
\[ Y = \frac{\text{Probability of success}}{\text{Probability of failure}} \]

\[ \ln Y = \text{logit} \]

The benefit of the respondent in the model is that both the ordering of person ability can be estimated, as well as the distance between each person. In contrast to what was mentioned in section 4.1, the amount of ability a person has compared to the rest of the sample can now be quantified. An example of the later is illustrated in Figure 4.2. The left of the figure represents the percent of students A-H on a test. The problem with using raw scores, like percentages, is that most scores tend to clump around the middle while the scores of the higher ability and lower ability students are not adequately contrasted. An example of the latter is the amount of ability required to go from a 50% to a 60% on a test, versus the ability in going from 80% to 90%. More ability is required for the second change compared to the first. Rasch analysis allows for the ability differences in each change to be properly represented, as illustrated on the right of the figure, which represents these same percents after a log transformation. The construct in question is now quantified, and person ability can now be measured.

4.5 Rasch Analysis and Cognition

The application of RMT is ideal to meet the challenge undertaken here, namely to create a bank of items in which both sources of information (what is obtained from the patient, and what is obtained through neuropsychological testing) are included, with a wide spectrum of difficulties, that also allows for individualized testing.

As mentioned in Chapter 3, some researchers believe there is enough evidence that perceived deficits and measured deficits are not clinically relevant, and may in fact be two different constructs. As a rebuttal, consider the following:

“In social science, the word "multidimensionality" usually implies that there are multiple dimensions, i.e. separate dimensions. But consider volume. We have three applications of the same dimension, not three "different" dimensions. Length, width, and height, measured in the same units for utility, give us the three "applications" of a single dimension needed to compute volume.”

Thus patient reported outcomes and neuropsychological testing may be to length, width, and height, as cognitive ability is to volume.
Using RMT, which tests data against a strict hypothesis of unidimensionality, we can begin to observe whether these concepts can indeed be placed on the same continuum of cognitive ability. Additionally, we can also begin to understand the clinical significance of perceived deficits and whether they contribute any equivalent or additional knowledge to neuropsychological tests. The latter has an enormous clinical impact, as it has the opportunity to allow clinicians to better respect and hear the patient’s voice. It may also prove useful in a setting where there is time only for a very short screening test. If the two prove equivalent in future testing, 5 patient reported questions could be asked instead of performing 5 neuropsychological tests.
Figure 4.1 The Probabilistic Rasch Model

 Taken from Development of a Method for Quantifying Cognitive Ability in the Elderly Using Adaptive Testing

1 Person “x” is represented by the red arrow, item “y” by the blue arrow. When person ability is less than the item difficulty, the probability of passing is less than 50% (as demonstrated by the left side of the figure). The rest of the figure should be read as such.
Figure 4.2 Diagrammatic Example of Quantifying Patient Ability Using Rasch Analysis.

The left of the figure represents students A–H in percentages, the right of the figure represents the students after a log transformation. Adequate contrasts between students is now achieved.

Taken from *Applying the Rasch model: fundamental measurement in the human sciences*\(^6^8^2\)

\(^2\) The left of the figure represents students A–H in percentages, the right of the figure represents the students after a log transformation. Adequate contrasts between students is now achieved.
CHAPTER 5

Rational and Objective for the Manuscript

5.1 Rationale

With a prevalence rate of 30-60%, cognitive deficits are one of the most predominant comorbidities in people with the Human Immunodeficiency Virus\(^1\). Moreover many studies are reporting a high frequency of self-reported complaints. Using memory loss as an example, in a population based study of HIV patients, self-reported complaints ranged from 20-70%\(^19\). Including patient symptoms in the definition of cognitive ability would be logical due to the high number of complaints, however it implies that they have clinical significance and are easily measurable. The literature currently lacks consensus on their meaning and their best method of testing.

As there are many sources of information upon which to judge cognitive impairment it is reasonable that an attempt is made to calibrate all these sources together onto the same linear continuum. Thus, an item bank which will include items from both perceived deficits from the patient and directly measured deficits from neuropsychological testing would be useful in a clinical setting where the possibility of doing neuropsychological testing may be restricted. Results from a feasibility study showed that cognitive capacity may indeed be measured on a continuum\(^50\). The paper and pencil tests combined with computerized tests that were subjected to Rasch analysis were shown to cover a range of ±3.2 standard deviations (SD)\(^50\). The next step is to add perceived deficit questionnaires to the model, and see if any additional information is obtained from including this additional source of information.

5.2 Objective

Hence, the objective of this study is to estimate the extent to which items of patient reported cognitive difficulties and items from direct measures of cognition form a unidimensional construct. The hypothesis is that a latent construct, labeled in this study as “cognitive ability” will emerge from these items and will include items from all three sources.
CHAPTER 6

Quantifying Cognitive Deficits in HIV: Combining Patient Reported Outcomes and Neuropsychological Tests using Rasch Analysis

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6.1 INTRODUCTION

Over the last decade, there have been significant advances in the management of HIV. With the advent of combination antiretroviral therapies (cART) in the late 1990’s\(^1\), the disease is now termed a “chronic illness”, as the prognosis of these patients is excellent. In the pre-ART era, life expectancy was 1-3 years but now, according to the results of a recent study, patients can now expect to live 13 years longer on average, and the severity of opportunistic infections has decreased\(^1, 2, 2-4\).

Despite these promising results, comorbidities in this population have increased; one of the most common being neurocognitive impairment. HIV-associated neurocognitive disorders (HANDs) is currently prevalent in 30-60% of patients\(^5\), with patients experiencing a slowly progressing form of cognitive deficit instead of what was once a rapidly progressing dementia\(^1\). Of particular importance is the fact that once diagnosed with a neurological disorder, patients have a diminished chance of survival, regardless of whether or not they are receiving cART\(^6\). A comorbidity such as this, with its increasing prevalence and potential effect on treatment, requires immediate attention.

The challenges to prevent and manage cognitive deficits are numerous, one of which is that the construct of cognition is incredibly complex. First, the gold standard used to measuring cognition is neuropsychological testing, which is costly, time consuming, and requires trained professionals\(^7\). The length of the test battery is also frustrating and discouraging for patients if they are continuously asked to do tasks that they do not understand, or are beyond their level of capacity\(^8\). As a partial response to the difficulty of implementing a full neuropsychological test battery, a number of screening tests have been developed to alert clinicians as to which patients are at high risk for cognitive impairment. Examples of such measures are the HIV-dementia
scale, and the Folstein’s Mini-Mental. While sensitive to detecting HIV-dementia, it is insensitive to detecting minor cognitive impairments \(^9-11\) and they are not optimized to measure change over time\(^12\). Hence screening measures such as this are no longer recommended for use in a population experiencing predominantly minor declines in cognitive ability.

Secondly, there are multiple sources of information on cognition, for example information obtained from the patients themselves, their care partners, or through neuropsychological testing. Currently, the research definitions for HAND consist of two categories for milder impairments termed “asymptomatic neurocognitive impairment” (AND), when signs of impairment are present, and “mild neurocognitive impairment” (MND), when both signs and patient symptoms are present\(^13\). Due to the cART regimens, more patients are now being classified into these two categories\(^1\), hence it is important that the definitions in these categories be accurate. Incorporating patient symptoms into the definition of MND is logical, as with other patient reported outcomes such as fatigue, mood, and pain\(^14\), there may be no better method of symptom estimation than to ask the patient directly. Using memory loss as an example, in a population based study, self-reported complaints ranged from 20-70\(^\%\)\(^1\). However, including patient symptoms in the definition would also imply that complaints have clinical significance and are easily measurable, yet the literature lacks consensus on their meaning, and the best method of testing.

Thirdly, there is a challenge in deriving a total score from a screening test, or patient reported measure of symptoms. While attractive to simply add up the values obtained for each item, this is now recognized as yielding invalid information\(^12\). The value assigned to a response option, while coded numerically, is not a numerical value; the distance between the category-assigned ordinal values may not be equal. Carrying out mathematical manipulations of these codes cannot
yield interpretable values\textsuperscript{12}. Additionally, this method weights each item equally in deriving the
tax total score when they may not contribute equally to the underlying construct being measured\textsuperscript{12}. This simplistic method of scoring may be reasonable for detecting the presence of a concerning level of deficit, but may not be ideal for measuring \textit{how much} cognition a patient possesses. The implication of the fact that the ordinal scoring system does not allow for adequate mathematical manipulation, is that it does not allow for the precise measurement of change over time\textsuperscript{15}.

Change over time is undoubtedly the concept inherent to the definition of “decline”. Therefore a new strategy is required in the field of HIV to improve measurement and more accurately assess patients before true and likely irreversible neurological damage sets in.

A solution is to use modern psychometric methods, more specifically Rasch Measurement Theory (RMT) which is a method of estimating the extent to which items relating to a latent construct form a unidimensional, linear continuum\textsuperscript{12}. The items which fit the underlying hypothesized linear model, form an item bank of calibrated items. An item bank is defined as “… a composition of coordinated questions that develop, define, and quantify a common theme and thus provide an operational definition of a variable…”\textsuperscript{16}. The advantage of an item bank is that it forms the basis of developing future measures fit for specific purposes. The evaluator can choose from this item bank, those items that best fit the evaluation situation and be confident that the response to the times selected will yield a total score for that patient that is interpretable as a quantity.

As there are many sources of information upon which to judge cognitive impairment it is reasonable that an attempt is made to calibrate all these sources together onto the same linear continuum. Thus, an item bank which will include items from both perceived deficits from the patient and directly measured deficits from neuropsychological testing would be useful in a
clinical setting where the possibility of doing neuropsychological testing may be restricted. When neuropsychological testing is available, the co-calibration of these items with those obtained from the patient himself, will provide information that relates to the patient’s experience and indicates clinically the potential impact for the patient. This has never before been attempted in the HIV literature. Results from a feasibility study showed that cognitive capacity may indeed be measured on a continuum. The paper and pencil tests combined with computerized tests that were subjected to Rasch analysis were shown to cover a range of ±3.2 standard deviations (SD). To put this in context, the theoretical range of a standard normal deviate is ±3.2 SD. The next step is to see if perceived deficits will fit in this model, and contribute any additional information to the precision of the scoring hierarchy.

Therefore the objective of this study is to estimate the extent to which items of patient and care partner reported cognitive difficulties and items from direct measures of cognition form a unidimensional construct. The hypothesis is that a latent construct, labeled in this study as “cognitive ability” will emerge from these items and will include items from all three sources.

6.2 METHODS

Participants
This cross sectional study included a convenience sample drawn from patients with scheduled appointments from the Immunodeficiency Clinic at the Montreal Chest Institute in the McGill University Health Center between July 2009 to February 2010. Inclusion criteria were those patients between the ages of 18-65 who were HIV positive, and able to communicate in either English or French. Exclusion criteria were patients with dementia, (defined by the DSM-IV criteria assessed by clinician and supplemented by MMSE < 23 or MoCA < 20), history of CNS
infection, other neurologic event likely to affect cognition, serious head injury, current substance abuse (except cigarettes), current use of psychoactive medication in doses likely to substantially interfere with cognition, or current Axis-I psychiatric disorder or current sleep disorder likely to substantially interfere with cognition. Post-recruitment exclusions were for exclusions identified at time of testing and missing data.

**Procedure/Data collection**

The protocol was approved by the Regional Ethics Board, and all patients and informants provided informed consent. All tests were administered by a trained research assistant, in the same session, in either English or French. A semi-structured interview to collect clinical information, and a chart review were also completed. Informants were asked to complete questionnaires in person or over the phone with a trained research assistant present.

**Measurement**

Due to the lack of consistency across disciplines on the terminology used to describe cognition, for the purposes of this paper, cognition is defined as “cognitive ability/deficit”. The components of cognitive ability/deficit consist of neurocognitive tests (computerized tests, neuropsychological tests, screening tests), labeled “directly measured deficits”, and subject’s answers to questions related to cognition (perceived deficit questionnaires, informant questionnaires), labeled “perceived deficits”. All measures chosen for the analysis are reliable and valid, and commonly used in the assessment of patients with HIV\textsuperscript{17, 18}.

**Directly Measured Deficits**

Measures include the Montreal Cognitive Assessment (MoCA)\textsuperscript{19}, the digit span\textsuperscript{20} verbal fluency-FAS\textsuperscript{21}, as well as 13 additional neuropsychological tests (see Appendix-1). A complete
description of the directly measured deficits and the categorization of all the data has previously been reported by Koski et al., 2011\textsuperscript{7,22}.

Test results that are reported as continuous data were categorized based on the distribution. For example “flanker effect”\textsuperscript{23} was divided into 6 categories (1= > mean (M) + 2 standard deviations (SD), 2 =M + 2 SD, 3=M+1SD to M+0.5 SD, 4= M+0.5SD to M-0.5SD, 5= M-0.5SD to M-1.0SD, 6 =<M-1.0SD).

**Perceived Deficits**

**a) Perceived Deficits Questionnaire (PDQ):** The PDQ is an ordinal questionnaire consisting of 20 negatively worded questions that assess retrospective memory, attention, prospective memory, and organization and planning. The ordinal response options are “never/rarely/sometimes/often/almost always”. The total score ranges from 0-80, with a higher score indicating more deficit\textsuperscript{24}.

**b) Multiple Sclerosis Neuropsychological Screening Questionnaire (MSNQ):** This questionnaire rates neuropsychological abilities required for daily living in two formats: self- and informant-rated. It consists of 15 negatively worded questions scored on an ordinal scale from 0 to 4 “never does not occur/very rarely, no problem/occasionally, seldom a problem/quite often, interferes with life/very often, very disruptive” with higher scores representing a greater risk of neuropsychological impairment. The total score ranges from 0-60\textsuperscript{25}.

**c) A modified Frontal Systems Behavioural Scale (FrSBe):** The Frontal Systems Behavioral Scale (FrSBe) theoretically assesses three observable behaviours, executive dysfunction (17 items), apathy/akinesia behaviour (14 items), and disinhibition/emotional dysregulation type of behaviour (15 items)\textsuperscript{26,27}. The FrSBe was modified through a Rasch analysis to consist of 24 of the original 46 items. The FrSBe is sensitive to frontal behavioral deficits in a wide range of
neurological diseases such as multiple sclerosis and Alzheimer’s Disease, as well as populations with differing pathologies such as eating disorders.

**Data Analysis**

A complete description of Rasch Measurement Theory (RMT) can be found elsewhere. In sum, RMT tests data against strict criteria of unidimensionality and invariance. If the data fit the Rasch model, it is basis for the development of a measure of one construct, in this case “cognitive ability”. Item difficulty and person ability interact to create a “ruler-based measure” on which items and persons are ordered hierarchically on a linear scale. The latter is achieved by the following formula: \( Y = \frac{\text{Probability of success}}{\text{probability of failure}}; \ln Y = \text{logit} \). Due to the interval nature of the scores, mathematical manipulation both between patients and within a single patient can be achieved.

A partial credit Rasch analysis was conducted using the Rasch Unidimensional Measurement Model program (RUMM 2020). Fit to the Rasch model is expressed by global fit, fit of individual items, and fit of individual people. Items should have a monotonic ordering of response options, in which persons with higher ability endorse higher categories on the response scale. When this condition is not met, the item thresholds, or the point at which the probability of endorsing one response option over another is at 50%, is disordered. Item responses should also be independent of other items on the scale, such that a response on an item cannot predict responses on another; violation of this assumption is referred to as *local dependence*, which is reflected in correlation of the standardized residuals. The criteria for the latter assumptions are achieved by examining the item and person standardized residuals, Chi-square \( (X^2) \), and F statistics as well as the model global fit \( X^2 \) statistic. A cut-off value of \( \pm 2.0 \) for standardized
residuals was used to identify misfitting items and persons. A significance level of \( p \geq 0.05 \) was used for \( X^2 \) and F-statistics. Bonferroni correction adjusting for the number of items being tested may be applied.

The potential for violation of the assumption of unidimensionality was assessed by a principal component analysis of the standardized item-person residuals. Lack of unidimensionality might be suspected if the proportion of variance explained by the first PCA is more than 10\%. Unidimensionality is assessed through the use of t-tests to identify the number of cases with statistically different scores on the two subtests identified from the PCA of the residuals. If the lower bound of the confidence interval contains 5\% then the scale is deemed to be unidimensional. If an additional component is suspected or suggested by the PCA, t-tests are used to define the magnitude of the dimensionality by comparing the person estimates in logits from the subset of items from the additional component to those of the entire set. Evidence for unidimensionality is provided if \( \leq 5\% \) of the t-tests are significant.

A total of 17 items were combined into 5 subtests. This was done based on administration of the tests, as several groupings of these items are scored as 1 item. An example of the latter is the clock test on the MoCA, as the three parts of drawing the clock (contours, numbers and hands) were combined into a single subtest.

A two-way analysis of variance was also conducted to ensure that there was no differential item functioning, that is to ensure that each item’s location is stable across the following factors: sex, age, education, language, and informant vs. patient report. These person factors were categorized based on the distribution of the data: age into 5 categories (\( >39, 40-44, 45-49, 50-54, \geq 55 \)), education into 2 (no university education vs. university educated), language into 2 (English test administered vs. French Canadian test administered), and depression into 4
based on the cut off scores of the Beck Depression Inventory-II (0-13 minimal depression, 14-19: mild, 20-28: moderate or 29-63: severe depression). A complete description of the sample has already been reported in Koski et al.\textsuperscript{7}.

For a 95\% confidence interval (CI) and for item calibration to be stable at \(\pm 0.5\) logits, a minimum sample size of 64 is needed\textsuperscript{37}. A total of 77 patients and 23 informants were entered into the analysis, for a total of 100; a sample size which should be sufficient for the purposes of this study.

Rasch analysis also produces an indication of internal reliability named the \textit{Person Separation Index} (PSI). It is interpreted the same way as Cronbach’s alpha, and is a better estimate of reliability as the variance calculated is based on a linear score instead of raw data. A Cronbach’s alpha was also calculated.

Content and construct validity was also evaluated. Before using RMT, a strong theoretical understanding of the construct, in this case “cognitive ability”, needs to be mapped out. A team of experts carefully selected items from the literature that they believed covered the range of cognitive domains typically affected in HIV. Additionally construct validity was evaluated through item-person hierarchy, and through a known-groups approach.

\section*{6.3 RESULTS}

\textit{Model}

A total of 80 participants were recruited, 3 were excluded at time of testing because further investigation uncovered exclusionary cognitive problems (drug use, MoCA score of \(<20\), a un-reported learning disability). A total of 51 care partners were also recruited to answer questions
on behalf of their loved ones, of which 28 were removed due to missing data, and an additional 4 were removed as they had only completed the FrSBe (which was later removed).

Of the informants, 58% had at least 1 item they did not respond to, and of the 77 patients, 18% had not responded to at least 1 item. Despite the missing data, RMT provides a total score for each patient that is entered into the analyses, without requiring missing data to be replaced\(^{31}\).

Of the total 128 participants recruited (see Table-6.1) 88.4% were men, 55% had a university education, 56% spoke French Canadian as their mother tongue.

The first analysis using all the items did not fit the Rasch model (DF 79; \(\chi^2 245.09; p=0.00\)). Of these original 95 items, 4 items were identified as extreme items (lion, year, place, and city) that is every person had either a perfect score or 0 on each of these items. These 4 items were deleted. All 24 items from the modified FrSBe were removed due to statistical, and conceptual misfit. Of the 71 remaining items, the response options of 21 items (30%) did not function as intended, that is their thresholds were disordered. The items with disordered thresholds were rescored and collapsed iteratively according to guidelines for optimal category usage\(^{26}\), 9 items were deleted due to extreme misfit. In an attempt to reduce local dependency, subtests were created, however this process did not improve the fit and these 32 items were subsequently set aside for further exploration. Items were observed in pairs, and those that had correlations ranging from 0.2-0.6 had one item of the pair deleted based on statistical fit and conceptualization. The greatest number of items removed from a cognitive domain was 13, which were classified under the domain of “memory”.

The final model consisted of 26 items (see Figure-6.1 item map, Figure-6.2 item response structure), 10 of which were tests of directly measured deficit, of which only 1 was a subtest (“clock drawing” on the MoCA), and 16 items of perceived deficit. Global fit to the
The Rasch model was confirmed, with all items and persons fitting (DF 26; $\chi^2$ 25.1; $p$ 0.51; mean item residuals: 0.21; SD 0.81; and person residuals: -0.06 ; SD: 0.84 logits), and with a PSI of 0.87. The items were recoded based both statistically and conceptually, and specific to an HIV population. The final model, with items in order of cognitive ability, is demonstrated in Figure-6.1, with the easiest perceived item, at -7.45 logits (“Often/almost always forget if you had already done something”), and the hardest item, also a perceived item, at 2.9 logits (“Never/Very rarely gets easily distracted”).

Model unidimensionality was assessed with t-tests, as 12.22% of the variance was explained by the first component in the PCA. Less than 5% of the t-tests were non-significant.

Differential item functioning due to age, sex, language, education, depression or informant vs. patient report was not found.

Figure-6.3 demonstrates person and item locations on the logit scale. The person location mean of 1.2 indicates that the model is mistargetted, in that the sample presented with more cognitive ability than what the average level of cognition the items measure. A number of items were too easy for this sample (ex. “Quite often/very often” need to be reminded to do tasks”), and items were missing from the high end of the scale to more accurately define the level of cognition for the patients with better ability.

**Internal Reliability:** The raw cronbach’s alpha for the final model was 0.68 (almost at the acceptable range), with raw standardized item total correlations ranging from 0.67-0.69 (acceptable).³⁹

**Construct Validity-Item-Person Hierarchy:** People and items line up as would be expected, as the MoCA items are at the lower end of the spectrum, while harder neuropsychological tests for
HIV, such as those involve attention, are on the higher end of the cognitive ability spectrum. These results are reflected in other studies as well.\textsuperscript{7, 22}

**Known Groups** A one-way analysis of variance, provided through RUMM, was used to test for known-groups validity amongst those patients with a university education vs. those without. The group with a university education scored significantly higher on the range of cognitive ability (1.2 logits \(\pm 1.14\) SD vs. 0.68 \(\pm 1.01\), \(p=0.01\)) than those without a university education.

6.4 DISCUSSION

The present study represents the first application of modern psychometric methods to combine items of perceived deficit and directly measured deficits in cognition. The final 26-item model contains items from both sources of information, with the easiest and hardest items being that of perceived deficit. It also covers a range of difficulty (2.57 to 3.06 logits) with an excess of items too easy for this sample, demonstrates an excellent PSI of 0.87, as well as content and construct validity. Based on our HIV sample, this item bank measures the following cognitive domains: distraction, short-term memory, spatial memory, fluency, processing speed/response inhibition, executive functioning, and abstraction. It is of interest to note that, on a linear continuum with a standard normal distribution (mean of 0, standard deviation (SD) of 1), we have identified in the top part of the cognitive ability distribution (SD 3 to 4), representing those people with high levels of cognition, that there were 5 perceived deficit items, and no items of directly measured deficit. For a SD of 2 to 3, there are 7 items of perceived deficit, and 4 from directly measured deficits; from SD 1 to 2 there are only 5 perceived deficit questions; from 0 to 1 SD there are 13 perceived deficit, and 1 directly measured; from SD -1 to 0 there are 9 perceived deficit and 3
directly measured; from SD -2 to -1 there are 5 perceived deficit and 4 directly measured; below -2 SD there are 4 perceived deficit and 2 directly measured deficits. Of particular significance is the fact that the perceived deficits cover the whole spectrum of cognitive ability, while the neuropsychological testing does not. The HIV cognition bank provides preliminary evidence that combining these two sources of information is possible. The combination would be of value in a clinical setting where a growing number of patients report difficulties with cognition that are not supported by their neuropsychological test results.27

Though a convenience sample, the population chosen for this study is representative of patients with HIV with early perceived cognitive deficit, as demonstrated by comparative years of age, education, and level of depression.40, 41

With a total of 95 items entered into the model describing different domains of cognition, it is interesting to note that the FrSBe items did not fit with the rest of the cognition items. This provides evidence suggesting that items measuring stereotypical frontal lobe behaviors may not be appropriate to include when measuring cognitive ability, and that behavior and ability may be two different constructs. An alternative argument is that the samples of patients answering these questionnaires diverged in cognitive ability.

Additionally, 13 of 32 items that were removed due to local dependency assessed memory, suggesting that closer observation is needed with regards to memory and the construct of cognitive ability; either through the creation of a subtest, or more consideration as to how this domain fits in conceptually with cognitive ability.
6.5 LIMITATIONS
The HIV cognition measure was created in a single convenience sample of HIV positive individuals, with very few females. Though this is typical in the HIV literature, to have studies be very gender biased\textsuperscript{40, 41}, recruitment of the female population needs to be pursued.

Further study is required to revalidate the scoring options of the items, and item stability, in a larger sample and also across time. Additionally more items need to be added to the model at the higher end of cognitive ability since those patients are of most interest, as the goal of the measure is to target those patients experiencing milder declines. A suggestion would be to hold focus groups with patients to properly determine what they believe their cognitive difficulties are. There is also a need for including other neuropsychological tests, as the present ones do not span the full range of cognitive ability. Additionally, in including other items into the bank, this could raise the internal consistency of $\alpha=0.68$ to the acceptable range.

6.6 CONCLUSION
The study developed a bank of 26 items that with further validation could be used to make a measure and help better understand perceived deficits in light of neuropsychological testing. The construct of cognition is complex and consists of many components, however the HIV cognition bank consists of items from 7 different cognitive domains. This is the first time that a bank of this nature has ever been attempted in the field of HIV, and begins to provide evidence that perceived deficits and directly measured deficits may be combined to create a construct of cognitive ability.
Table 6.1- Demographics of Sample

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Count</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gender (M/F)</td>
<td>69/8</td>
</tr>
<tr>
<td>Age</td>
<td></td>
</tr>
<tr>
<td>&gt;39</td>
<td>12</td>
</tr>
<tr>
<td>40-44</td>
<td>14</td>
</tr>
<tr>
<td>45-49</td>
<td>18</td>
</tr>
<tr>
<td>50-54</td>
<td>15</td>
</tr>
<tr>
<td>≥ 55</td>
<td>16</td>
</tr>
<tr>
<td>missing</td>
<td>2</td>
</tr>
<tr>
<td>Education</td>
<td></td>
</tr>
<tr>
<td>No university</td>
<td>33</td>
</tr>
<tr>
<td>University</td>
<td>42</td>
</tr>
<tr>
<td>missing</td>
<td>2</td>
</tr>
<tr>
<td>Mother Tongue</td>
<td></td>
</tr>
<tr>
<td>English</td>
<td>23</td>
</tr>
<tr>
<td>French</td>
<td>43</td>
</tr>
<tr>
<td>missing</td>
<td>11</td>
</tr>
<tr>
<td>Depression</td>
<td></td>
</tr>
<tr>
<td>Minimum</td>
<td>35</td>
</tr>
<tr>
<td>Mild</td>
<td>14</td>
</tr>
<tr>
<td>Moderate</td>
<td>16</td>
</tr>
<tr>
<td>Severe</td>
<td>10</td>
</tr>
<tr>
<td>missing</td>
<td>2</td>
</tr>
<tr>
<td>Informant</td>
<td>51</td>
</tr>
<tr>
<td>Average MSNQ score</td>
<td></td>
</tr>
<tr>
<td>(informant) Mean ± standard deviation</td>
<td>13.56 ± (11.56)</td>
</tr>
<tr>
<td>Average MSNQ score</td>
<td></td>
</tr>
<tr>
<td>(patient) Mean ± Standard Deviation</td>
<td>18.09 ± (10.68)</td>
</tr>
</tbody>
</table>
The left of the figure represents the person locations in order of cognitive ability from highest to lowest (+4 to -4 logits). The right of the figure represents the item thresholds hierarchically from highest level of difficulty to lowest, with the most difficult item at 2.9 logits, and the least difficult at -3.15 logits.
Figure 6.2- Diagrammatic Representation of Items in Final Model with Response Structure

Items are ordered by level of cognition from worst to best, top to bottom. Lighter shading indicates a higher level of cognitive ability. Perceived deficits are highlighted in light grey, directly measured deficits are white. For perceived deficits, the numbers in parenthesis represent item logit locations, for directly measured deficits, the response option followed by the logit location are given in parenthesis. M=mean, SD=Standard deviation

<table>
<thead>
<tr>
<th>Item #</th>
<th>Item Mean Location</th>
<th>Item Name</th>
<th>Ordinal Response Options (MSNQ/PDQ)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td>0-“Very Often, Very Disruptive”/”Almost Always”</td>
</tr>
<tr>
<td>ST 01</td>
<td>-3.15</td>
<td>Clock Drawing (MoCA)</td>
<td></td>
</tr>
<tr>
<td>52</td>
<td>-2.08</td>
<td>Line Drawing (MoCA)</td>
<td></td>
</tr>
<tr>
<td>68</td>
<td>-1.76</td>
<td>Repeat Sentence 1 (MoCA)</td>
<td></td>
</tr>
<tr>
<td>21</td>
<td>-1.42</td>
<td>“Does he/she have to be reminded to do tasks?”</td>
<td>(-7.55)</td>
</tr>
<tr>
<td>34</td>
<td>-1.35</td>
<td>“Forget if you had already done”</td>
<td>(-8.16)</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>---</td>
<td>---</td>
<td>---</td>
<td>---</td>
</tr>
<tr>
<td>41</td>
<td>-1.17</td>
<td>“Find your mind drifting?”</td>
<td>(-8.66)</td>
</tr>
<tr>
<td>71</td>
<td>-1.01</td>
<td>Abstraction “train-bike” (MoCA)</td>
<td></td>
</tr>
<tr>
<td>5</td>
<td>-1.02</td>
<td>Subtractions, raw score (MoCA)</td>
<td>1 and 2 subtractions correct</td>
</tr>
<tr>
<td>43</td>
<td>-0.80</td>
<td>“Forget to do things like turn off the stove or turn on the alarm clock?”</td>
<td></td>
</tr>
<tr>
<td>27</td>
<td>-0.12</td>
<td>“Does he/she laugh or cry with little cause?”</td>
<td></td>
</tr>
<tr>
<td>69</td>
<td>-0.05</td>
<td>Repeat Sentence 2 (MoCA)</td>
<td></td>
</tr>
<tr>
<td>48</td>
<td>0.12</td>
<td>“Have trouble making decisions?”</td>
<td>(-1.93)</td>
</tr>
<tr>
<td>16</td>
<td>0.24</td>
<td>“Is he/she slow when</td>
<td>(-2.11)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>trying to solve problems?&quot;</td>
<td></td>
</tr>
<tr>
<td>---</td>
<td>---</td>
<td>---------------------------</td>
<td>---</td>
</tr>
<tr>
<td>39</td>
<td>0.56</td>
<td>“Forget the date unless you looked it up?”</td>
<td>(-0.29)</td>
</tr>
<tr>
<td>31</td>
<td>0.59</td>
<td>“Forget what you came into the room for?”</td>
<td>(-1.77)</td>
</tr>
<tr>
<td>20</td>
<td>0.63</td>
<td>“Does he/she need to have instructions repeated??</td>
<td>(-1.31)</td>
</tr>
<tr>
<td>18</td>
<td>0.70</td>
<td>“Does he/she forget what he/she reads?”</td>
<td></td>
</tr>
<tr>
<td>4</td>
<td>0.73</td>
<td>Self-ordered spatial working task</td>
<td>(# of errors) M + 1 SD to &gt;M + 2 SD</td>
</tr>
<tr>
<td>45</td>
<td>0.78</td>
<td>“Have trouble holding phone numbers in your head, even for a few seconds?”</td>
<td>(-1.23)</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>4 and 5 numbers correct</td>
</tr>
<tr>
<td>---</td>
<td>---</td>
<td>---</td>
<td>-------------------------</td>
</tr>
<tr>
<td>2</td>
<td>0.79</td>
<td>Forward Digit Span</td>
<td></td>
</tr>
<tr>
<td>49</td>
<td>1.09</td>
<td>Verbal Fluency-FAS</td>
<td>&lt;30 words</td>
</tr>
<tr>
<td>29</td>
<td>1.11</td>
<td>“Lose your train of thought when speaking”</td>
<td></td>
</tr>
<tr>
<td>14</td>
<td>1.19</td>
<td>“Does he/she get easily distracted?”</td>
<td></td>
</tr>
<tr>
<td>24</td>
<td>1.35</td>
<td>“Does he/she have difficulty keeping track of two things at once?”</td>
<td></td>
</tr>
<tr>
<td>32</td>
<td>1.38</td>
<td>“Have trouble getting things organized?”</td>
<td></td>
</tr>
<tr>
<td>13</td>
<td>2.69</td>
<td>Flanker Effect</td>
<td>(reaction time) &gt;M +2 SD</td>
</tr>
</tbody>
</table>
The top of the figure represents the location of patients on the cognitive ability continuum, from -9 logits to +6 logits. The bottom of the figure represents the item locations. The person location mean is at 1.2 logits.
Appendix-I

List of Measured Deficits

Reversal Learning
Emotion Recognition Task
Letter 2-back Task
Stop-signal Task
Go Reaction Time
Serial 7’s (MoCA) total raw score
Flanker Task-Congruent/Incongruent
Flanker Effect
Corsi Block Test
Self-ordered Spatial Working Memory Task
MoCA
Digit Span Forward/Backward
Verbal Fluency-FAS
Grooved Pegboard Dominant/Non-Dominant
Reference List


(2) HIV InSite. Clinical Overview of HIV Disease.  8-12-2009.

(3) AIDS.gov. Aging with HIV/AIDS.  11-2-2010.


Despite the better prognosis since the advent of cART, HIV still remains incredibly complex in its’ treatment, and very wide in its’ spread around the world\textsuperscript{19}. The face of the disease keeps changing, and one such consequence of the latter is an increase in patients experiencing mild cognitive deficits\textsuperscript{19}. It is not only important to understand the impact of these deficits on a patient’s life, but to understand these deficits from their perspective, which has often been overlooked. A patient should be an active participant in their own treatment and management of their illness, and this thesis aims at trying to understand the patient’s voice in light of well-understood neuropsychological testing.

The manuscript aims at combining neuropsychological tests, or directly measured deficits, with a patient’s perception of their ability, or perceived deficit, using Rasch Measurement Theory. RMT allows patient and items to be ordered along a single hierarchical interval scale in order of difficulty and patient ability\textsuperscript{70}. The latter allows for mathematical manipulation of total scores to be performed, which allows for adequate measurement of change over time to be calculated. The manuscript is the first attempt of creating a measure in this population that combines both sources of information. A 26-item measure, comprising of 16 perceived deficit items and 10 directly measured items was created. As demonstrated in Figure-6.1 and accompanying Figure 6.2, both the easiest and hardest items on the logit scale are items of perceived deficit, and an additional level of gradiency is obtained when using both sources of information than when simply using neuropsychological testing alone.

These findings are important for clinical practice, as currently there are no screening measures that properly assess all domains of cognitive deficit seen in patients with HIV. Additionally, the patient perspective is often overlooked, and this provides an opportunity for better understanding of this source of information.
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(92) Fellows L. Feasibility Study Data- Convenience Sample. 2011.
Selection of Measures for the Manuscript

A mix of computerized tests as well as pencil and paper tests were chosen in an effort to get a well-rounded measure of cognitive ability.

*Perceived Deficit Questionnaires:* These measures were selected based on the following criteria: if the measure is amenable to Rasch analysis, and if there is an informant version of the test. Informant reports are shown to be a good way of aiding in assessment of cognition, as they have been shown to correlate highly with patient scores on neuropsychological testing\(^7\)\(^1\). The following measures were also chosen by the cognition specialists on our team, who have much experience measuring cognitive ability in other disease populations with generalized brain lesions like those found in HIV. One such disease population is multiple sclerosis, and a recent neuroimaging study has shown that HIV demonstrates multiple sclerosis-like neurological impairments\(^16\). These measures also target deficits seen in HIV\(^7\)\(^2\).

1. Perceived Deficits Questionnaire: Is an ordinal measure that consists of 20 questions and assesses retrospective memory, attention, prospective memory, and organization and planning\(^7\)\(^3\). Each question has 4 response options, with 0 representing “never” and 4 representing “almost always”. The total score is obtained by adding the numerical value of each item together, and the range of scores is from 0-80, with higher scores representing more deficit\(^7\)\(^4\). This measure is also amenable to Rasch analysis\(^7\)\(^5\).

2. Multiple Sclerosis Neuropsychological Screening Questionnaire (self and informant): Is an ordinal measure consisting of 15 questions which ask the patient about neuropsychological abilities required for daily living. Each item has 4 response options with 0 representing “never, does not occur” and 4 representing “very often, very disruptive”. This measure also consists of an informant report, where the questions asked
are the same as in the patient report. Higher scores on both the patient and informant report represent risk of neuropsychological impairment; the cutoff scores being greater than 22 for patient report, and greater than 23 for informant report. Additionally, this measure was created using Rasch analysis.  

3. Ultimate Frontal Systems Behavioural Scale (self and informant): has just recently undergone Rasch analysis. This measure demonstrates validity for the assessment of frontal sub-cortical brain circuits, and identifies early behaviour changes in executive functioning. It is also sensitive to executive functioning deficits in a wide range of neurological populations with differing pathologies, such as multiple sclerosis and Alzheimer’s Disease. This measure consists of 22 items hierarchically ordered by patient ability and item difficulty. Scores range from 0-49, with high scores representing more impairment.

*Measured Deficits (Pencil and paper):* The MoCA was chosen as it is widely used to assess mild cognitive deficit, and commonly used in the HIV literature. The following neuropsychological measures (Digit Span, Verbal Fluency) were chosen based on the fact that they are common tests used in the HIV literature, and have demonstrated the ability to measure areas of impairment common to patients with HIV in the cART era. Therefore these tests represent the current standard in the field.

1. Montreal Cognitive Assessment (MoCA): is a measure that is used to detect mild cognitive impairment. It assesses a range of cognitive domains such as executive functioning and attention, and is scored based on the MoCA website. The total possible score is 30, with a score over 26 representing no risk of cognitive impairment. It has also been shown to be amenable to Rasch analysis.

2. Digit Span (forward and backward): measures attention and working memory. The task requires patients to repeat a series of numbers given to them. With every correct response, the patient moves to the next trial, which consists of a series that is one longer
than the last. In the backwards form of the task, the patient is asked to repeat the numbers in a backwards order.

3. Verbal Fluency-FAS: measures phonemic verbal fluency, and asks patients to produce as many words as possible beginning with the letters F, A, and S. It has been show to be sensitive in measuring frontal lobe deficits.

Measured Deficits (Computerized Testing): These computerized tests were created to measure specific regions of ability in the frontal lobes, as it is a deficit that is not well measured in standard HIV screening tests. A benefit to using computerized tests is the precision of measurement, as responses can be measured in milliseconds. The latter is especially important when measuring frontal lobe functions, such as executive functioning and mental slowing, as the responses for these tasks require reaction times. Therefore, using computerized screening measures is one method at best measuring the deficits seen in HIV.

1. Emotion recognition from faces: In this task, patients are asked to label pictures of black and white faces with the following emotions: happy, sad, angry, afraid, disgusted, and surprised. The difference between the ratings given to the neutral faces and the ratings given to the faces with emotion is what is defined as “emotion recognition”.

2. Letter 2-back task: Patients are asked to view one letter at a time on a screen, and asked to press a button when the letter on the screen is the same as the letter that was seen 2 trials previously. This task measures the ability to store and manipulate verbal information in working memory.

3. Eriksen flanker task: Patients are asked to press an arrow key either in the corresponding direction of the arrow that is on the screen, or in the opposite manner, as quickly as possible. The task also allows for correction of errors, if the patient believes to have made one. This task measures error processing speed.
4. Stop-signal task: This task is similar to the Eriksen flanker task, in that patients are asked to press an arrow key in the corresponding direction of the arrow on the screen. However in 25% of trials, a tone is heard before a response is demanded from the patient, where patients have to stop themselves from pressing the arrow key. This task measures response inhibition \(^{87}\).

5. Spatial working memory task: This task asks the patient to retain spatial location of information, while the computer provides delays and interfering input \(^{88}\).

6. Visuo-spatial span (assessed with a modified Corsi Block Task): requires patients to remember the sequence of highlighted squares on the screen. After the patient successfully repeats the sequence, the number of boxes in the sequence increases by one. This task can also be performed backwards, in which patients are asked to repeat the sequence in reverse order that what is presented. This task measures spatial short-term memory \(^{89}\).
<table>
<thead>
<tr>
<th>Type of Test</th>
<th>Specific Index or measure</th>
<th>Reliability</th>
<th>Validity</th>
<th>References</th>
</tr>
</thead>
<tbody>
<tr>
<td>Paper and Pencil</td>
<td>MOCA (original and Rasched version)</td>
<td>Internal consistency: 0.52 (but when Rasched with computerized tests it’s 0.75)</td>
<td>Positive Predictive Value and Negative Predictive Value (89% and 91% respectfully)</td>
<td>(Koski et al., 2011)50; (Nasreddine et al. 2005)81</td>
</tr>
<tr>
<td></td>
<td>Digit Span (forward and backward)</td>
<td>Internal consistency: 0.90; test retest: 0.08-0.89</td>
<td>Fair measurement of general intellectual functioning (0.05-0.69)</td>
<td>(Strauss et al., 2006)90</td>
</tr>
<tr>
<td></td>
<td>FAS (to assess phonemic verbal fluency)</td>
<td>Cronbach’s Alpha= 0.83; test retest: 0.7</td>
<td>Correlates moderately with verbal IQ (0.42-0.48)</td>
<td>(Strauss et al., 2006)90</td>
</tr>
<tr>
<td>Perceived Deficit</td>
<td>Perceived Deficits Questionnaire</td>
<td>Excellent: (cronbach alpha 0.93); test retest: (in impaired and non impaired patients) 0.84, and 0.85 respectfully.</td>
<td>Moderate: Pearson correlation 0.45</td>
<td>(National MS Society)71,(Fischer et al. 1999)74, (Marrie et al., 2003)91</td>
</tr>
<tr>
<td></td>
<td>Multiple Sclerosis Neuropsychological Screening questionnaire (self and informant)</td>
<td>Both informant and patient have cronbach alphas of 0.94 and 0.93 respectfully; Test retest: patient (0.9), informant (0.93)</td>
<td>informant report higher validity than patient report (0.33-0.64) vs. (0.17-0.44) as it related highly to certain neuropsychological items</td>
<td>(Benedict et al., 2003)76</td>
</tr>
<tr>
<td></td>
<td>(rasched)Frontal Systems Behavioural Inventory (self and informant)</td>
<td>uFRSBE: 0.89 cronbach alpha, reliability of hierarchies 0.91 person, 0.98 item</td>
<td>Construct validity: evidence provided by “by fit to the model with hierarchies ordered as expected.”</td>
<td>(Malloy et al., 2005)79; (Stout et al., 2003)78;</td>
</tr>
</tbody>
</table>
Table B- Psychometric Properties of the Computerized Battery for the Manuscript

<table>
<thead>
<tr>
<th>Test</th>
<th>Effect size for Difference between HIV and Control</th>
<th>Crude Agreement (N=45)</th>
<th>Within 1 SD (N=45)</th>
<th>Effect size for Difference in Test-Retest Means</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>N</td>
<td>%</td>
<td>N</td>
</tr>
<tr>
<td>2-back d’</td>
<td>-0.471</td>
<td>7</td>
<td>15.5</td>
<td>23</td>
</tr>
<tr>
<td>go RT</td>
<td>-0.705</td>
<td>20</td>
<td>44.4</td>
<td>36</td>
</tr>
<tr>
<td>SSRT</td>
<td>-0.517</td>
<td>6</td>
<td>13.3</td>
<td>26</td>
</tr>
<tr>
<td>SWM errors</td>
<td>-0.08</td>
<td>11</td>
<td>24.4</td>
<td>37</td>
</tr>
<tr>
<td>RL score</td>
<td>-0.447</td>
<td>7</td>
<td>15.5</td>
<td>39</td>
</tr>
<tr>
<td>ER</td>
<td>-0.515</td>
<td>5</td>
<td>11.1</td>
<td>35</td>
</tr>
<tr>
<td>Corsi Span</td>
<td>-0.091</td>
<td>17</td>
<td>37.8</td>
<td>40</td>
</tr>
<tr>
<td>Flanker effect</td>
<td>-2.0</td>
<td>8</td>
<td>17.8</td>
<td>24</td>
</tr>
</tbody>
</table>

PERCEIVED DEFICITS QUESTIONNAIRE (PDQ)

The following questions describe several situations in which a person may encounter problems with memory, attention or concentration. If you are marking your own answers, please check the appropriate response based on your cognitive function during the past 4 weeks. Please answer every question. If you are not sure which answer to select, please choose the one answer that comes closest to describing you.

During the past 4 weeks, how often did you....

1. Lose your train of thought when speaking?
   Never   Rarely   Sometimes   Often   Almost always
   [ ]   [ ]   [ ]   [ ]   [ ]

2. Have difficulty remembering the names of people, even ones you have met several times?
   Never   Rarely   Sometimes   Often   Almost always
   [ ]   [ ]   [ ]   [ ]   [ ]

3. Forget what you came into the room for?
   Never   Rarely   Sometimes   Often   Almost always
   [ ]   [ ]   [ ]   [ ]   [ ]

4. Have trouble getting things organized?
   Never   Rarely   Sometimes   Often   Almost always
   [ ]   [ ]   [ ]   [ ]   [ ]

5. Have trouble concentrating on what people are saying during a conversation?
   Never   Rarely   Sometimes   Often   Almost always
   [ ]   [ ]   [ ]   [ ]   [ ]

6. Forget if you had already done something?
   Never   Rarely   Sometimes   Often   Almost always
   [ ]   [ ]   [ ]   [ ]   [ ]

7. Miss appointments and meetings you had scheduled?
   Never   Rarely   Sometimes   Often   Almost always
   [ ]   [ ]   [ ]   [ ]   [ ]
8. Have difficulty planning what to do in the day?
   Never  Rarely  Sometimes  Often  Almost always
   □       □         □         □         □         □

9. Have trouble concentrating on things like watching a television program or reading a book?
   Never  Rarely  Sometimes  Often  Almost always
   □       □         □         □         □         □

10. Forget what you did the night before?
    Never  Rarely  Sometimes  Often  Almost always
    □       □         □         □         □         □

11. Forget the date unless you looked it up?
    Never  Rarely  Sometimes  Often  Almost always
    □       □         □         □         □         □

12. Have trouble getting started, even if you had a lot of things to do?
    Never  Rarely  Sometimes  Often  Almost always
    □       □         □         □         □         □

13. Find your mind drifting?
    Never  Rarely  Sometimes  Often  Almost always
    □       □         □         □         □         □

14. Forget what you talked about after a telephone conversation?
    Never  Rarely  Sometimes  Often  Almost always
    □       □         □         □         □         □

15. Forget to do things like turn off the stove or turn on your alarm clock?
    Never  Rarely  Sometimes  Often  Almost always
    □       □         □         □         □         □

16. Feel like your mind went totally blank?
    Never  Rarely  Sometimes  Often  Almost always
    □       □         □         □         □         □
17. Have trouble holding phone numbers in your head, even for a few seconds?

<table>
<thead>
<tr>
<th>Never</th>
<th>Rarely</th>
<th>Sometimes</th>
<th>Often</th>
<th>Almost always</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

18. Forget what you did last weekend?

<table>
<thead>
<tr>
<th>Never</th>
<th>Rarely</th>
<th>Sometimes</th>
<th>Often</th>
<th>Almost always</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
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<td></td>
</tr>
</tbody>
</table>

19. Forget to take your medication?

<table>
<thead>
<tr>
<th>Never</th>
<th>Rarely</th>
<th>Sometimes</th>
<th>Often</th>
<th>Almost always</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
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</tr>
</tbody>
</table>

20. Have trouble making decisions?

<table>
<thead>
<tr>
<th>Never</th>
<th>Rarely</th>
<th>Sometimes</th>
<th>Often</th>
<th>Almost always</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
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</tr>
</tbody>
</table>
**INSTRUCTIONS:**
The following questions ask about problems that you may experience. Rate how often these problems occur **AND** how severe they are. Base your ratings on how you have been over the last **three months**.

Please check the appropriate box.

<table>
<thead>
<tr>
<th>Question</th>
<th>Rating Options</th>
</tr>
</thead>
<tbody>
<tr>
<td>Are you easily distracted?</td>
<td>Occasionally</td>
</tr>
<tr>
<td>Do you lose your thoughts while listening to somebody speak?</td>
<td>Occasionally</td>
</tr>
<tr>
<td>Are you slow when trying to solve problems?</td>
<td>Occasionally</td>
</tr>
<tr>
<td>Do you forget appointments?</td>
<td>Occasionally</td>
</tr>
<tr>
<td>Do you forget what you read?</td>
<td>Occasionally</td>
</tr>
<tr>
<td>Do you have trouble describing shows or programs recently watched?</td>
<td>Occasionally</td>
</tr>
<tr>
<td>Do you need to have instructions repeated?</td>
<td>Occasionally</td>
</tr>
<tr>
<td>Do you have to be reminded to do tasks?</td>
<td>Occasionally</td>
</tr>
<tr>
<td>Do you forget errands that were planned?</td>
<td>Occasionally</td>
</tr>
<tr>
<td>Do you have difficulty answering questions?</td>
<td>Occasionally</td>
</tr>
<tr>
<td>Do you have difficulty keeping track of two things at once?</td>
<td>Occasionally</td>
</tr>
<tr>
<td>Do you miss the point of what someone is trying to say?</td>
<td>Occasionally</td>
</tr>
<tr>
<td>Do you have difficulty controlling impulses?</td>
<td>Occasionally</td>
</tr>
<tr>
<td>Do you laugh or cry with little cause?</td>
<td>Occasionally</td>
</tr>
<tr>
<td>Do you talk excessively or focus too much on your own interests?</td>
<td>Occasionally</td>
</tr>
</tbody>
</table>
## Ultimate Frontal Systems Behavioural Scale

<table>
<thead>
<tr>
<th>Statement</th>
<th>Almost Never</th>
<th>Seldom</th>
<th>Sometimes</th>
<th>Frequently</th>
<th>Almost Always</th>
</tr>
</thead>
<tbody>
<tr>
<td>State things but fails to finish them, &quot;peters out&quot;</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Does or says embarrassing things</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Fidgets too much</td>
<td></td>
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</tr>
<tr>
<td>Has difficulty starting an activity, lacks initiative, motivation</td>
<td></td>
<td></td>
<td></td>
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<td></td>
</tr>
<tr>
<td>Makes a mistake, over and over, does not learn from past</td>
<td></td>
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</tr>
<tr>
<td>Mixes up a sequence, gets confused when doing several things at a time</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Declines having problems or is unaware of problems or mistakes</td>
<td></td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>Sits around doing nothing</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Is disorganized</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Has difficulty starting an activity, lacks initiative, motivation</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>Laughs or cries too easily</td>
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<td></td>
<td></td>
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<tr>
<td>Makes inappropriate sexual comments and advances, is too flirtatious</td>
<td></td>
<td></td>
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<td></td>
<td></td>
</tr>
<tr>
<td>Cannot do two things at once (for example, talk and prepare a meal)</td>
<td></td>
<td></td>
<td></td>
<td></td>
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</tr>
<tr>
<td>Does risky things just for the thrill of it</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Loses control of voice or bowels and it doesn't seem to bother him/her</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Says one thing, then does another thing</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Is easily angered or inflamed, has emotional outbursts without reason</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Neglects personal hygiene</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Has lost interest in things that used to be fun or important to him/her</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Has no sense of humour, has childish sense of humour</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Shows little emotion, is unconcerned and unresponsive</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Makes up realistic stories when unable to remember something</td>
<td></td>
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<td></td>
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<td></td>
</tr>
</tbody>
</table>
# Montreal Cognitive Assessment (MOCA)

**Version 7.1 Original Version**

## Visuospatial / Executive
- **Copy Cube**
- **Draw Clock (Ten past eleven) (5 points)**

<table>
<thead>
<tr>
<th>Points</th>
<th>Contour</th>
<th>Numbers</th>
<th>Hands</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

### Naming

<table>
<thead>
<tr>
<th>Animal</th>
</tr>
</thead>
<tbody>
<tr>
<td><img src="image1" alt="Rhino" /></td>
</tr>
</tbody>
</table>

### Memory
- Read list of words, subject must repeat them. Do 2 trials, even if 1st trial is successful. Do a recall after 5 minutes.

<table>
<thead>
<tr>
<th>FACE</th>
<th>VELVET</th>
<th>CHURCH</th>
<th>DAISY</th>
<th>RED</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

#### 1st trial

#### 2nd trial

### Attention
- Read list of digits (1 digit/sec.). Subject has to repeat them in the forward order.
- Subject has to repeat them in the backward order.

<table>
<thead>
<tr>
<th>Digit</th>
<th>2</th>
<th>1</th>
<th>8</th>
<th>5</th>
<th>4</th>
</tr>
</thead>
<tbody>
<tr>
<td>Digit</td>
<td>7</td>
<td>4</td>
<td>2</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

### Serial 7 Subtraction Starting at 100

<table>
<thead>
<tr>
<th>99</th>
<th>98</th>
<th>97</th>
<th>96</th>
<th>95</th>
<th>94</th>
</tr>
</thead>
</table>

#### 4 or 5 correct subtractions: 3 pts, 2 or 3 correct: 2 pts, 1 correct: 1 pt, 0 correct: 0 pt

### Language
- Read aloud: “John is the one to help today.”
- The cat always hid under the couch when dogs were in the room.

### Fluency / Name maximum number of words in one minute that begin with the letter F

#### (N \geq 11 words)

### Abstraction
- Similarity between e.g., banana–orange–fruit
- Train–bicycle
- Watch–ruler

### Delayed Recall
- With No Cue
- Category cue
- Multiple choice cue

### Orientation
- Date
- Month
- Year
- Day
- Place
- City

© Z. Nasreddine MD

Website: [www.mocastest.org](http://www.mocastest.org)

Normal: 26 / 30

**TOTAL**

---

77
### A2.0 Construct Map**

<table>
<thead>
<tr>
<th>Visuospatial</th>
<th>Attention/Working Memory</th>
<th>Orientation</th>
<th>Dexterity?</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cube Drawing (MoCA)</td>
<td>“A” Fingertap (MoCA)</td>
<td>Orientation Questions (MoCA)</td>
<td>Pegboard</td>
</tr>
<tr>
<td>Clock Drawing (MoCA)</td>
<td>Digit Span (MoCA)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Spatial Working Memory Task</td>
<td>Serial 7s (MoCA), Serial 7 total raw score</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Line Drawing (MoCA)</td>
<td>Digit Span</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Corsi Block Test</td>
<td>Letter 2-back</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Recall/Short-Term Memory/Distraction</th>
<th>Abstraction</th>
<th>Processing Speed/Response Inhibition</th>
</tr>
</thead>
<tbody>
<tr>
<td>Word Recall (MoCA)</td>
<td>Abstraction 1 and 2 (MoCA)</td>
<td>Flanker</td>
</tr>
<tr>
<td>M1, M2, M6, M7</td>
<td>Emotion Recognition</td>
<td>Go Reaction Time</td>
</tr>
<tr>
<td>P1, P14, P17</td>
<td>M12</td>
<td>Stop Signal Reaction Time</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Executive Functioning/Frontal Lobe</th>
<th>Memory</th>
<th>Fluency/Language</th>
<th>Miscellaneous</th>
</tr>
</thead>
<tbody>
<tr>
<td>M13, M14, M15</td>
<td>M4, M5, M8, M9</td>
<td>Animal Naming (MoCA)</td>
<td>F31</td>
</tr>
<tr>
<td>P4, P8, P12, P20</td>
<td>F25, F3</td>
<td>Repeat 1 and 2 (MoCA)</td>
<td></td>
</tr>
<tr>
<td>F10, F14, F15, F8, F9, F28, F16, F2, F11, F21, F30, F20, F24</td>
<td>P2, P3, P6, P7, P10, P11, P15, P18, P19</td>
<td>Fluency (MoCA)</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>Fluency FAS</td>
<td></td>
</tr>
</tbody>
</table>

** All items in red are included in the final model. M= MSNQ, P=PDQ, F=FrSBE