Influence of Age and Cognitive Reserve on Cognitive Function in HIV-infected South African Adults

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Abstract

Background. HIV remains a significant global public health concern. South Africa is one of the hardest-hit countries, housing more than 7 million people living with HIV (PLWH), a figure that represents more than 12% of the global infected population. Globally, HIV-associated cognitive impairment is present in almost 45% of PLWH, with 72% of that total burden found in Sub-Saharan Africa (Wang et al., 2020). The severity and trajectory of that impairment is, however, influenced by numerous risk and protective factors. This study aimed to investigate the strength of influence that two of these factors (cognitive reserve and age) have in a sample of HIV-positive South African adults. *Method.* Participants were 32 HIV-infected and virally suppressed adults (27 women; M_{age} = 41.13±9.34). They were administered the Cognitive Reserve Index Questionnaire (CRIq) and a comprehensive neuropsychological battery that assessed performance on tests of motor function, attention and working memory, information processing speed, language, memory, and executive function. They also provided 3T magnetic resonance imaging data. Bivariate correlations, independent-sample *t*-tests, and hierarchical regression models tested the prediction that age and cognitive reserve (as indexed by CRIq scores, fractional anisotropy, white and gray matter volume, education level, and IQ score), both independently and in interaction, will have significant effects on cognitive test performance (i.e., that increasing age and lower levels of cognitive reserve will be independently associated with poorer performance, and that older adults with lower levels of cognitive reserve will display the worst performance). *Results.* Regarding the association of age with global cognitive function (average performance across all tests), analyses detected a moderate negative correlation (r = -.425, p = .015.), a significant between-group difference (participants ≥ 45 years worse than those < 45 years, p = .012), and a significant proportion of variance accounted for (R^2 = .18, p = .016). There were no significant main effects of cognitive reserve, and no significant age x

cognitive reserve interaction effect, on cognitive test performance. *Conclusion.* The current analyses confirmed the influence of age on cognition in PLWH but did not provide support for the same influence of cognitive reserve. Although neuroscience research attaches increasing importance to the construct of cognitive reserve, the lack of a universally-applied definition (and hence a standard measure) of the construct hampers investigations such as this and makes cross-study comparisons difficult. From a policy-making perspective, the contrasting findings regarding age and cognitive reserve is crucial because it is imperative that intervention efforts focus only on those modifiable factors that significantly impact cognitive function, especially in countries such as South Africa that are characterized by high HIV disease burden and limited clinical and infrastructural resources.

CHAPTER 1:

Introduction

The human immunodeficiency virus (HIV) is a substantial global health concern. Although rates of infection have declined markedly in recent years, South Africa is still home to the highest number of people living with HIV (PLWH). Given that the virus often has significant negative effects on cognitive and behavioural functioning, HIV places a high burden of disease on South African society.

The severity and trajectory of cognitive dysfunction (i.e., impaired mental abilities, especially as reflected by poor performance on standardized neuropsychological tests and by deficiencies in completing everyday activities) in PLWH is influenced by a host of protective and risk factors, with complex interactions and relationships beyond the scope of investigation that can be contained within any single study (De Francesco et al., 2020; Fazeli et al., 2014; Wallace et al., 2017). This thesis focuses on the influence of cognitive reserve and age, two of the most prominent individual factors that affect cognitive functioning in PLWH (Cassimjee & Motswai, 2016; Guaraldi et al., 2019).

The concept of *cognitive reserve* refers to the individual variability in capacity to stave off negative symptoms of brain pathology due to accumulated cognitive resources acquired throughout the lifespan (Cody & Vance, 2016; Foley et al., 2012; Kaur et al., 2019). Hence, PLWH with higher levels of cognitive reserve are likely to maintain relatively stable cognitive function and independent living abilities longer than those with lower levels (Kaur et al., 2020; Shapiro et al., 2014; Thames et al., 2011).

The concept of *accelerated aging* or '*inflammaging'* in HIV suggests that the trajectory of normal age-related cognitive decline is steeper in PLWH. Hence, elderly PLWH show significantly more cognitive dysfunction, and increased susceptibility to neurological deficits, than age-matched cohorts (Cohen et al., 2015; Kuhn et al., 2019; Scott et al., 2011).

The overall aim of this thesis was to investigate the strength of influence that cognitive reserve and age have on cognitive function in a sample of HIV-positive South African adults. Understanding these effects has the potential to enhance screening, treatment, and management strategies, and to improved resource distribution to PLWH (Kaur et al., 2020).

The thesis is structured as follows: Chapter 2 is a review of the literature describing HIV-associated cognitive dysfunction. The chapter begins by summarising the epidemiology, neuropathology and neuropsychology of HIV, specifically the effects on domain-specific cognitive functions. Then it explores current knowledge on the concepts of cognitive reserve, specifically its passive and active aspects, and how it's measured. Finally, literature regarding accelerated aging in HIV is presented. Chapter 3 outlines the study's aims and hypotheses, and Chapter 4 describes its methods. Chapter 5 presents the study's results, and Chapter 6 presents a general discussion of the findings, including consideration of the study's limitations and some directions for future research.

CHAPTER 2:

Literature Review

Epidemiology of HIV in South Africa

HIV is a serious global health concern that affects approximately 36.9 million people. South Africa is one of the hardest-hit countries, with more than 7 million HIV-positive residents (12.6% of the global infected population). The burden of infection extends beyond the direct impact on the individual and places severe strain on the resources of national healthcare systems, caregivers, and families (Avedian et al., 2019; Cañizares, Cherner, & Ellis, 2014; Pulerwitz et al., 2019; Rosenberg et al., 2020; Simbayi et al., 2017).

The South African National HIV Prevalence, Incidence, Behaviour and Communication Survey (Avedian, 2018) found 231 100 new incidences between 2012 and 2015, noting that at the time of its publication only 62.3% of HIV-infected individuals (in raw numbers, 4 401 872 people) were on antiretroviral treatment (ART). With reference to the Joint United Nations Programme on HIV/AIDS (UNAIDS) 90-90-90 goals proposed in September 2016 (i.e., to have 90% of HIV-infected individuals diagnosed, 90% of those diagnosed on ART, and 90% of those on ART to be virally suppressed by 2020), Avedian (2018) reported that the South African statistics were 84.9% diagnosed, 70.6% on ART, and 87.5% virally suppressed. This survey also reported an estimated infection prevalence of about 7.9 million, which is higher than previous estimations. Finally, the survey noted that a significant number of people living with HIV (PLWH) were not aware of their status, that this was especially true among males, and that trends showed recent increases in risky sexual behaviour. Thus, South Africa continues to face many challenges related to the HIV pandemic. Research into detection and treatment efforts must help address those challenges.

Neuropathology of HIV

Genetic mechanisms allow HIV to invade the brain and the body. HIV is a type of retrovirus that infects the ribonucleic acid (RNA) of the host body to incorporate itself into the host's genetic material (i.e., its genome). The infectious RNA form of HIV transforms itself into a pro-viral DNA (the building blocks of the host genes) through a virally encoded enzyme, and then incorporates itself into the host cell genome through reverse transcriptase. Through such mechanisms, HIV causes pathogenic effects on both the immune system and the central nervous system (CNS). Both these systems use chemical mediators (chemokines) to regulate multifaceted communication between their cells. HIV disrupts this communication, resulting in the breakdown of signalling between, as well as the chemical processes of, these two systems.

The virus first gains access to the CNS during seroconversion (i.e., at the earliest stages of infection, approximately 3–6 weeks after contracting the virus) through a 'Trojan horse' mechanism. Immune cells of the CNS (viz., macrophages and microglia) are triggered by viral proteins, cytokines, and chemokines. Once the body's immune response is activated in this way, the viral bodies of HIV attach to, and become internalised in, the macrophages. Hence, they have now infiltrated the host cells and have become a 'Trojan horse.' The viral bodies are therefore able to cross the blood-brain barrier, bypassing the defences by which the brain would normally halt viral infections. As the host body's immune response continues, it therefore counter-intuitively facilitates infection (Agrawal et al., 2020; Cysique et al., 2013; Ellis et al., 2007; Nolan & Gaskill, 2019; Shapiro et al., 2014; Shapshak et al., 2017).

Once inside the brain, the HIV viral bodies cause a chronic inflammatory reaction that leads to a gradual cascade of neurotoxic effects. Among these effects, synaptodendritic injury

and neurodegeneration are the primary theorised biological mechanisms underlying HIV-associated cognitive impairment.

Crucial to understanding these mechanisms is that HIV does not directly infect neurons. Instead, it has a 'bystander effect', causing injury to surrounding cells (affecting, in particular, perivascular astrocytes, macrophages, and microglia). These infected 'bystander cells' have degenerative effects on neurons because they release toxins such as viral proteins, cytokines, and chemokines. Through various chemical and molecular mechanisms (e.g., neurotransmitter metabolism perturbation, platelet-activating factor, excitatory amino acids and free radicals, Ca^{2+} overload, oxidative stress, excitatory toxicity, and energy homeostasis disturbance), these toxins eventually lead to synaptic loss. Synaptic degeneration and loss occur through (1) NMDAR hyper-activation by macrophages, (2) synaptic abnormalities induced by cytokines aberrant activation, and (3) increased release of chemokines. (Ellis et al., 2007; Green et al., 2019; Irollo et al., 2021; Williams et al., 2019; Yilmaz et al., 2019).

Significant neuronal loss is associated with late-stage HIV or acquired immunodeficiency syndrome (AIDS), with some infected individuals showing HIV-associated encephalitis (HIVE). Neuronal death is commonly reported especially in the frontal cortex. Neuronal death is observed as synaptic degeneration, dendritic beading and dendritic spine loss, and axonal injury (Eggers et al., 2017; Rojas-Celis et al., 2019; Ru & Tang, 2017; Yuan & Kaul, 2019).

Neuropsychology of HIV

Cognitive impairment affects a significant number of HIV-infected individuals. Some global estimates suggest that between 50% and 60% of PLWH experience such impairment (Schouten et al., 2014; Su et al., 2016; Williams et al., 2019). (Of note here, however, is recent criticism levelled against the body of studies reporting these estimates. Critiques primarily revolve around the estimates being overly liberal and the substantial cross-study

variability in the methods and measures used to define and determine cognitive impairment (Underwood et al., 2019)).

Despite the majority of the HIV disease burden being localised to the African continent, non-African epidemiological research and published findings remain dominant in the literature (Yusuf et al., 2017). There are numerous reasons why prevalence studies are difficult to conduct in African countries. Perhaps the most significant are inadequate funding and resources and a lack of contextually suited measures of cognitive impairment. For instance, a study conducted in three East African countries (Kenya, Tanzania, and Uganda) reported that the International HIV Dementia Scale (Sacktor et al., 2005) showed poor sensitivity (56%) and specificity (64%) in the diagnosis of HIV-associated cognitive impairment, and concluded that the instrument is not a culturally fair measure of such impairment (Milanini et al., 2018).

Nonetheless, there is a growing body of recent literature describing the prevalence of HIV-associated cognitive impairment in Africa. For instance, Yitbarek and colleagues' (2020) systematic review and meta-analysis reported that the pooled prevalence of HIV-associated cognitive impairment in sub-Saharan African countries was 44.46%.

Research on the prevalence of HIV-associated cognitive impairment in South African PLWH is also limited. The most widely-cited study suggests that 25% of HIV-infected individuals in this country experience severe cognitive impairment, while 42% experience mild-to-moderate impairment (Joska et al., 2011). Of note here, again, are recent criticisms of the way that criteria for HIV-associated cognitive impairment have been applied in South Africa. These critiques point out the high false positive rates and the fact that the complex influences and interactions of medical comorbidities and socioeconomic factors in producing cognitive impairment are not taken into account (Nightingale et al., 2021).

Cognitive dysfunction in HIV is often formally defined as constituted by the three categories of HIV-associated neurocognitive disorders, or HAND (Antinori et al., 2007). *Asymptomatic cognitive impairment* (*ANI*) refers to cases where performance in two or more cognitive domains is > 1 *SD* below the mean performance of a demographically appropriate standardization sample, and there are no measured or reported declines in everyday functional abilities. *Mild cognitive disorder* (*MND*) refers to cases where performance in two or more cognitive domains is > 1 *SD* below the mean performance of a demographically appropriate standardization sample, and there are at least mild declines in everyday functional abilities. *HIV-associated dementia* (*HAD*) refers to cases where performance in two or more cognitive domains is > 2 *SD* below the mean performance of a demographically appropriate standardization sample, and there are significant declines in everyday functional abilities.

The widespread dissemination of combination ART (cART), also referred to as highly active ART (HAART), brought about increases in life expectancy and retention of healthy immune function among PLWH. However, cognitive dysfunction persists even in the face of this viral load suppression. Research suggests that this persistence is due to the CNS serving as a reservoir site for HIV so that the virus cannot be completely eliminated because it has integrated itself into the host genome. The persistent presence of this latent form of the virus triggers an enduring low-grade immune response that continues the cascade of neurotoxin release, synaptodendritic injury, and eventual neuronal death (Bui et al., 2017; Fields et al., 2014; Rosenbloom et al., 2017; Wong et al., 2019).

The co-occurrence of widespread dissemination of cART and persistent cognitive dysfunction has led to controversy and debate about the CNS penetration efficacy (CPE) of the medication regimens. On the one hand are claims that certain ART drugs are more effective than others in penetrating the CNS, and are thus better at mitigating the neurotoxic effects of HIV. On the other are claims that too-high CPE might have neurotoxic effects.

Numerous studies have investigated this question and, overall, results have been equivocal (see, e.g., De Benedetto et al., 2020; Lanman et al., 2019; Santos et al., 2019; Yuan & Kaul, 2021). Nonetheless, many studies comparing ART-naïve to ART-experienced groups show that treatment adherence improves cognitive performance (Carvalhal et al., 2016; D'Antoni et al., 2018; Gao et al., 2020; Mora-Peris et al., 2018; Vecchio et al., 2020).

Neuroimaging studies investigating HIV-associated cellular injuries have consistently reported on the degradation of white matter structural integrity and reduced cortical thickness, which occurs despite compliant ART (Kuhn et al., 2019; Mahmood et al., 2019; Underwood et al., 2017; Y. Zhuang et al., 2017). A substantial number of studies find significant differences in cortical thickness between HIV-infected and healthy control groups, albeit in varying regions. These regions include: (1) for cortical gray matter, the primary motor and sensory cortices, and temporal and frontal lobes; (2) for subcortical gray matter, the basal ganglia, the caudate-striatal region, and the thalamus; and (3) for white matter, the frontostriatal circuits, specifically the anterior cingulate cortex (ACC) and the corpus callosum (Hassanzadeh-Behbahani et al., 2020; Kapetanovic et al., 2020; Sanford, Ances, et al., 2018; Sanford, Cruz, et al., 2017; Shin et al., 2017; Williams et al., 2020). Meta-analyses suggest the variable findings are due to divergent sample characteristics (e.g., differing treatment regimens, durations of infection, ages, etc.) across studies (Corrêa et al., 2016; Israel et al., 2019; O'Connor et al., 2018; Sanford, Fernandez Cruz, et al., 2017).

Domain-Specific Cognitive Dysfunction in HIV

The presence and severity of cognitive dysfunction in cART-treated HIV-positive patients are often defined and characterised based on one of three sets of diagnostic criteria: (1) the DSM-5 criteria (APA, 2013), (2) the Frascati criteria (Antinori et al., 2007), or (3) the Gisslén criteria (Gisslén et al., 2011).

The DSM-5 criteria classify HIV-related cognitive impairment into two broad categories: (1) Major Neurocognitive Disorder due to HIV-infection (with two subsections, one including and the other excluding behavioural disturbances), and (2) Minor Neurocognitive Disorder due to HIV-infection.

The Frascati criteria and the Gisslén criteria are similar to each other in that the former established specific categories of classification and the latter expanded on those with more detailed criteria for each category. The Frascati criteria established the HIV-associated neurocognitive disorder (HAND) criteria, in descending order of severity, as (1) HIV-associated dementia (HAD), (2) mild neurocognitive disorder (MND), and (3) asymptomatic neurocognitive impairment (ANI). The Gisslén criteria expanded on these categories by providing more clearly defined conditions to meet the criteria, based on the degree of deviation from normative performance on neuropsychological tests and interference in daily functioning. These expansions were as follows: (1) HAD is characterised by markedly impaired functioning (2 *SD* below a standardization norm) in two or more cognitive domains and interference in daily functioning; (2) MND is characterised by impaired functioning (at least 1 *SD* below the norm) in at least two cognitive domains and interference in daily functioning; and (3) ANI is characterised by impaired functioning (at least 1 SD below the norm) in at least two cognitive domains and no interference in daily functioning.

Although these sets of criteria have varying levels of agreement with each other, and although each has its uses in different settings (see Tierney et al., 2017b), they bear some similarity to each other because they all list several domains of cognitive functioning (from lower- to higher-order processing) that have reportedly been affected by HIV to at least a mild degree (Antinori et al., 2007; Antinori et al., 2013; APA, 2013; Gisslén et al., 2011; Tierney et al., 2017b).

The DSM-5, Frascati, and Gisslén criteria all include in their definitional statements that cognitive impairment must be present in each of (or a subset of) these six specific domains: motor function, information processing speed (psychomotor speed), attention (and working memory), learning and memory, language (verbal fluency), and executive functioning (De Francesco et al., 2020; Rosenberg et al., 2020; Tierney et al., 2017). Because different studies in this field use different criteria, and therefore investigate different sets of these domains, results can be quite variable. Nonetheless, a general profile of cognitive impairment in HIV has emerged from the past two decades of work.

Psychomotor Function. Both gross motor functioning and fine motor coordination (dexterity) can be affected by HIV infection (Prabhakar et al., 2020; Uebelacker, 2017). However, fine motor deficits are more prevalent than gross movement disorders (e.g., bradykinesia), and are often found to be mild. Fine motor deficits typically only present in later stages of HIV, even in virally suppressed individuals. However, more severe presentations of fine motor deficits have been reported in the early stages of HIV in untreated PLWH (Kayungwa et al., 2016; Montoya et al., 2019; Prabhakar et al., 2020; Underwood et al., 2017; Yuan & Kaul, 2019). Neuroimaging data corroborates these reports of more severe fine motor deficits, with studies often finding reduced cortical volume in motor cortices (Anderson et al., 2016; Prabhakar et al., 2020; Sanford et al., 2018). Some longitudinal studies report that although general cognitive function can remain stable in virally suppressed PLWH (or can even improve after ART initiation), motor deficits can continue to decline over time (Elicer et al., 2018; A. Monroe et al., 2017).

Information Processing Speed. The construct of information processing speed (often called psychomotor speed) refers to how rapidly the brain can process information. It is a foundational cognitive domain that supports optimal functioning in other domains (Chiaravalloti et al., 2003, 2018; Reicker et al., 2007; Rivera Mindt et al., 2020). Even in the

cART era, decreased information processing speed is one of the most prominent cognitive features of HIV infection (Katzef et al., 2019). Moreover, performance on tests of processing speed shows the steepest decline as the disease progresses in severity (Anand et al., 2010; Vance et al., 2012). Some studies even suggest that performance on tests of information processing speed may be most predictive of overall cognitive functioning in PLWH (Fellows et al., 2014; May et al., 2020).

Impaired information processing speed has been linked consistently with damage to white matter and subcortical structures (Zhu et al., 2013). Neuroimaging studies have also reported associations between progressively abnormal neurotransmitter levels and poor performance on tests of information processing speed (May et al., 2020; Saylor et al., 2016).

Information processing speed has been found to be particularly vulnerable to the interacting effects of increased age and HIV. Several studies investigated the effect of age on multiple different cognitive domains in HIV samples, and found information processing speed to be the most vulnerable. These studies also suggest that poor performance on tests of information processing speed is associated with difficulties in completing activities of daily living, such as initiating or maintaining medical regimens (Giesbrecht et al., 2014; Paolillo et al., 2019; Van Dyk et al., 2015; Vance et al., 2012).

Attention and Working Memory. Attention might be broadly defined as neural mechanisms through which sensory information is taken into the conscious mind (Fabio & Antonietti, 2019; Fernández-Marcos et al., 2018; McAvinue et al., 2012). The construct is often operationalized into two systems: (1) top-down attention, which is the goal-directed action of training focus onto a specific stimulus in order to absorb it, and (2) bottom-up attention, which refers to more passive guidance of primarily background information (Katsuki & Constantinidis, 2014; Keller et al., 2019). Top-down attentional mechanisms are conceptualized as consisting of several discrete components (e.g., selective, sustained, and

divided attention) while bottom-up mechanisms, generally known as exogenous, are passively guided by external stimuli and processed by primary sensory cortices (Giollabhui et al., 2019; Gunn et al., 2018; Middlebrooks et al., 2017).

Working memory is defined as a limited-capacity cognitive system that supports the ability to temporarily hold and manipulate information (Baddeley et al., 2019; Sepp, 2019; Wen et al., 2019). Working memory is often conceptualised as having two components, namely audio-verbal and visual-spatial. Thus working memory is separated into two modality specific components where sensory-specific information can be manipulated and further processed and utilised by other cognitive functions (Cohen et al., 2018; Fraser & Cockcroft, 2020).

Both attention and working memory are foundational cognitive processes that play important roles in ensuring that numerous higher-level cognitive processes operate efficiently (Allen et al., 2017; Engle, 2018; May et al., 2020). This foundational involvement is due largely to the fact that neither of these cognitive systems is localised to any one brain region; instead, both are distributed widely across regions. Hence, integrity of white matter tracts is essential to the optimal operation of both attention and working memory systems.

Performance on tests of attention and of working memory is frequently impaired in PLWH (Kayungwa et al., 2016; A. Monroe et al., 2017; Sanford, Fellows, et al., 2018a; Su et al., 2015). Indeed, poor working memory performance is one of the most commonly reported cognitive deficits in HIV and is often linked to deficits in higher-level executive functioning, such as decision making and reasoning (Martin et al., 2018; Walker & Brown, 2019; Wilson et al., 2017). At the neural level, increased white matter density is positively correlated with better attention performance in PLWH (Saylor et al., 2016; Underwood et al., 2017). At the level of functional adaptation, some studies have found associations between impaired

attention / working memory and risk-taking behaviour in PLWH (Anand et al., 2010b; Anderson et al., 2016; Khurana et al., 2015; Rowe et al., 2020).

Language. Although basic receptive and expressive language difficulties are sometimes present in PLWH, executive language difficulties (e.g., language or verbal-base executive functions, such as verbal fluency) are observed more frequently (Kallail et al., 2015; Thames, Foley, et al., 2012). In neuropsychological research (including that on HIV-associated cognitive dysfunction), expressive language is most commonly measured using confrontation naming tasks, whereas executive language is most commonly measured using verbal fluency tests (Kallail et al., 2015; Tartar et al., 2014; Woods et al., 2010). These verbal fluency tasks include one or more of the following three trials where as many words as possible must be generated within specific restrictions: (1) semantic fluency (words that fit into a certain category, e.g., animals, or fruits and vegetables); (2) phonemic fluency (words beginning with specific letters); and 3) action fluency (verbs).

Roughly 50% of PLWH present with verbal fluency deficits in the earlier stages of infection; these tend to worsen as the disease progresses (Iudicello et al., 2012; Kayungwa et al., 2016; Koenig et al., 2016). PLWH are three times more likely to show clinically significant deficits on action fluency tasks than on semantic or phonemic fluency tasks, and performance on action fluency tasks also appears to be a better predictor of daily functioning than performance on other fluency tasks (Iudicello et al., 2007; Woods et al., 2005, 2009).

Learning and Memory. The cognitive processes of learning and memory are often paired because the terms refer to related functions: the encoding (or learning) of material, and subsequent retrieval of (or memory for) that material. Additionally, neuropsychologists often refer to the material specificity of the encoded and retrieved stimuli, stipulating that it is of either verbal or non-verbal (i.e., visual or visuospatial) form (Forsberg et al., 2020; Icht et al., 2020; Jakobson et al., 2008). Verbal learning and memory, the form most studied in HIV

neuropsychology literature, is often measured using list-learning tests (see, e.g., Morgan et al., 2009; Nakata, 2008; Rubin et al., 2015; Witten et al., 2015). Visual memory tests, in contrast, typically use pictures or drawings as stimuli (Keutmann et al., 2017; E. Martin et al., 2018; O'Connor et al., 2017).

Verbal learning and memory deficits are observed more commonly in PLWH than are visual learning and memory deficits (Kanmogne et al., 2021; Watson et al., 2019). Indeed, verbal learning and memory impairments are some of the most consistently reported HIV-associated cognitive deficits, reportedly appearing in 40–60% of PLWH and with severity increasing progressively as the disease moves into its later stages (Fogel et al., 2017; Seider et al., 2014; Woods et al., 2009). The pattern of HIV-associated impairment usually involves both encoding and retrieval difficulties, with some studies identifying a 'frontal' pattern that indicates a dysexecutive type of memory impairment (Ciccarelli et al., 2017; Rubin et al., 2015; Sullivan et al., 2020; Witten et al., 2015).

Neuroimaging research has identified the medial temporal lobes, prefrontal cortex, and subcortical structures such as the hippocampus, all of which are important memory processing centres, to be particularly vulnerable to HIV neuropathology (Kamkwalala et al., 2020; Sanford, Cruz, et al., 2017). Structural imaging studies have found that volumes in these neuroanatomical regions are smaller in PLWH than in healthy controls (Rubin et al., 2016, 2017; Thames et al., 2018). Further, impaired hippocampal functioning is associated with poorer verbal encoding and retrieval performance in PLWH than in uninfected controls (Fama et al., 2014; Israel et al., 2019; Rubin et al., 2016).

Of further interest is that HIV-associated impairment in the domain of learning and memory can have significantly effects on everyday functioning. Learning and memory are crucial to competent everyday functioning and impairments in these can have serious consequences, such as medication adherence and doctors' appointments, recalling important

information such as banking details and passwords (Avci et al., 2018; Heaton, Marcotte, Rivera Mindt, et al., 2004; Woods et al., 2008, 2017). Additionally, learning and memory in PLWH have been found to be particularly vulnerable to stress, trauma, and adverse social conditions. Exposure to such experiences or situations appears to compounding the negative effects of the infection itself (Kasper, 2017; Rubin, Cook, et al., 2015; Rubin, Pyra, Cook, et al., 2016; Watson et al., 2019).

Executive Functioning. The psychological construct of executive function refers to a collection of higher-order cognitive processes, typically localised to the frontal lobes and related circuitry, that includes inhibition (mental control), set shifting (mental flexibility), planning and organization (strategy), reasoning, problem solving, decision-making (self-regulation), and others. Although theoretical conceptualizations and empirically-based research models of executive function vary widely, most include all or some combination of these components (see, e.g., Baggetta & Alexander, 2016; Kanmogne et al., 2018; McLaurin et al., 2017; Walker & Brown, 2019). Moreover, regardless of which model is used, researchers and clinicians accept that the cognitive processes comprising executive function can be interlinked reciprocally with one another. It is for this reason, among others, that neuropsychological tests assessing executive function most often measure several of its different components simultaneously (Cohen et al., 2018; Moore et al., 2020; Van Rheenen et al., 2019). For instance, the Stroop Color-Word Test measures inhibition, cognitive flexibility, and error monitoring (Macleod, 1991; Periáñez et al., 2021; Scarpina & Tagini, 2017), while the Trail Making Test measures inhibition and set-shifting (Fellows et al., 2017; Macpherson et al., 2017) and the Wisconsin Card Sorting Test measures abstraction, reasoning, error monitoring, and perseveration (Kopp et al., 2021; Lie et al., 2006).

Executive dysfunction is observed commonly in the advanced stages of HIV disease, although there is some evidence of related dysfunction and neuronal injury during early-stage

infection (Hines et al., 2015; Jiang et al., 2015; Woods et al., 2009). Several studies have found that set shifting, planning, sequencing, error monitoring, multitasking, inhibition, impulse control, judgement and decision making, and even strategic aspects of memory encoding and retrieval, are all components of executive functioning that are compromised in HIV (Fama et al., 2016; Saylor et al., 2016; Walker & Brown, 2019).

HIV-associated executive function deficits have been associated with decreased volume in subcortical gray matter structures, specifically the right putamen, the right globus pallidum, the left nucleus accumbens, and the caudate nucleus bilaterally (Corrêa, Zimmermann, Netto, et al., 2016; O'Connor et al., 2018b). Moreover, although some studies have found no significant structural differences between the cortical volume of PLWH and uninfected controls, they did find markers of focal inflammation in the anterior and posterior cingulate (gray matter) and corpus callosum (white matter) to be associated with poorer executive function performance (Garvey et al., 2014; Halloran et al., 2019). One study highlighted the anterior cingulate (specifically its dorsal region) as a potential marker of impending executive impairment due to it being one of the earliest affected by HIV and showing significant damage in the later stages of the disease (Jiang et al., 2015).

Performance on tests of executive function has consistently been found to be impaired in older PLWH (Fazeli et al., 2017; Moore et al., 2020b; Paul et al., 2018). For example, a 4-year longitudinal study investigating cognitive function in HIV administered multiple neuropsychological tests to four groups of participants (older PLWH, younger PLWH, older seronegative group, and younger seronegative) in order to examine the influence of age and infection separately and in interaction. Results suggested a marked decline in executive function in the PLWH groups compared to the seronegative groups, as well as a global cognitive decline in the two older groups compared to the two younger groups. Taken together, it appeared that executive function was significantly affected by HIV, but that the

combination of HIV and older age was particularly deleterious (Haynes et al., 2018). Several studies have also noted that, in older PLWH, impaired executive function performance is associated with decreased brain volume in subcortical gray matter bodies (such as the putamen and caudate), general decreased gray matter volume, and white matter hyperintensities (Pluta et al., 2019; Sanford, Fellows, et al., 2018b; Watson et al., 2017).

HIV-associated executive dysfunction is also significantly associated with impairment in instrumental activities of daily living (e.g., medication adherence), specifically due to poor planning, organization, decision making and problem solving (Heaton, Marcotte, Mint, et al., 2004; Minassian et al., 2013; Sullivan et al., 2020). It is also associated with higher impulsivity, risk-taking behaviour, and concomitant substance abuse (Giesbrecht et al., 2014; Martin et al., 2004).

Cognitive Reserve

Cognitive reserve is a theoretical construct that attempts to explain individual differences in vulnerability to cognitive, behavioural, or functional impairment due to neuropathological or age-related brain changes (Stern et al., 2018). However, much debate surrounds the exact definition, and consequently the measurement, of cognitive reserve.

The concept of cognitive reserve has been observed and investigated since the 1960s, when it was referred to as ‘individual resilience’ arising from observed inconsistency between cognitive performance and brain disease burden across individuals (Blessed et al., 1968; Garmezy & Masten, 1986; Geerlings et al., 1999; Rutter, 1987; Schmand et al., 1997; Stern et al., 1999, 2019a). Since then, the construct referring to individual variability in cognitive outcomes as it relates to brain pathology has been called several different names (e.g., brain reserve, brain maintenance, compensation, cognitive resilience) and has been housed within several different theoretical frameworks (Jones et al., 2011; Stern et al., 2019b; Whalley et al., 2016).

The dominant theoretical framework, perhaps because it has accumulated the most empirical support, is closely associated with the work of Yaakov Stern. He proposed that cognitive reserve could be understood as a compensatory mechanism that preserves cognitive function in the presence of a damaging force until the threshold of clinical symptoms, which is variable between individuals, is reached (Barulli & Stern, 2013; Foley et al., 2012; Stern, 2002, 2003; Thames et al., 2011). This compensatory mechanism comprises passive and active aspects that work independently and synergistically to counteract decreased functional capacity consequent to neuropathology.

Passive Aspects of Cognitive Reserve

These are the structural (i.e., physical, anatomical) properties of the brain that afford individuals the ability to maintain adequate levels of cognitive functioning despite structural damage (Cody & Vance, 2016; Kesler et al., 2010; MacPherson et al., 2017; Stern et al., 2019a). The most striking of these properties is larger brain size, which translates to increased volume as well as larger neuronal and synaptic count. Larger brain size (and consequent increased neuronal count) is also associated with increased redundancy within, and complexity of, neural networks. The property of redundancy (or 'scaffolding') is particularly important in that it allows the brain to continue achieving targeted goals even when some aspects of the network are compromised. Several studies propose that the prefrontal cortex is a particularly noteworthy site of redundant, scaffolded networks (Goha & Park, 2009; Oschwald et al., 2020; Pettigrew & Soldan, 2019; Sadiq et al., 2021).

The structural properties that are often referred to as 'brain reserve' are measured in brain size, gray and white matter volume, neuronal count, and similar neuroimaging outcomes. Individual differences in 'brain reserve' are proposed to be determined by biological factors, such as genes or age (Clewett et al., 2015; Steffener & Stern, 2012; Stern et al., 2019b; Whalley et al., 2016).

Recent investigations emphasize the importance of passive aspects of cognitive reserve (see, e.g., Knížková & Rodriguez, 2020; Pietzuch et al., 2019). For instance, Groot et al. (2018) found that, in a sample of 663 patients with Alzheimer's Disease, both active elements (measured by proxy through educational attainment) and passive elements (measured through intracranial volume) of cognitive reserve independently mitigated the negative effects of the neurodegenerative disorder. Although active elements were stronger mitigating factors in the prodromal stages of the disease, greater intracranial volume appeared to be more beneficial as the disease progressed

Active Aspects of Cognitive Reserve

These are the efficiency, flexibility, and adaptability of available brain resources and neural connections that actively compensate for physically damaged areas and that are thought to be enhanced by life experiences and activities (Bott et al., 2019; Clare et al., 2017; Evans et al., 2018; Stern et al., 2019c). The flexibility and adaptability of the brain, especially in the wake of pathological insults, is often called *neuroplasticity*. Formally, this term is defined as the brain's compensatory ability to switch between and recruit different neural networks to maintain functioning and to adapt to structural brain changes (Dorszewska et al., 2020; Pestana & Sobral, 2019; Stern et al., 2018)

Neuroplasticity can be either negatively or positively influenced by events across the lifespan. Exposure to negative neuroplastic events, such as stress or depression, or simply experiencing a lack of stimulating events or novel environments, produces weaker neural networks and brain atrophy (Begega et al., 2017; Cody & Vance, 2016). The negative effects occur on a cellular level as, at one end of the spectrum, chronic stress triggers a persistent cycle of activation and deactivation of the hypothalamic-pituitary-adrenal axis which causes damage to particular brain areas (i.e., hippocampus, hypothalamus, amygdala) over time through dysregulation and desensitization. At the other end of the spectrum, chronic

depression and lack of stimulation results in degeneration of brain areas through mechanisms related to neurotransmitters and metabolic regulations, i.e. decreased use leads to decreased blood flow and activation which leads to degeneration (Phillips, 2017; Tolahunase et al., 2018).

In contrast, positive neuroplastic events are those that produce stronger neural connections. Typically, these events are associated with enriched environments and exposure to novel stimuli; hence, they include educational attainment, occupational success, higher levels of crystallised intelligence (e.g., as measured by verbal IQ tests), and constructive stimulation by leisure activities/pursuits. Many of these have consistently been shown to correlate with increased brain volume or capacity, especially in the context of brain injury, and hence many have become popular proxy measures for cognitive reserve (Dorszewska et al., 2020; Opdebeeck et al., 2015; Stern, 2002). Further details of these measures are provided in the next sub-section.

Several studies have investigated, using neuroimaging techniques and metabolic measures, the physical effects that active aspects of cognitive reserve can have on the brain (Franzmeier et al., 2017; Mazzeo et al., 2019; Šneidere et al., 2020; Teixeira-machado et al., 2019; van Loenhoud et al., 2017). A recent systematic review (Anthony & Lin, 2018) summarized this literature and reported that both structural neuron recruitment and measurable cognitive outcomes were associated with higher cognitive reserve (as measured by at least 1 proxy measure, such as education or an intelligence measure) in individuals presenting with age-related cognitive decline, mild cognitive impairment, or cognitive impairment due to Alzheimer's disease. Brain regions that appear to be associated with higher levels of cognitive reserve were: (1) the medial temporal and cingulate areas (areas associated with memory processing; persons with increased neuronal count in these regions tended to have better cognitive reserve), and (2) the prefrontal and dorsal regions of the

frontal lobes (areas associated with attention networks; increased neural count in these regions was associated with flexibility and adapting compensatory neural pathways.

Another recent review (Gallo et al., 2020) investigated the neural and cognitive mechanisms through which bilingualism (a proxy for cognitive reserve) can improve neuroplasticity and protect against age-related cognitive decline. The review reported that bilingualism was a significant factor in protecting against gray matter volume loss and related cognitive decline due to age, particularly in life-long bilingual subjects who continued to use their second language past retirement. The study emphasized the value and role of social and personal factors, such as bilingualism, in strengthening neuronal structure to foster healthy aging and to stave off cognitive decline (i.e., to enhance cognitive reserve).

Measures of Cognitive Reserve

As noted above, cognitive reserve is a theoretical construct. Hence, it cannot be measured directly, but must instead be defined operationally before it can be studied scientifically. Unfortunately, there is no universally agreed-upon operational definition, and so different research groups tend to use different proxy measures (i.e., variables believed to be related to or to directly influence cognitive reserve) in order to estimate it and to investigate its influences and effects (Bettcher et al., 2019; Jones et al., 2011; Stern, 2003). Of course, this can make cross-study comparisons difficult, and so it is worthwhile creating a general taxonomy of the different proxy measures of cognitive reserve.

Broadly speaking, four types of proxy measures (each based on specific theoretical notions about the construct) appear in the published literature on cognitive reserve: (a) crystallized intelligence, (b) educational attainment, (c) neuroimaging variables, and (d) social activity.

Crystallized intelligence. This is typically measured using standardized IQ scales. These include, among many others, the Verbal index or the Full-Scale index of the Wechsler

Adult Intelligence Scale (WAIS; Wechsler, 1981), and word reading / vocabulary tests such as the Wechsler Test of Adult Reading (WTAR; Wechsler, 2001) or the National Adult Reading Test (NART; Nelson, 1982). This proxy measure of cognitive reserve is often problematic in low- or middle-income countries because most standardized IQ, word reading, and vocabulary tests have been developed in high-income countries of the global north, feature English-language stimulus items, and have no local normative standards (Fernald et al., 2017; Hoshen & Werman, 2017; Panicker, 2012).

Educational attainment. This is typically measured using the number of years of formal education completed successfully. This measure can be problematic because it fails to account for the quality of the education received by the individual. Quality of education is an important variable to account for in low- or middle-income countries such as South Africa, where there are often great disparities between the resources offered at schools in different communities and across urban and rural settings (Fyffe et al., 2011; Moloi & Strauss, 2005; Moses et al., 2017; Spaull, 2013). In South Africa, student academic performance has been linked to quality of education, which can be captured by several different variables (e.g., whether the school is private or public; whether it is located in an urban or rural setting; school resources; availability of additional learning resources). Hence when 'educational attainment' is measured by highest level of education, two South Africans who have achieved the same grade may not have had the same quality of education and hence may not have achieved the same level of academic performance (Gamaldo et al., 2018; Moolman et al., 2020; Wills & van der Berg, 2020).

Neuroimaging variables. These estimate physical attributes thought to be related to cognitive reserve (e.g., brain volume, neuronal count, metabolic activity). The exact method and focus of neuroimaging investigations in the cognitive reserve literature is extremely variable, especially because studies emerge from numerous different disciplines ranging from

medicine to social sciences. Some studies investigate how the structural composition of the brain supports cognitive reserve (especially the passive aspect of 'brain reserve'), using methods such as magnetic resonance imaging (MRI) and modalities like diffusion tensor imaging (DTI). Other studies use functional MRI or positron emission tomography (PET) scans to investigate ways in which the functional and metabolic workings of the brain support cognitive reserve (Bettcher et al., 2019; Reed et al., 2010; Stern et al., 2005; Stern & Barulli, 2019).

Social measures. They attempt to capture variability in lifetime experiences and activities (e.g., occupational attainment, leisure pursuits, and cultural exposure) that have been associated with resilience to cognitive decline in the face of neuronal injury. The idea here is that the more one engages in enriching experiences and activities, the more likely one's cognitive resilience will increase. Similar to the difficulty with neuroimaging variables, the exact nature of these measures varies widely between studies and disciplines (Dekhtyar et al., 2019; Karp et al., 2006; Sauter et al., 2019; Schooler & Mulatu, 2001).

Because most researchers in this field recognize the abovementioned problems with each of these proxy measures, they attempt to improve their empirical studies by using more than one of the measures to estimate cognitive reserve. Most often, this means capturing the participant's educational attainment and administering an IQ test (Fazeli et al., 2014; Kaur, Dendukuri, Fellows, Brouillette, & Mayo, 2020; Kaur et al., 2019; Morgan et al., 2012; Van Rheenen et al., 2019). Nonetheless, using only a limited subset of these proxy measures underestimates the complexity of cognitive reserve, neglects the influence of those aspects of the construct not estimated, and does not account for how these variables interact to shape cognitive reserve.

In an attempt to remedy some of these difficulties, Nucci, Mapelli, and Mondini (2012) created the Cognitive Reserve Index questionnaire (CRIq), a standardised scale

designed to produce a quantifiable measure of cognitive reserve. The scale consists of three sections (education, occupation, and leisure time), with each section consisting of various questions answered on a Likert-type scale. An accompanying set of online formulas calculates a score for each individual section, as well as a total cognitive reserve score. The scale functions similarly to those for IQ scores, with the mean being 100 and the standard deviation 15 for the total cognitive reserve score.

Although this scale does attempt to provide some standardized way of measuring cognitive reserve, and although it has been used widely in recent years (see, e.g., Fenu et al., 2018; Franzmeier et al., 2017; Kartschmit et al., 2019; Kaur et al., 2020; Nunnari et al., 2014), it is not a panacea for all long-standing problems in this literature. For instance, it is a purely self-report measure that offers no objective IQ estimate. It focuses purely on sociodemographic and social variables and does not measure crystallized intelligence or the theorised physical aspects (e.g., brain volume or neuronal count) of cognitive reserve.

Additionally, the fact that the CRIq was developed in a high-income Westernised environment means it is potentially biased when used in relatively socially and economically disadvantaged populations. The sources of these potential biases are numerous. First, the CRIq does not take quality of education into account, measuring educational achievement only by the number years of formally completed schooling. Second, it does not take into account the influence of economic hardship or restricted or limited access to resources. For example, there are items asking about the frequency of driving or using smart technology; people who live in low- or middle-income countries may not have access to such technology. Third, and similarly, although research has shown that leisure activities are a key aspect of cognitive reserve (Ihle et al., 2018; Wells et al., 2019), the types of leisure activities enquired about by the CRIq are luxuries not accessible to many people outside of high-income countries.

Cognitive Reserve in Summary

In summation, the passive aspects of cognitive reserve, which are often referred to as 'brain reserve', are the structural resources (in crude terms, the number of neural networks) that confer a physically greater capacity of the brain to tolerate erosion before a certain threshold of symptomatic cognitive impairment is reached. In contrast, the active aspects of cognitive reserve are the adaptive and flexible ways the brain recruits those structural resources to accomplish functional tasks (especially when it is seeking to compensate for neuronal injury). These passive and active aspects appear to work both independently and synergistically; that is to say, the brain cannot recruit and adapt to the use of multiple neural networks if those networks do not exist. Some use the computer science analogy of 'hardware' and 'software' to illustrate how these passive and active aspects of cognitive reserve function together (Stern et al., 2019a).

There are alternative theoretical models of cognitive reserve. One of these is based on animal models of brain adaptation, and is more grounded in biological mechanisms of neurodegeneration and age-associated neuropathology. This theoretical framework aims to investigate common cross-species biological mechanisms of brain-related decline (see, e.g., Engle et al., 2016; Lester et al., 2017; Newell et al., 2020; Samson & Barnes, 2013). This translational research option is viable because many non-human animal species are vulnerable to the same kinds of age-related neurodegeneration and cognitive decline as humans are. An advantage of such approaches is that they can be supported by more detailed anatomical investigations than are possible with human samples. Another advantage is that studies within this framework can be conducted outside of the mass of social, psychological, and societal variables that confound human studies (Medaglia et al., 2017; Stern et al., 2019a).

Regardless of the various theoretical models that try to account for it, cognitive reserve has consistently been observed through empirical investigation to be a robust and valuable protective process found in neurodegenerative, neurological, and psychiatric conditions (e.g., Alzheimer's disease, Parkinson's disease, multiple sclerosis, traumatic brain injury, anxiety, and depression) and in studies of normal, pathology-free, aging processes (see, e.g., Colangeli et al., 2016; Evans et al., 2019; Fenu et al., 2018; Hindle et al., 2016; Kaur et al., 2019; Sandry et al., 2016; Van Rheenen et al., 2019). In short, the influence and value of cognitive reserve as an explanatory theory to account for individual variability in cognitive dysfunction has been consistently established in the literature and is a valuable aspect to consider in the investigation of HIV-associated cognitive impairment.

Cognitive Reserve and HIV

A small body of literature investigates whether higher levels of cognitive reserve mitigate effects of HIV infection on cognitive function and on ability to complete activities of daily living successfully. Broadly speaking, these studies suggest that cognitive reserve and cognitive performance bear a significant association to each other in PLWH, and that cognitive reserve appears to be associated with the severity of the disease's impact, i.e., the higher cognitive reserve, the less the cognitive fallout from the disease (Foley et al., 2012; Kayungwa et al., 2016; Morgan et al., 2012; Shapiro et al., 2014).

A recent systematic review and meta-analysis (Kaur et al., 2020) examined data from 10 papers, published between 1996 and 2016, investigating cognitive reserve in HIV. The authors found significant associations between cognitive performance and indicators used to estimate cognitive reserve. PLWH with low levels of cognitive reserve were more likely to experience cognitive difficulty and to require more intensive treatment and management. However, the review concluded that due to the limited quantity and scope of existing research

more systematic investigation into the relationship between cognitive reserve and HIV-associated cognitive dysfunction was required to make more definitive claims.

Few individual empirical studies have investigated questions regarding whether cognitive reserve has differential effects depending on HIV severity. In one of those few studies, Alvarez-Tostado et al. (2016) found that cognitive reserve was a more significant protective factor during the middle (latent) stage of HIV, rather than at either the early or the late stage. However, regardless of the stage of HIV, higher levels of cognitive reserve were significantly associated with better overall cognitive performance.

Less than a handful of South African studies have investigated cognitive reserve in HIV. One such study reported that, in sample of 5 059 adults aged ≥ 40 years (54% female) recruited in 2015 from rural areas across the Mpumalanga province in northeast South Africa, age was a significant negative influence on cognitive function (Kobayashi et al., 2019). The authors noted a mediating effect of cognitive reserve, however: The effect of age on cognition decreased as cognitive reserve increased. That study, along with the few other South African studies in this literature, emphasize the importance of cognitive reserve and the potential benefits of increasing cognitive reserve through intervention efforts to mitigate HIV-associated cognitive impairments.

In summary, cognitive reserve appears to protect HIV-infected individuals against cognitive dysfunction. However, a major risk factor threatening cognitive function in PLWH is the damaging interaction between the infection and the aging process.

Accelerated Aging in HIV

The introduction of cART changed the prognosis of HIV from a terminal illness to a manageable chronic condition where life expectancy is expected to reach 50 years and older (Wallace et al., 2017; Wilson et al., 2015). Epidemiological estimates suggest that 75% of the total PLWH population will be aged 50 or older by 2030, which means there is a rapidly

increasing population of older adults with HIV infection (Aung et al., 2019; Cody & Vance, 2016; Oliveira et al., 2015).

The relationship between aging and declining cognitive function (even in the absence of neurodegenerative disorder) is well established both clinically and in research. Aging results in accumulative cellular and genetic damage that continues throughout the lifespan. This damage manifests in metabolic, structural, and functional brain changes, although the exact mechanisms behind these changes are complex, multifactorial, and still not fully understood (Farokhian et al., 2017; Luu & Palczewski, 2018; Moreno-García et al., 2018; Zhuang et al., 2021).

Several well-established features are associated with the normal neural aging process. These include: (1) cortical volume loss and thinning, (2) white matter fibre degradation, and (3) decreased cerebral blood flow and other metabolic dysfunction. All of these features are related to age-related physiological homeostatic decline (i.e., the increasingly unstable regulation of cellular and metabolic processes), which ultimately leads to cellular senescence, dysfunction, and eventual death (Luu & Palczewski, 2018; Mattson & Arumugam, 2018).

Cortical thinning and volume loss involves the gradual decrease in the size (and, later, the numbers) of neuronal bodies that comprise the cortical gray matter. Decreasing size and, ultimately, death of neuronal bodies can be directly attributed to genetic (e.g., the presence of the APOEƐ4 genotype, which negatively impacts neuron functional integrity) or environmental (e.g., poor lifestyle choices) factors (Afonso et al., 2017; Aycheh et al., 2018; Rast et al., 2018).

Degradation of white matter (i.e., brain tissue that connects neurons) results in a breakdown of neuronal networks, connectivity, and communication. White matter integrity is particularly sensitive to the aging process, with studies suggesting mechanisms attributable to negative genetic influences (e.g., specific genes or combination of genes and the variance in

their phenotypic expression). Damage to the integrity of white matter appears to affect the frontal lobes, and consequently performance on tests assessing executive functioning, more than other brain regions (Glahn et al., 2013; Hodgson et al., 2017; Vinke et al., 2018; Zhuang et al., 2021).

Disruptions of cerebral blood flow (e.g., decreased blood flow due to hypotension or damaged arteries resulting from arterial stenosis) can result in inefficient resource supply to the brain, the effects of which accumulate over time. For example, neuronal bodies will decrease their size to adjust to the available blood supply, and interrupted or decreased blood supply can result in white matter lesions (Catchlove et al., 2018; Jefferson et al., 2018; Tarumi & Zhang, 2018).

Considering all of these features of associated with the normal neural aging process, it is unsurprising that older PLWH (i.e., those aged > 50 years) are more vulnerable to cognitive dysfunction than their younger counterparts, particularly in the domains of information processing speed, verbal memory, and motor speed/coordination (Boerwinkle et al., 2021; DeVaughn et al., 2015; Fellows et al., 2014; Hoare et al., 2013; Seider et al., 2014). Older HIV-infected adults also tend to report poorer quality of life and medication adherence, as well as inferior ability to complete activities of daily living successfully (Hinkin et al., 2004; Kapetanovic et al., 2020; Rodriguez-Penney et al., 2013).

The mechanisms through which age exacerbates cognitive dysfunction in PLWH include: (1) processes of chronic inflammation and immune activation (Guaraldi et al., 2019; May et al., 2019; Oliveira et al., 2015), and (2) an acceleration of the normal biological aging process (Deeks & Phillips, 2009; Levine et al., 2016; Underwood et al., 2018). Regarding the first of these, the presence of HIV in the body (even when viral load is suppressed and controlled) results in a persistent low-grade immune activation that can eventually cause a chronic state of inflammation. This sustained state of immune activation and inflammation,

sometimes termed ‘inflammaging’ (Franceshi et al., 2000), stimulates the release of reactive oxidative chemicals that over time cause DNA damage. This damage leads to cellular injury akin to that found in normal aging processes (Oliveira et al., 2015; Sundermann et al., 2019).

Regarding the concept of ‘accelerated’ (or ‘accentuated’) aging, this term refers to a process whereby HIV-associated structural damage takes place via degradation of white matter integrity, exacerbation of abnormalities in white matter structure, and increases in brain atrophy. At the molecular level, HIV has been shown to cause a gradual accumulation of damage to cellular structures, not just in the brain but throughout the body (Mackiewicz et al., 2019; Mahmood et al., 2019; Petersen et al., 2020). This damage persists even when patients are virally suppressed on effective cART (Gao et al., 2020; Guaraldi et al., 2019). At the behavioural level, the consequences of accelerated aging at the biological level have been reported consistently in HIV research (Cohen et al., 2015; Kuhn et al., 2019; Mahmood et al., 2019; Seider et al., 2016).

Research studies use several different clinical markers to index accelerated aging in HIV. These include indicators of chronic immune activation, excitotoxicity, oxidative stress, and, most commonly, DNA telomere length (Malan-Müller et al., 2013; Pathai et al., 2013). Recently, DNA methylation (a chemical process whereby methyl groups are added to DNA nucleotides, thereby stably changing the gene expression of a cell) has been used as an epigenetic mechanism marker for aging and has been found to be an extremely accurate measure of cellular aging (Levine et al., 2016; Gross et al., 2016).

The damaging interaction between age and HIV infection has significant repercussions for cognition (including problem solving and judgement), behaviour (especially regarding risk-taking actions), independent living ability, quality of life, and medication adherence (Hinkin et al., 2004; Rodriguez-Penney et al., 2013). Older PLWH also appear to have increased risk of frailty, lower physiological reserve, and poorer functional capability,

as well as increased susceptibility to non-communicable diseases and other conditions (Guaraldi et al., 2019; Rasmussen et al., 2015). Additionally, age also appears to influence prognosis and cART efficacy negatively. That is to say, the later a person is diagnosed and the later cART is initiated, the worse the prognosis (Hontelez et al., 2011; Justice, 2010).

The literature reviewed above suggests strongly that age is an important risk factor for cognitive dysfunction in PLWH. There is, however, a detectable individual variability in the outcomes of cognitive performance and functional capability among older PLWH; where some show markedly decreased performance and capacity, others do not (see, e.g., Bauer, 2018; Hines et al., 2016; Jones et al., 2018; Harrison et al., 2017; Rubin et al., 2018). The resilience to decline in some older PLWH, and the overall variability in the population, appears to be influenced by various individual environmental and behavioural factors, including diet quality, degree of lifestyle activity, mental health, stress, trauma, substance use, and mental stimulation (Addington et al., 2020; Clare et al., 2017; Fleck et al., 2019; Guaraldi et al., 2019; Pope et al., 2020).

In summary, the negative effects of both age and HIV on cognitive function, both independently and synergistically, have been well established in literature. However, the potential for protective factors emerging from research into cognitive reserve has yet to be as definitively established and warrants further investigation.

CHAPTER 3:

Rationale, Aims and Hypotheses

HIV is a significant global health concern, not least because some degree of cognitive dysfunction is present in an estimated 50–60% of infected individuals. The question of why some people living with HIV (PLWH) experience cognitive dysfunction and others do not has led researchers to investigate how individual difference factors can influence the trajectory of HIV-associated cognitive impairment.

Research into describing each factor, and then enumerating the strength of each in independent and interactional influence on cognitive function, is complex but necessary. The primary aim of this study was to investigate two such individual difference factors: cognitive reserve and age. Previously published studies suggest that both have an impact on cognitive function in PLWH. However, very few studies (a recent systematic review included only 10; Kaur et al., 2020) have been conducted on the influence of cognitive reserve on cognitive function in the context of HIV. None of those studies were conducted using an African sample, despite 70% of the global HIV burden carried by sub-Saharan Africa and roughly 20 million PLWH in eastern and Southern Africa (Mushi, 2017; Poteat et al., 2017). Additionally, the measures of cognitive reserve used in the literature are disparate and heterogenous.

The research presented in this thesis incorporates the first study to investigate cognitive reserve in the context of an African sample of PLWH. The study also uses comprehensive and diverse measures of cognitive reserve (i.e., the self-report Cognitive Reserve Index Questionnaire as well as MRI measures of brain volume).

In summary, the present study set out to examine the strength of influence that cognitive reserve and age have on cognitive function in a South African sample of PLWH. The study's design allowed these specific hypotheses to be tested:

1) Cognitive reserve is a significant predictor of cognitive test performance in PLWH; specifically, higher levels of cognitive reserve are associated with better performance.
2) Age is a significant predictor of cognitive test performance in PLWH; specifically, increasing age is associated with poorer performance.
3) The interaction of cognitive reserve and age is a significant predictor of cognitive test performance; specifically, older individuals with lower cognitive reserve will display poorest cognitive performance.

CHAPTER 4

Methods

Design and Setting

This study used an exploratory, relational, and cross-sectional design to investigate the influence of cognitive reserve and age on cognitive performance in people with HIV. The study was nested within two longitudinal parent studies. The first of these is based in the University of Cape Town (UCT) Division of Neurology and investigates the role of inflammation in accelerated aging and anti-retroviral treatment (ART) toxic neuropathy in HIV (Borkum et al., 2014; Wearne & Okpechi, 2016). The second is based in the UCT HIV Mental Health Research Unit and investigates the relationship between cognitive impairment, ART adherence, and the presence of cerebrospinal fluid (CSF) discordance.

Hence, cognitive and behavioural data were collected at the UCT Division of Neurology and the UCT HIV Mental Health Research Unit, both of which are located in Groote Schuur Hospital (GSH). Neuroimaging data were collected in the Cape Universities Body Imaging Centre (CUBIC), also located in GSH.

Participants

I originally recruited 35 participants (27 women), using opportunistic sampling, from the participant pools of the two parent studies. All resided in Cape Town and surrounding communities, and all were Xhosa first-language speakers (except for one, a Shona first-language speaker).

Eligibility criteria. Participants had to be aged >18 years. They had to have had a positive diagnosis of HIV infection made within the 6 months prior to enrolment in one of the parent studies, and had to have been established on cART for at least 6 months prior to enrolment in one of those studies. They were also required to have none of the following: (a) a positive history of moderate-to-severe head injury (including loss of consciousness for > 30

mins; information obtained via the study-specific questionnaire described below); (b) severe cognitive impairment (indicated by a score of ≤ 12 on the Mini-Mental State Examination (MMSE; Folstein et al., 1975)) that would preclude the ability to provide informed consent for participation; (c) uncontrolled viral load, measured by archival medical data indicating that that load is at undetectable level or CD4 count is below 2000 cell/mm3 and; (d) a significant history or current presence of psychiatric disorder, as indicated by the Mini International Neuropsychiatric Interview (M.I.N.I version 5.0.0; Sheehan et al., 2006); (e) a significant history of alcohol or drug abuse, as indicated by the M.I.N.I; and (f) any contraindication to magnetic resonance imaging (screened for by the CUBIC consent form).

Measures

Screening Instruments

These instruments were used to determine participant eligibility and to gather information regarding potentially confounding variables.

Screening questionnaire. This study-specific questionnaire (see Appendix A) collected data regarding lifestyle variables (e.g., alcohol and substance use), family history, and medical history.

Mini-Mental State Examination (MMSE). This widely used instrument screens for cognitive impairment in dementing diseases, HIV-associated cognitive disorders, and cerebrovascular disorders (Folstein et al., 1975; Mai et al., 2016; Stein et al., 2015). It is an assessment of general cognitive function that contains items measuring orientation, attention, learning, memory, language, calculation, and visuospatial/visuoconstructional ability. Each item carries a score value of between 1 and 5 points, depending on the number of tasks required; overall, higher scores denote better general cognitive functioning.

The instrument's psychometric properties have been extensively researched. Several studies have reported on the reliability of the MMSE, with test-retest reliability reported to be

highly correlated, between r = .82 and r = .98 (Monroe & Carter, 2012; Stein et al., 2015). A meta-analysis of 34 studies using the MMSE reported that its sensitivity ranged from 79.8% to 85.5%, while its specificity ranged from 81.3% to 95.6% (Siedlecki et al., 2009). Globally, it is the most commonly used cognitive screening tool (Gross et al., 2019; Mateos-Álvarez et al., 2017; Vissoci et al., 2019). It has been used extensively in South African research studies (see, e.g., James et al., 2020; Joska et al., 2016; Skorga & Young, 2015).

Mini International Neuropsychiatric Interview English version 5.0.0 (M.I.N.I.). This structured clinical interview (Sheehan et al., 2006) assesses for the presence of 16 different psychiatric disorders through short yes-no questions which, depending on their answers, lead to more questions or a disconfirmation of the presence of the disorder under consideration. The M.I.N.I takes roughly 15 to 20 minutes to administer and was designed to be used by clinicians and lay counsellors, though the latter require more training and preparation.

Regarding psychometric properties, reported sensitivity ranges from 74% to 93% and specificity ranges from 70% to 92% (Amorim et al., 1998; Lecrubier et al., 1997; Myer et al., 2008). The M.I.N.I. also has good test-retest reliability, with Cronbach's α values ranging from .76 to .93 (Lecrubier et al., 1997). It has been used globally and in numerous cross-cultural studies (see, e.g., Chamali et al., 2020; Chellamuthu et al., 2017; Nejati et al., 2020). Several South African research studies have employed the instrument successfully (see, e.g., Abrahams et al., 2018; Bankole et al., 2017; du Toit et al., 2020).

Morisky Green Levine Medication Adherence Scale (MGLS). This brief self-report instrument (Morisky et al., 1986) measured participants' adherence to their antiretroviral (ARV) medication. It consists of four yes-no questions assessing factors that can influence adherence: memory, medication complexity, knowledge, and attitude. Each

item is scored 1 for a negative response and 0 for a positive response, so that the higher the total score the better the adherence to medication.

A systematic review of the MGLS' psychometric properties reported internal consistency coefficients ranging from .43 to .89 and an intraclass correlation of .82 (Pérez-Escamilla et al., 2015). Another systematic review of multiple medicine adherence measures reported the MGLS to have good sensitivity (72.2%) and specificity (74.1%) for detecting non-adherence (Srimongkon et al., 2019). The instrument has been translated and validated for use in China, Sri Lanka, and Indonesia, and has been found to have good reliability and validity in those settings (Ernawati & Islamiyah, 2019; Kumara et al., 2020; Tan et al., 2019).

Lawton Instrumental Activities of Daily Living Scale. This instrument (Lawton & Brody, 1969) is one of the most commonly used self-report measures of competence in completing activities of daily living (ADLs). Its most recent revision (Graf, 2008) was used in this study. This revision consists of eight items, one each relating to the following instrument activities of daily living (IADLs): telephone use, shopping, meal preparation, housework, laundry transport, medication, and finances. Each item has between 3 and 5 descriptions illustrating the level of capability. For example, the descriptions for the item related to laundry are: (1) Does laundry completely; (2) Can launder small items; or (3) Laundry must be done by others. Respondents select the description that most closely matches their current functional level. Each description is either scored 0 or 1, with higher scores indicating higher levels of ADL competence.

This instrument is reported to have good inter-rater reliability (r =.85), as well as good internal consistency (Cronbach's α values ranging from .70 to .91 Gold, 2012; Graf, 2013; Sikkes et al., 2009). Although it has not been formally validated for use in South Africa, it has been used frequently in South African research studies (Joska et al., 2011;

Morgan et al., 2013), and has been validated for use in several other low to middle income countries (Isik et al., 2020; Kadar et al., 2018; Siriwardhana et al., 2018).

Cognitive Tests

A battery of standard neuropsychological tests assessed performance within the seven domains of cognitive functioning most commonly affected in HIV: motor skills, information processing speed, attention, working memory, language, learning and memory, and executive functioning. The tests described below comprise the battery because they (a) are commonly used in HIV-related research (see, e.g., Almeida et al., 2018; Gouse et al., 2020; Joska et al., 2011; Morgan et al., 2013), and (b) have either been validated for use with South African samples or have been used in previous South African studies (Cross et al., 2013; Joska et al., 2016).

Grooved Pegboard Test (GPT). This instrument assesses motor speed and coordination (Klove, 1963). The stimulus material consists of 25 metal pegs and a metal board on which 25 holes are arranged in a 5 x 5 pattern. The test taker is required to insert one peg into each hole as quickly as possible, moving across rows in a systematic order and completing the array first with the dominant hand and then with the non-dominant hand. For each hand, the primary outcome variable is time taken to complete the task; hence, the longer this time is, the greater an indication of motor impairment.

The GPT is a well-validated measure of motor function that is used frequently in clinical and research settings (Bryden & Roy, 2005; Erdodi et al., 2018; Hanks et al., 2008; Schmidt et al., 2000). It has not, however, been validated completely for use with South African samples, and recent studies have found that, despite it being widely used in South African clinical settings, results from this country were widely disparate from US normative standards (Hoare et al., 2010; Van Wijk, 2019).

Color Trails Test (CTT). The two tasks comprising this instrument assess information processing speed, attention, and executive function (in particular, cognitive flexibility) (D'Elia et al., 1996). On both tasks, the participant is presented with a sheet of paper showing a scattering of encircled numbers and is required to draw a line connecting the numbers, in ascending order, as fast as possible. On the first task (CTT 1), the stimuli are the numbers 1–25, with each number enclosed within either a pink or a yellow circle. On the second task (CTT 2), there are distractor stimuli present: Each of the numbers 1–25 appears twice, once enclosed in a pink circle and once in a yellow circle. Here, the participant must connect the numbers sequentially while switching between the colours (e.g., 1 pink, 2 yellow, 3 pink, etc.). For each task, the primary outcome variable is time taken to complete the task (i.e., the longer the time taken, the greater an indication of impairment).

CTT 1 is a reliable and valid measure of information processing speed. CTT 2 is a reliable and valid measure of cognitive flexibility. Test-retest reliability is reportedly .90 for CTT 1 and .91 for CTT 2 (Guha et al., 2016; Tavakoli et al., 2015). The CTT has been used frequently in South African research studies (Joska, Westgarth-Taylor, Hoare, et al., 2011) and has been deemed a culture-fair instrument (Dugbartey, Townes, & Mahurin, 2000; Elkin-Frankston et al., 2007).

Verbal Fluency Tests. These tests, which require the participant to generate as many words as possible within 60 seconds under given certain instructional parameters, assess expressive language and generativity (Butters et al., 1987; Woods et al., 2005). In this study, I used semantic fluency tasks that required the participant to generate words from within category of *animals* first and *fruits and vegetables* next. I also used an action fluency task, which required the participant to generate only verbs. The primary outcome variable for each task is the number of correct words generated within the 60-s time limit; hence, the lower number of words generated, the more impaired language and generativity is indicated.

Verbal fluency tests appear to be valid and reliable measures of executive language abilities, such as word knowledge and generativity (Aita et al., 2019; Yeung & Chan, 2020). Studies have reported variable but overall good ranges of sensitivity (81% - 90%) for semantic fluency, in both healthy and neuropsychologically impaired populations, in detecting language based executive dysfunction. Test-retest reliability for semantic fluency was reported to be good, with one study reporting a correlation of $r = .73$ over a roughly 10 year period (Heun et al., 1998; Hurtubise et al., 2020; Sugarman & Axelrod, 2015; Woods et al., 2005). Verbal fluency tests are used frequently in South African clinical and research settings (Ferrett et al., 2014; Joska, Westgarth-Taylor, Hoare, et al., 2011; Lara et al., 2021).

Hopkins Verbal Learning Test-Revised (HVLT-R). This instrument, which assesses verbal learning and memory, consists of three learning trials and a delayed recall trial (Brandt, 1991). Initially, the test taker is read a list of 12 words and is then immediately asked to verbally reproduce as many words as possible from the list, in any order. This process is repeated twice more. After the third learning trial and a filled delay of roughly 20 minutes, the delayed recall trial is administered. On that trial, the test taker is asked to verbally reproduce as many of the 12 words as possible, in any order. The primary outcome variables are the total number of correct words produced across the three learning trials and the total number of correct words produced on the delayed recall trial. The lower the number of words the test-taker is able to recall, the greater an indication of impaired verbal learning and memory.

The HVLT is a valid and reliable measure of learning and memory. Its sensitivity and specificity for detecting memory impairments have been reported as 94% and 100%, respectively (Brandt, 1991). The instrument's test-retest reliability over a 14 to 134 day period has been calculated as $r = .78$ for the learning trials and $r = .74$ for the delayed recall trial (Benedict et al., 1998). Finally, studies report good construct validity, with Spearman's ρ

= .63 (Woods et al., 2005). The HVLT-R has also been used in numerous HIV neuropsychology studies, including some based in South Africa (Scott et al., 2020; Witten et al., 2015).

Rey-Osterrieth Complex Figure Test (ROCFT). This test, which assesses visuospatial skills, visual learning and memory, and elements of executive functioning such as planning and organization, consists of a copy trial, an immediate recall trial and a delayed recall trial (Strauss et al., 2006). Initially, the test taker is asked to copy the complex figure, which is presented as a black-and-white line drawing on an A4 page placed on the desk in front of the person. The immediate recall trial is administered 5 minutes after the copy stimulus is removed, and the delayed recall trial 20 minutes after completion of the immediate recall trial. On each of those trials, the participant is asked to draw the figure again from memory. On each of the copy, immediate recall, and delayed recall trials the test administrator records the time taken to complete the drawing as well as the strategy used to make the copy (i.e., in what order each element of the figure is drawn).

In this study, the accuracy of the copy, immediate recall, and delayed recall figures were scored using the standard 36-point scoring system (see Appendix B). These were the primary outcome variables. Another outcome variable was the Rey Complex Figure Organizational Strategy Score (RCF-OSS; Anderson et al., 2001; see Appendix C) for the copy trial. The RCF-OSS is a 7-point scoring system that captures the level of strategy employed to copy the figure. The RCF-OSS is often used to supplement the standard 36-point scoring system as the former takes into account which elements of the complex figure are placed first, which affects the quality of the copy, while the latter is a more qualitative score of the completed copy (Gouse et al., 2016; Rubiales et al., 2018). For both scoring systems, then lower the test taker's score, the greater an indication of impairment.

The ROCFT is a widely used and well validated neuropsychological test with reported specificity ranging from 91% to 97.9% in detecting both visual memory and executive function deficits (Ashendorf, 2019; Rubiales et al., 2018; Sugarman et al., 2016). The inter-rater reliability between ROCFT 36-point scores and the RCF-OSS scores are reported to be very high (r = .96; Davies et al., 2011). The RCF-OSS is also reported to have good inter-rater reliability, with values ranging from r =.85 to.92 (Anderson et al., 2001; Salvadori et al., 2019; Tupler et al., 1995). The ROCFT is also frequently used in the South African setting and some studies have produced normative data for both English and isiXhosa speaking groups, reporting that the ROCFT had adequate sensitivity (73.3% – 76.7%) to distinguish healthy controls from participants with dementia (Human et al., 2013; Ramlall et al., 2014; Shuttleworth-Edwards et al., 2014).

Measures of Cognitive Reserve

As noted at length in Chapter 2, cognitive reserve is a hypothetical construct that cannot be measured directly but can be estimated using proxy measures. Here, I used three such proxy measures, each of which features frequently in this literature. Brain reserve, often referred to as the passive aspect of cognitive reserve, was measured using magnetic resonance imaging (MRI) techniques. Active aspects of cognitive reserve, such as premorbid (crystallised) intelligence and psychosocial functioning, were measured using a standardised IQ Test and the Cognitive Reserve Index Questionnaire (CRIq), respectively.

Magnetic Resonance Imaging. I used standard anatomical magnetic resonance imaging methods, such as T1 contrast and diffusion tensor imaging (DTI), to measure gray matter volume and white matter integrity, respectively, as biological indices of cognitive reserve. Imaging data for each participant were obtained using a 3T Siemens Skyra full body scanner, housed at the Cape Universities Body Imaging Centre (CUBIC) within Groote Schuur Hospital. T1 high resolution structural imaging (MEMPRAGE, 1mm iso iPATx3;

acquisition time 5:21) and 3D susceptibility weighted imaging (SWI3D; t2 swi3d tra p2 1.5mm; acquisition time 4:54) were used to collect structural and volumetric data. Other scan sequences such as field mapping (acquisition time 1:10) and resting state activity (ep2d resting; acquisition time 6:08) were also obtained. Total acquisition time was approximately 45 minutes. The primary outcome variables were the fractional anisotropy score from the DTI acquisition, as an overall standardised score of white matter density, and the total gray and white matter volumes from the structural imaging acquisition. The fractional anisotropy score represents a scalar value, ranging between 0 and 1, that describes the degree of anisotropy of water molecules in the measured brain region (i.e. the degree to which they diffuse freely in any direction). This diffusion can be affected by myelin structure, fibre density, axonal diameter, or other structural properties of the surrounding tissue; hence, the fractional anisotropy score allows inferences about the integrity of that tissue (Grieve et al., 2007).

Kaufman Brief Intelligence Test-Second Edition (KBIT-2). This test (Kaufman & Kaufman, 1997) assesses verbal and performance (non-verbal) domains of intelligence. A total score, comprised of the aggregate across those domains, represents an overall IQ score (i.e., a measure of crystallised intelligence).

The *Verbal Knowledge* subtest asks the participant to indicate which one of six images best illustrates a vocabulary word presented by the examiner, or best answers a question asked by the examiner. The *Matrices* subtest requires the participant to indicate which one of six pictures best completes an incomplete pattern presented by the examiner, or identifies a relationship presented by the examiner. The *Riddles* subtest requires the participant to generate a response to a verbal riddle asked by the examiner. Raw scores from each subtest are converted to age-adjusted standardised scores (AASS) using the published normative data (Bryan, 2011; Desideri et al., 2016). A verbal IQ score is calculated by combining the AASS from the Verbal Knowledge and Riddles subtests. A non-verbal IQ

score is calculated using the AASS from the Matrices subtest. A full-scale IQ score is calculated by combining the verbal and non-verbal IQ scores.

It is important to note that language, cultural, and measurement biases affect task performance when standardised IQ tests developed in the global north are used in South Africa (and in other LMICs; Sunderaraman et al., 2016; Wicherts et al., 2010). Even those IQ tests developed or adapted for the South African population, such as the Senior South African Individual Scales-Revised (SSAIS-R; Van Eden, 1997) or the South African adaptation of the Weschler Adult Intelligence Scale Version-Third Revision (WAIS-III; Foxcroft & Aston, 2006; Wechsler, 1997), fall short due to flaws related to language and cultural biases, outdated norms, and questionable predictive validity (Jacklin & Cockcroft, 2012; Shuttleworth-Edwards et al., 2004, 2016;). Hence, although one might question the suitability of the KBIT-2 for use in studies such as this, it may be a reasonable estimate of premorbid/crystallised intelligence if only the non-verbal IQ score is taken, which is less likely to be affected by language and cultural biases (Saccuzzo et al., 1992).

Cognitive Reserve Index Questionnaire (CRIq). This self-report instrument (Nucci et al., 2012; see Appendix D) gathers information that allows an estimate of the individual respondent's cognitive reserve. It contains questions about behaviour within three domains (education, occupation, and leisure time activities) used frequently to estimate cognitive reserve. The *education* component is estimated by adding years of formally completed education to years of additional vocational training (if any). The *occupation* component is estimated by the number of years employed (rounded up to intervals of 5 years) in one of five levels of working activity (determined by degree of intelligence and responsibility required for the job). The *leisure time* component is estimated by rating the frequency (on a 4-point scale) of 14 activities completed in weekly, monthly, and yearly increments, as well as the number of years in which the respondent engaged in the activity. Hence, the CRIq produces

sub-scores for education, occupation, and leisure time, as well as a global cognitive reserve score covering all three of those domains and calculated using an algorithm embedded into an accompanying MSExcel spread sheet. All CRIq index scores are normed around a distribution with $M = 100$ and $SD = 15$.

Procedure

Recruitment and Timeline

Potential participants were recruited telephonically by two trained research assistants (RAs) who followed a set script. Because most of the participant pool consisted of Xhosa first-language speakers, both RAs were fluent in both that language and in English. The script contained an explanation of the study's purpose, basic procedures, and benefits, as well as possible contraindicated MRI factors such as pregnancy and metallic implants. After a potential participant gave verbal agreement for involvement in the study, the RA scheduled a date and time for the initial screening session.

The recruitment and data collection processes started in June 2019 and concluded in November 2019. Potential participants were scheduled according to their earliest convenience within this 6-month period, and with three exceptions (e.g., due to family emergency or MRI technical difficulty) completed the screening and data collection processes within a single visit. On the few occasions it was necessary for a participant to return, they received additional compensation for their time and travel expenses.

Screening

After the potential participant had arrived at GSH and had been directed to the CUBIC facility, I verbally informed them about the study's purpose, procedure, and potential risks and benefits. This information was translated by one of the RAs. The RA then asked the potential participant to read and sign the informed consent document (see Appendix E) as well as CUBIC's standard MRI screening form (See Appendix F). Any questions the

potential participant had about the contents of either of those documents were addressed thoroughly.

If the potential participant indicated their willingness to proceed by signing both the informed consent document and the MRI screening form, I, with the help of one of the RAs, immediately administered the MMSE to confirm that they were cognitively competent and capable of providing informed consent. Once this was established, the RA administered the rest of the screening scales (in this order: screening questionnaire, MGLS, Lawton IADLs, M.I.N.I.).

Individuals meeting any of the exclusion criteria were excluded from further participation and, after complete debriefing, were reimbursed for their study involvement and allowed to leave.

Cognitive Assessment

After screening was complete and the individual's eligibility to continue with study procedures had been established, the test battery was administered in a private room within the CUBIC facility. I administered all tests while accompanied by a bilingual English-Xhosa RA, who acted as a translator. Each test session lasted between 45 and 55 minutes.

To minimize interference effects (MacLeod & MacDonald, 2000), the first block of tests had this administration order: ROCFT copy trial, ROCFT immediate recall trial, HVLT-R learning trials, GPT, CTT, ROCFT delayed recall and recognition trials, HVLT-R delayed recall and recognition trials, verbal fluency. Once this part of the session was completed, the participant was allowed a 15-minute break during which they were offered light refreshments. Thereafter, the KBIT-2 and the CRIq were administered. Once this part of the session was completed, the participants were allowed another 15-min break during which they were again offered light refreshments.

Neuroimaging

The RA and I prepared the participant for this session by explaining the general scanner procedure (including the fact that it is non-invasive) and warning them about the loud noises they would hear. We offered to accompany the participant into the scanner and to hold their hand if they were anxious. Once the participant verbally confirmed they were comfortable and the CUBIC screening form had been verbally re-presented, they were taken to a private room to change into gowns provided and remove all personal items.

The participant was then guided to the scanning room, provided with noise-cancelling earpieces and headphones, and asked to lay comfortably on the table using the provided pillows and blankets. We then read standard scanner instructions (e.g., "keep as still as possible, try to relax and ignore the loud noises") and gave the participant a panic button to press should they have the need to end the session urgently. A specialised mirrored device was positioned over the participant's head, allowing them to view relaxing nature scenery projected behind the MRI scanner. Soothing meditative music was piped in to further reduce anxiety.

Once the participant verbally confirmed they were comfortable, an MRI technician secured the participant with a head coil, maneuvered the table into the scanner, and commenced the imaging protocol. At the conclusion of the scanning session, the participant was debriefed, compensated, and invited to ask any questions regarding study procedures. Finally, they were accompanied to a commuter area outside GSH where public transport for them was secured.

The MRI data were acquired for 34 of the 35 recruited participants (1 participant had a contraindication to MRI, as determined by the CUBIC screening form). Datasets for another 2 participants were excluded from final statistical analyses because they had a significant history of alcohol or drug abuse (as determined by their M.I.N.I. screening). Hence, the final sample that provided data for statistical analyses was $N = 32$.

Ethical Considerations

This study followed the ethical guidelines for research with human subjects described by the Health Professions Council of South Africa (HPCSA) and the University of Cape Town (UCT) Codes for Research. The study obtained ethical approval from the Research Ethics Committee of the UCT Faculty of Health Sciences and operated additionally under the ethical approval obtained by both parent studies from the same body (REC REF 236/2018, REF 397/2014, and REF 241/2018; see Appendix G).

Informed Consent/Assent and Confidentiality

All participants read and signed a general informed consent document (Appendix E) in addition to any consent forms already signed for the parent studies. They were also asked to complete an additional document (viz., the standard CUBIC screening form; see Appendix F) in order to signal their consent to participate in the neuroimaging aspect of the study. Participants were assured both verbally and via the consent form that all data collected from them during the study would be kept confidential and would be used for research purposes only. All consent procedures were conducted in the participant's home language. The participants were informed that their consent was voluntary and that they could end their participation at any time without penalty and without affecting any on-going medical treatment at GSH.

Potential Risks and Benefits

There were no direct medical benefits to participation. Standard user safety protocols were followed with regards to the neuroimaging procedures (http://www.cubic.uct.ac.za/bookings). No component of the study held any potential for significant physical, psychological, or psychosocial risk, and participants were thoroughly debriefed.

Costs and Compensation

There were no costs to participation. Any study-related spending by the participants (e.g., on transportation to the study site) was reimbursed in full. Participants were further compensated ZAR250 (at the time of the study, approximately US$16) for their involvement.

Data Management and Statistical Analysis

Data Processing

As paper-based data collection proceeded, tests and other instruments were scored according to the standard methods described in the relevant manuals and administration booklets (see, e.g., GPT; Klove, 1963, CTT; D'Elia et al., 1996, verbal fluency tests; Butters et al., 1987, HVLT-R; Brandt, 1991, ROCFT; Strauss et al., 2006, RCF-OSS; Anderson et al., 2001). The relevant values were then transferred to electronic data sheets.

Missing Data and Outliers. Certain cognitive tests had upper response limits for time. That is to say, standard administration called for the test to be discontinued if the participant had not completed the required tasks within a particular time limit (e.g., for the GPT and CTT tests, the time limit was 300s and 240s, respectively). However, to keep from discouraging participants during data collection, they were allowed to continue beyond the standard time limit until they completed the test or discontinued of their own volition. In cases such as this, where the recorded data exceeded the standard time limit, the relevant values were adjusted to be equal to the standard maximum allowable time (see Appendix H).

I used SPSS (version 26.0) to scan the entire dataset so as to determine the extent of missing data and to attempt to discern any meaningful patterns. This diagnostic scan indicated that 98.66% of the dataset was complete and that 59 data points spread across seven variables (1.34% of the dataset) were missing. The scan detected no particular pattern in the missing data, suggesting there was no systematic fault to be addressed in this regard.

Only 1 data point was missing from the cognitive test data and therefore it was deemed unnecessary to replace that piece of data (e.g., using a multiple imputation

technique). Although this method has the benefit of not reducing variability in the dataset and is commonly used in neuropsychological studies, the percentage of missing data was deemed low enough to keep the dataset in its original state.

Cognitive Test Data. I used a regression-based norming method (Oosterhuis et al., 2016) to calculate a performance score for each participant on each test. The data upon which the regression equations were based were collected from a sample of healthy adults (N = 233) which, in aggregate, very closely matched the current sample's sex distribution and average age and level of educational attainment. The normative dataset was generously provided by UCT's HIV Mental Health Research Unit, which is based in the university's Department of Psychiatry and Mental Health (see, eg., Breuer et al., 2011; Gouse et al., 2020b; Munsami et al., 2020).

Using the normative data, I plotted a regression model of the normative performance on each test outcome variable using the standard linear regression equation:

$$Y = \acute{\alpha} + \beta x + \varepsilon$$

I took the performance of the normative population on each test to determine the constant for each test outcome, with age, education, and gender inserted in turn to determine their influence on the test performance outcome:

Y (test outcome variable) = (norm population intercept) + (norm population slope coefficient)(predictor variable [age, education or gender]) + residual standard error*

This equation produced normative coefficients for age, education, and gender for each of the tests as well as residual standard errors. These coefficients were then entered into an equation to predict the outcome of each of the study participant's performance based on their age, education, and gender:

Predicted score = test constant (mean) + norm age coefficient(participant age)- norm education coefficient*(participant education) + norm gender coefficient*(participant gender)*

In the above equation, age and education are given in years, and gender is coded as 0 for female and 1 for male. So, for example, for the GPT a 43-year-old female with 12 years of education would be predicted to score [*test constant* (86.60) + *norm age coefficient* (0.17)**participant age*(43) - *norm education coefficient* (2.14)**participant education*(12) + *norm gender coefficient*(2.69)**participant gender*(0)] = 68.23.

This predicted score was then subtracted from the participant's actual test score, and the difference was divided by the residual standard error score of the test's equation in order to standardize it, i.e. to produce a *z*-score representing the participant's performance on the test in question. The *z*-score was then converted into a *T*-score using the standard formula:

$T = (z*10) + 50$

The *T*-score was then classified into deficit score categories to determine whether the study participant's performance was impaired and, if so, to what degree (see Table 1).

Table 1

T-score classification to deficit score and description

T-score	Deficit score	Impairment descriptor
≥ 40	0	Normal / Intact
39 – 35	1	Mild impairment
34 – 30	2	Mild-to-Moderate impairment
29 – 25	3	Moderate impairment
24 – 20	4	Moderate-to-Severe impairment
≤ 19	5	Severe impairment

Note. Taken from (Carey et al., 2004)

I then calculated a global *T*-score for each participant by adding each of their individual test *T*-scores dividing that sum by the total number of tests (i.e., the global *T* was a

simple average of all *T*-scores). Using the same process, I calculated a global deficit score for each participant.

These global scores were used as the primary outcome variables to measure cognitive functioning. Each participant's *T*-score and deficit score for each test were used as secondary outcome variables when further analyses were conducted into the separate domains that comprise global cognitive functioning. For this study, these domains were the seven recommended by the HIV Neurobehavioral Research Center (HNRC) Group, and used commonly in HIV neuropsychological literature (Campbell et al., 2020; Heaton et al., 2011; Woods et al., 2004): motor function, attention and working memory, information processing speed, language, audio-verbal memory, visual-spatial memory and executive function. Where more than one outcome variable was assigned to a particular domain, I conducted a reliability test to ensure that the internal consistency of the domain remained strong enough. Specifically, I checked that Cronbach's alpha correlation coefficient, representing the inter-correlation among t-scores within the domain, was at least .70 (Phillips et al., 2018).

Cognitive Reserve Data. CRIq outcome scores are calculated automatically using a proprietary algorithm contained within an MSExcel spreadsheet that is distributed alongside the test materials (Nucci et al., 2012; http://www.cognitivereserveindex.org). Participant responses are transcribed onto paper forms and then entered into the spreadsheet. The sheet then generates scores for the three sub-domains (CRI-Education, CRI-WorkingActivity, and CRI-LeisureTime) as well as a CRIq Total Score that is an average of the sub-domain scores. Because age is often a significant influence on CRIq scores (see, e.g., Artemiadis et al., 2020; Maiovis et al., 2010, 2016), I conducted a series of bivariate correlational analyses (using Pearson's *r* correlation coefficient) to determine the strength of association between each of the four CRIq outcomes and age. Each of these analyses yielded moderate to strong positive association, rs > .353, ps < .680, which were found to be significant $p < .05$. Hence, to ensure

that age did not play a disproportionate role in subsequent analyses, I standardized each CRIq outcome using a method described by Maiovis et al. (2016). Briefly, I created linear regression models with age as the predictor variable and CRIq score as the outcome variable. The standardised score resulting from each of the four models was then transposed using a scale with a mean of 100 and a standard deviation of 15, as was used in the original CRIq development (Nucci et al., 2012). Each participant's standardised CRIq scores were then classified using the rubric published in the development study: high (> 130), medium-high (115–130), medium (85–114), medium-low (70–84), and low (< 70).

Neuroimaging pre-processing. Acquisition and processing followed procedures described by previous studies conducted at the CUBIC facility at GSH (see, e.g., Engelbrecht, 2019; Paul et al., 2017). First, the MR images were screened for quality control. Each was visually inspected in the DICOM format for unwanted noise/motion abnormalities, dropout slices, and artifacts, and each was adjusted for proper positioning in the field of view. Freesurfer (version 5.1) software *(*Martinos Center, Harvard University, Boston, MA; http://surfer.nmr.mgh.harvard.edu) pipeline logs and segment results showed the MP-RAGE analysis had acceptable quality. The diffusion MRI registration quality was checked by superimposing the fractional anisotropy maps onto the population average fractional anisotropy Map. Again, this check found the quality to be good. Finally, the fibre bundle reconstruction was assessed and checked for incorrect fibres using 3D visualization; this assessment found the reconstruction to be accurate.

Freesurfer (version 5.1) software was used to quantify volumetric MRI data. The MP-RAGE scans were converted to a space template, with the skull removed, where the gray matter, white matter, and ventricles were segmented. Brain images were then parcellated into cortical and subcortical regions of interest (ROIs). The ROIs for this study included the total gray and white matter of the caudate, the putamen, and the thalamus. These areas were

selected based on previous literature suggesting that HIV neuropathogenesis can affect them disproportionately (Ances et al., 2006; Ernst et al., 2002; Fama et al., 2014; Wright et al., 2016). Volumetric measures from each hemisphere were aggregated to create a composite measure for each of the ROIs.

The FSL statistical and analytic toolbox was used for processing diffusion metrics (Jenkinson et al., 2012). The diffusion-weighted images (DWIs) were scanned and corrected for eddy-current and motion-related errors or artifacts using FSL FLIRT through affine registration to the baseline volume. Subsequently, corrections were made for the orientation of the gradient encoding direction, and the brain matter images were extracted from the DWIs using the FSL brain extraction tool (Zhang et al., 2007), with a 0.45 fraction threshold. The DTI acquisitions (i.e., T1 and T2) were used to create a white matter atlas specific to this study's ROIs. From this atlas, a template DTI was created by iteratively deforming and averaging all the imaging data using a tensor-based deformable registration algorithm. This algorithm was used with the deviatoric tensor similarity metric and finite strain tensor reorientation.

The template DTI was then used to define the boundaries masks of the ROIs (i.e., inclusion and exclusion masks for specific bundles). These included the corpus callosum (CC), the uncinate fasciculus (UNC), the cingulum bundle (CING), and the anterior thalamic radiation (ATR). To define each of these bundles, two inclusion and one exclusion masks were drawn in the template, using ITK-SNAP (Yushkevich et al., 2006). Each of these bundles was then processed and computed to produce specific metrics. First, the bundle boundary masks were used against the template to create native space, using DTI-KT registration. Tractography of the whole brain was then performed using the native space, with a step size of 1 mm, four jittered seeds, and tricubic interpolation per voxel. Termination criteria included (1) minimum fractional anisotropy of 0.15, 2) a 45-degree threshold angle,

and 3) fibre lengths of above 10 mm. The resulting curve averages of these bundle metrics were then computed into the fractional anisotropy, axial diffusivity (AD), radial diffusivity (RD), and mean diffusivity (MD) of white matter for each participant, averaged across both hemispheres.

Inferential Statistical Analyses

I conducted all of these analyses using SPSS (version 26.0). Unless otherwise stated, decisions regarding statistical significance were made with α set at.05.

Before proceeding with the inferential analyses, a comprehensive set of descriptive analyses characterized the sample in terms of sociodemographic, psychosocial, and medical/psychiatric attributes and described the sample's performance on the neuropsychological test battery and self-reports on the CRIq. With this done, the inferential analyses then proceeded across three discrete steps.

Bivariate correlations. These analyses sought to establish which predictor variables were statistically significantly related to one another, and therefore which should be used in subsequent regression model building. The first set of correlations investigated associations between the primary variables related to the main hypotheses of the study (viz., age, cognitive reserve [as estimated by age-standardized CRIq total score, fractional anisotropy, white matter volume, gray matter volume, highest level of education, and IQ score], and cognitive functioning [as estimated by the global *T*-score]). The second set of correlations investigated associations between age, cognitive functioning as measured by performance within separate domains, and cognitive reserve as measured by fractional anisotropy in the regions of interest (ROI).

Between-group differences. Two independent-sample *t*-tests were conducted to investigate the first basic hypotheses, namely that age and cognitive reserve each significantly predict cognitive functioning (as measured here by the GDS score).

For the first *t*-tests, I divided the study sample ($N = 32$) into two age-based groups. The division point between the groups was set at 45 years of age. This cut-off is used commonly in age-related research (see e.g., Hearps et al., 2012; Cohen, Seider, & Navia, 2015; Fumaz et al., 2015). Although many other HIV neuropsychology studies use the cut-off of 50 years as the threshold between younger and older adults (see e.g., Levin & Montano, 2019; Mcmaster et al., 2010), I chose the younger cut-off to ensure that the analysis was not biased by being skewed to the oldest participants in my sample.

For the second *t*-test, I divided the study sample into two CRIq-based groups (participants with standardised Total Score < 100 and those with standardised Total Score ≥ 100).

To protect against Type I error in these analyses, the Bonferroni correction (Emerson, 2020) was applied to the threshold for statistical significance. Thus, in these two independent-sample *t*-tests, the following equation was applied to adjust the threshold for statistical significance:

$$p = \alpha/\mathrm{x}$$

$$p = .05/19$$

$$p = .0026$$

Regression Models. Various regression models were built to explore the value and strength of age and cognitive reserve in predicting global cognitive functioning of the HIV-infected sample group, as well as more in-depth exploration of the separate cognitive domains. The first step in building all the regression models described below was examining the assumptions of normality, independence (multi-collinearity), and homoscedasticity for the cognitive performance outcome variables (global *T*-score and score in each separate cognitive domains). I also carefully examined the residual plots, error plots, normality distribution, and

measures of influence (Cook's distance, tolerance, and the variance inflation factor) for all models (see Appendix I).

The first model focused on the CRIq standardised scores, wherein the effect of age was statistically incorporated. The second model involved age and other variables which have been used in published studies as proxy measures of cognitive reserve, as well as exploring the interaction effects between these. The third model investigated the effect HIV-infection variables added to the model. Finally, once a primary regression model was established, which used the global measure of cognitive function as an outcome variable, the model was then applied to the separate cognitive domains.

CHAPTER 5

Results

Sample Characteristics

Table 2 presents a summary of the sample's sociodemographic, psychosocial, and medical/psychiatric characteristics. As the Table shows, most of the 32 participants were right-handed, female, Xhosa first-language speakers. Most participants (24 of 32; 75%) were aged over 35 years and most (29 of 32; 90.6%) had at least a Grade 10 education. All reported intact function in terms of instrumental activities of daily living.

All participants were virally suppressed and showed good ART adherence (i.e., scored at least 3 out of 4 on the MGLS). Although estimated duration of infection ranged widely, most participants reported that their infection had been diagnosed more than 5 years previously. The sample overall reported few medical co-morbidities and risk factors, although 24 (75%) fell in the BMI ranges conventionally classified as "overweight" (25–29.9 kg/m2) or "obese" (≥30 kg/m2; Bakal et al., 2018).

Ten participants were found to have some mild psychiatric symptoms (predominantly of anxiety and/or depression; screened for by the MINI and the self-made questionnaire). However, because none of those participants had been formally diagnosed and none were taking psychotropic medication they all remained included in the study.

Table 2

Sample Sociodemographic, Psychosocial, and Medical/Psychiatric Characteristics (N = 32)

Variable	*M* (*SD*)	Range Minimum	Range Maximum
Age (yrs)	41.13 (9.34)	23	57
Highest level of education (yrs)	10.47 (2.29)	1	13
Body mass index	30.04 (7.49)	17.20	48.37
IADL score	7.81 (0.54)	6	8
Estimated duration of HIV infection (mos)	98.34 (65.85)	12	254
ART adherence[a]	3.66 (0.60)	2	4
Fractional anisotropy[b]	0.43 (0.02)	0.38	0.46

Variable	*f* (%)					
Handedness (R:L:U)	27 (84.38)		2 (6.25)		3 (0.94)	
Gender (F:M:U)	27 (84.38)		5 (15.63)		0 (0.00)	
Home language (X:S:U)	29 (90.63)		1 (3.13)		2 (6.25)	
Income range (0:1:2:3:4:5)	14 (43.75)	1 (3.13)	1 (3.13)	2 (6.25)	10 (31.25)	4 (12.50)

Variable	Yes	No
Alcohol use	13 (40.63)	19 (59.38)
Smoker	4 (12.50)	28 (87.50)
Substance use	0 (0.00)	32 (100.00)
Hypertension	5 (15.63)	27 (84.38)
Diabetes (Type 2)	2 (6.25)	30 (93.75)
Cholesterol	2 (6.25)	30 (93.75)
Migraine	7 (21.88)	25 (78.13)
Stroke and/or TBI	0 (0.00)	32 (100.00)
TB	8 (25.00)	24 (75.00)

Note. IADL = Lawton Instrumental Activities of Daily Living Scale; ART = antiretroviral therapy; TBI = traumatic brain injury; TB = history of tuberculosis infection; M.I.N.I. = *Mini International Neuropsychiatric Interview. The variable Handedness* was coded as right, left, or undeclared; *Gender* was coded as female, male, or undeclared; *Home language* was coded as Xhosa, Shona, or undeclared; *Income range* was coded as 0 = no income, 1 = ZAR1-499, 2 = ZAR500-999, 3 = ZAR1000-1999, 4 = ZAR2000-4999, or 5 = ZAR5000-9999.

[a]Scored out of 4 on the Morisky Green Levine Medicine Adherence Scale (Morisky et al., 1986).

[b]Scored conventionally, i.e., as a scalar value between 0 and 1 that describes degree of anisotropy of a diffusion process.

[c]Casual or social use (participants with heavy alcohol consumption were screened out).

Cognitive Performance: Descriptive Statistics

Table 3 shows the cognitive domain to which each individual test was assigned, the intra-domain correlations, and the internal consistency values for each domain. (The two test statistics are based on participant *T*-scores.) The data in the Table confirm that Cronbach's alpha values were all above .65, indicating acceptable internal consistency reliability. Of note, however, is that performance on the Action Fluency test did not correlate strongly with performance on the semantic fluency tests, and so its data were not used in calculating the internal consistency value for the Language domain (when those data were included, the Cronbach's α value for that domain decreased from .795 to .532). Data from that test were included in calculation of Cronbach's α for the entire test battery, however; that value, which might be said to represent the internal consistency of a battery measuring global cognitive functioning, was .749.

Table 3

Cognitive Test Battery: Intra-domain correlations and internal consistency values (N = 32)

Cognitive Domain / Test	*r*	Cronbach's α
Motor function	.810	.895
Grooved Pegboard Test		
Dominant hand		
Nondominant hand		
Information processing speed	----	----
Color Trails Test 1		
Attention and working memory	----	----
Color Trails Test 2		
Language	.643	.795
Semantic fluency: Animals		
Semantic fluency: Fruits and vegetables (Action Fluency)		
Memory: Audio-verbal	.561	.724
HVLT-R		
Learning		
Delayed recall		
Memory: Visual-spatial	.854	.921
ROCFT		
3-min recall		
30-min recall		
Executive function	.510	.676
ROCFT		
Copy		
Organizational Strategy Score		

Note. HVLT-R = Hopkins Verbal Learning Test-Revised; ROCFT = Rey-Osterrieth Complex Figure Test.

Table 4 presents descriptive statistics for the sample's performance on the neuropsychological test battery. Although performance on the subtests ranged quite widely, on average the poorest performance (i.e., highest deficit scores) was on the Grooved Pegboard Test and the ROCFT (copy trial). In terms of global cognitive functioning, the sample's mean performance fell within the range conventionally described as "average" (z = -0.58±0.85, T = 43.76±9.35, GDS = 0.77±0.61).

Table 4

Cognitive Test Performance: Descriptive statistics (N = 32)

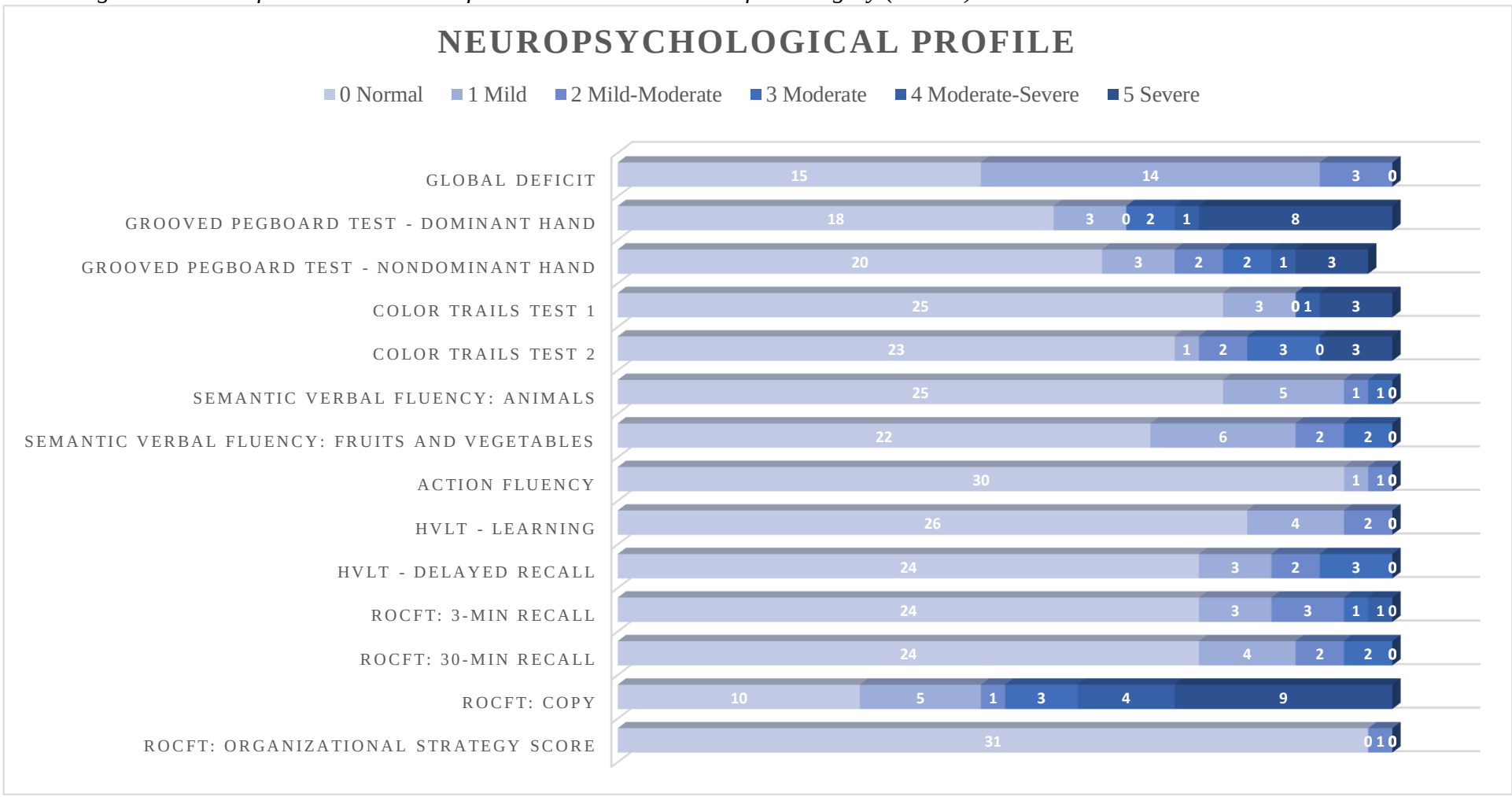
	Raw Score			Deficit Score		
		Range			Range	
Cognitive Domain / Test	*M* (*SD*)	Minimum	Maximum	*M* (*SD*)	Minimum	Maximum
Mini Mental State Examination	26.56 (2.18)	19	29	----	----	----
Motor function						
Grooved Pegboard Test						
Dominant hand	96.44	55	330	1.66 (2.18)	0	5
Nondominant hand	92.06	52	172	1.03 (1.70)	0	5
Information processing speed						
Color Trails Test 1	69.31	25	230	0.69 (1.60)	0	5
Attention and working memory						
Color Trails Test 2	144.38	65	364	0.91 (1.65)	0	5
Language						
Semantic Fluency: Animals	11.66 (3.73)	4	22	0.31 (0.69)	0	3
Semantic Fluency: Fruits and vegetables	12.88 (3.19)	8	21	0.50 (0.88)	0	3
Action Fluency	10.50 (2.44)	5	16	0.09 (0.39)	0	2
Memory: Audio-verbal						
HVLT-R						
Learning	24.59 (3.71)	18	32	0.25 (0.57)	0	2
Delayed recall	8.00 (2.26)	4	12	0.50 (0.98)	0	3
Memory: Visual-spatial						
ROCFT						
3-min recall	11.97 (6.62)	1	24	0.50 (1.02)	0	4
30-min recall	12.19 (7.08)	3	27	0.44 (0.88)	0	3
Executive function						
ROCFT						
Copy	25.09 (6.27)	13.5	36	2.41 (2.12)	0	5
Organizational Strategy Score	4.78 (0.61)	3	6	0.06 (0.35)	0	2

Note. HVLT-R = Hopkins Verbal Learning Test-Revised; ROCFT = Rey-Osterrieth Complex Figure Test.

Figure 2 presents finer-grained data on the global deficit score as well as the deficit scores for each individual subtest. Global deficit score data indicated that 15 participants (46.87%) were cognitively intact (score < 1), 14 (43.75%) presented with mild cognitive impairment (score between 1 and 2), and 3 (9.37%) presented with mild-to-moderate impairment (i.e., score between 2 and 3). The data presented in the Figure are consistent with those presented in Table 4, showing that on most subtests few participants showed deficits classified as moderate-to-severe or severe. Tests on which performance was most intact were action fluency and HVLT-R (learning trial). Tests on which performance was poorest were the Grooved Pegboard Test (dominant hand) and ROCFT (copy trial).

Figure 1

Cognitive Test Performance: Number of individuals within each deficit category (N = 32)



Note. HVLT-R = Hopkins Verbal Learning Test-Revised; ROCFT = Rey-Osterrieth Complex Figure Test.

Cognitive Reserve: Descriptive statistics

Before creating the set of descriptive statistics, I standardized the CRIq scores using the steps outlined in Chapter 4 (Inferential Statistical Analyses subsection, page 63). Table 5 presents the results of these analyses, which sought to determine the influence age had on the calculation of these scores. As the Table shows, all three of the CRIq sub-scores (Education, Work, and Leisure) correlated significantly with age.

Results of the linear regression models that were subsequently run to age-standardise the CRIq scores are reported in Table 6.

Table 5

Bivariate Correlations: Strength of association between age and CRIq scores (N = 32)

	1	2	3	4	5
1. Age	1.00				
2. CRIq-Total	-.254	1.00			
3. CRIq-Education	.445*	.477**	1.00		
4. CRIq-Work	-.353*	.680**	.075	1.00	
5. CRIq-Leisure	-.565**	.619**	-.271	.342	1.00

Note. Data are Pearson's *r* correlation coefficients. CRIq = Cognitive Reserve Index questionnaire.

*$p < .05$. **$p < .01$.

Table 6

Linear Regression Models that Served to Age-Standardise CRIq Scores (N=32)

Predictor/Outcome	*b*	*SE b*	*β*
CRIq-Total	-.387	.269	-.254
CRIq-Education	.475	.174	.445
CRIq-Work	-.559	.270	-.353
CRIq-Leisure	-.600	.160	-.565

Note. CRIq = Cognitive Reserve Index questionnaire.

CRIq-Total: $\Delta R^2 = .065$, $\Delta F(1, 30) = 2.08$, $p = .160$.

CRIq-Education: $\Delta R^2 = .198$, $\Delta F(1, 30) = 7.42$, $p = .011$.

CRIq-Work: $\Delta R^2 = .125$, $\Delta F(1, 30) = 4.28$, $p = .047$.

CRIq-Leisure: $\Delta R^2 = .320$, $\Delta F(1, 30) = 14.10$, $p = .001$.

Table 7 presents descriptive statistics for the sample's CRIq self-reports. The raw scores indicate that the range of cognitive reserve is very narrow and is skewed towards lower (i.e., low average) levels, which might speak to the negative influence of age on cognitive reserve. Age-standardized scores covered a wider range that is also more evenly distributed between lower and higher levels of cognitive reserve.

Table 7

Cognitive Reserve Index Questionnaire (CRIq): Descriptive statistics (N = 32)

		Raw Score Range		Age-Standardized Score[a] Range	
CRIq Outcome Variable	*M* (*SD*)	Minimum	Maximum	Minimum	Maximum
Total	86.13 (6.14)	73	101	64	132
Education	88.41 (8.76)	57	103	46	125
Work	89.41 (5.90)	80	103	65	124
Leisure	91.28 (8.80)	71	114	61	135

Note. [a]Standardised around a mean of 100 and standard deviation of 15.

Bivariate Correlational Analyses

The first set of correlations investigated associations between the primary variables related to the main hypotheses of the study (viz., age, cognitive reserve, and cognitive functioning). As Table 8 shows, the analyses detected significant associations between age and cognitive functioning, as measured by the global *T*-score, $p = .015$, but no significant associations between any of the variables estimating cognitive reserve (age-standardized CRIq total score, fractional anisotropy, white matter volume, gray matter volume, highest level of education, and IQ estimate) and cognitive functioning.

Of interest is that, within that set of cognitive reserve outcome variables, there was only one significant association (between highest level of education and CRIq total score, $p = .000$).

Table 8

Bivariate Correlational Analyses: Associations between the study's primary outcome variables (N = 32)

	1	2	3	4	5	6	7	8	9
1. Global *T*-score	----								
2. Age (yrs)	**-.425***	----							
3. CRIq total[a]	-.157	.254	----						
4. Fractional anisotropy	.195	-.283	-.298	----					
5. White matter volume	.022	.026	.130	-.021	----				
6. Gray matter volume	.110	-.333	-.163	-.131	**.732****	----			
7. Education (yrs)	.126	-.127	**-.651****	.181	-.209	.054	----		
8. Performance IQ	.274	-.205	-.222	.199	.115	.249	.345	----	
9. Estimated duration of HIV infection (mos)	-.231	**.364***	.104	.010	.141	.035	.018	-.052	----

Note. Data presented are Pearson's *r* correlation coefficients. Statistically significant associations are highlighted in boldface font. CRIq = Cognitive Reserve Index Questionnaire.

[a]Age-standardized CRIq total score.

*$p < .05$. **$p < .01$.

A follow-up set of correlations investigated associations between age, cognitive functioning as measured by performance within separate domains, and cognitive reserve as measured by fractional anisotropy in the regions of interest (ROI). As Table 9 shows, the analyses detected significant associations between age and performance in the cognitive domains of (a) motor function, $p = .016$, and (b) executive function, $p = .030$. There were also significant associations between (c) fractional anisotropy in the anterior thalamic radiation and performance on tests of visual-spatial memory, $p = .044$, and (d) fractional anisotropy in the cingulum bundle and performance on tests assessing language function, $p = .033$.

Table 9

Bivariate Correlational Analyses: Associations between age, cognitive performance by domain, and fractional anisotropy in regions of interest (N = 32)

	1	2	3	4	5	6	7	8	9	10	11	12	13
1. Age	----												
Cognitive domain													
2. Motor function	**-.428***	----											
3. Attention and working memory	-.242	.118	----										
4. Information processing speed	-.160	**.417***	**.514****	----									
5. Language	-.321	.190	.184	.166	----								
6. Memory: Audio-verbal	-.093	.096	.191	**.447***	.273	----							
7. Memory: Visual-spatial	.127	.081	.098	**.365***	.037	.223	----						
8. Executive function	**-.383***	.235	**.410***	**.374***	.119	-.110	**.423***	----					
Fractional anisotropy													
9. Total	-.283	-.112	.117	.033	.286	.343	.275	.210	----				
10. Anterior thalamic radiation	-.295	-.128	-.056	.065	.218	.344	**.358***	.197	**.909****	----			
11. Cingulum bundle	-.343	-.069	.158	.031	**.378***	.225	.194	.196	**.852****	**.783****	----		
12. Uncinate fasciculus	-.263	.025	.117	.087	.300	.208	.135	.250	**.705****	**.537****	**.574****	----	
13. Corpus callosum	-.314	-.069	.159	-.026	.321	.325	.300	.271	**.961****	**.846****	**.798****	**.684****	----

Note. Data presented are Pearson's *r* correlation coefficients. Statistically significant associations are highlighted in boldface font.

*$p < .05$. **$p < .01$.

Between-Group Comparisons: Independent-sample t-test

The first of these analyses assessed magnitude of difference in cognitive performance and in cognitive reserve between two age groups (participants aged < 45 years and those aged ≥ 45 years). As Table 10 shows, these groups were well matched in terms of estimated duration of HIV infection and self-reported ART adherence. Regarding cognitive performance, the analyses detected no significant between-group differences once the Bonferroni correction was applied. There was a strong trend toward a significant between-group difference with regard to global *T*-score and performance within the domain of executive functioning. Regarding cognitive reserve, the analyses only detected significant between-group differences for CRIq Leisure, although the fractional anisotropy score showed a strong trend towards significance.

The second of these analyses assessed magnitude of difference in cognitive performance and in cognitive reserve between two CRIq-based groups (participants with standardised Total Score < 100 and those with standardised Total Score ≥ 100). As Table 11 shows, these groups were well matched in terms of age, estimated duration of HIV infection, and self-reported ART adherence. Regarding cognitive performance, the analyses detected no significant between-group differences after the Bonferroni correction was applied. There was a strong trend toward a significant between-group difference with regard to performance within the domains of motor function and information processing speed. As expected, given how the groups were constituted, there were also strong trends towards significance with regard to all three CRIq subscales, as well as with regard to highest level of education.

Table 10

Age-Based Between-Group Comparisons: Descriptive statistics and independent-sample t-tests (N = 32)

Variable	Group: Younger adults (*n* = 18)	Group: Older adults (*n* = 14)	*t*	*p*	95% CI: LL	95% CI: UL
Cognitive performance						
Global *T*-score	47.58 (6.49)	38.84 (10.35)	-2.764	***.012****	-15.32	-2.16
Motor function	45.22 (15.60)	27.96 (28.03)	-2.007	.061	-35.38	0.853
Attention and working memory	47.83 (15.18)	38.41 (28.62)	-1.116	.279	-27.12	8.27
Information processing speed	47.97 (12.47)	41.79 (14.88)	-1.251	.223	-16.36	3.99
Language	49.79 (8.04)	43.84 (9.42)	-1.889	.070	-12.43	0.53
Memory: Audio-verbal	50.90 (8.31)	46.80 (9.94)	-1.242	.226	-10.89	2.69
Memory: Visual-spatial	47.78 (11.91)	45.95(6.60)	-0.552	.585	-8.63	4.97
Executive function	35.05 (6.24)	23.28 (15.16)	-2.111	***.043****	-23.17	-0.37
Cognitive reserve						
Education (yrs)	10.56 (2.53)	10.36 (2.02)	-0.247	.807	-1.85	1.44
Performance IQ	67.00 (20.34)	59.50 (14.14)	-1.229	.229	-19.97	4.97
Fractional anisotropy	.4377 (.0159)	.4196 (.0209)	-2.682	***.013****	-.0319	-0.00411
White matter volume	407228.48 (37892.80)	417618.42 (50878.21)	0.639	.529	-23239.01	44018.89
Gray matter volume	528587.21 (57295.01)	519568.41 (50470.62)	-0.473	.640	-48029.19	29991.61
CRIq[a]						
Total	96.78 (14.94)	104.14 (14.55)	1.404	.171	-3.37	18.11
Education	95.03 (16.36)	106.39 (10.40)	2.391	.023	1.65	21.09
Work	97.78 (12.78)	102.85 (17.54)	0.909	.373	-6.46	16.59
Leisure	92.24 (11.13)	109.98(13.57)	3.963	**.001*****†	8.52	26.95
Estimated duration of HIV infection	88.72 (57.14)	110.71 (76.01)	0.902	.376	-28.37	72.36
Adherence[b]	3.61 (0.70)	3.71 (0.47)	0.499	.621	-0.32	0.53

Note. Columns 2 and 3 present data for *M*(*SD*). Equal variance not assumed. CRIq = Cognitive Reserve Index questionnaire; CI = confidence interval; LL = lower limit; UL = upper limit. Statistically significant between-group differences are highlighted in boldface font in the *p* column. Statistically significant associations prior to the Bonferroni correction applied are highlighted in bold italicized font. [a]All CRIq scores are age-standardized. [b]Scored out of 4 on the Morisky Green Levine Medicine Adherence Scale (Morisky et al., 1986). *$p < .05$. **$p < .01$. ***$p < .001$. ***†$p < .0026$.

Table 11

CRIq-Based Between-Group Comparisons: Descriptive statistics and independent-sample t-tests (N = 32)

	Group				95% CI	
Variable	Lower cognitive reserve (n =15)	Higher cognitive reserve (n =17)	t	p	Lower	Upper
Cognitive performance						
Global *T*-score	45.31 (11.39)	42.39 (7.20)	-0.86	.402	-9.99	4.15
Motor function	49.13 (9.62)	28.80 (26.74)	-2.92	***.008*** **	-34.85	-5.82
Attention and working memory	34.36 (53.92)	23.15 (38.81)	-0.67	.511	-45.81	23.39
Information processing speed	50.31 (8.39)	34.45 (17.36)	3.33	***.003*** **	-25.71	-6.02
Language	42.68 (27.66)	44.62 (16.82)	0.24	.816	-15.09	18.97
Memory: Audio-verbal	47.51 (14.64)	43.28 (12.93)	-0.86	.396	-14.29	5.83
Memory: Visual-spatial	46.89 (10.36)	47.46 (8.00)	0.17	.864	-6.22	7.36
Executive function	49.16 (11.28)	49.10 (7.10)	-0.03	.975	-7.11	6.89
Cognitive reserve						
Education (yrs)	9.47 (2.65)	11.60 (0.99)	-3.08	***.006*** **	-3.57	-.69
Performance IQ	67.27 (16.61)	60.59 (19.14)	-1.06	.299	-19.58	6.23
Fractional anisotropy	.43 (.02)	.43 (.02)	0.14	.891	-.0137	.0157
White matter volume	412192.52 (51057.63)	411299.86 (35045.93)	0.06	.954	-	32289.59
Gray matter volume	511432.42 (56668.93)	539611.76 (47698.28)	-1.53	.137	-	9513.24
CRIq[a]						
Education	94.57 (15.78)	106.15 (11.71)	-2.37	***.024*** *	-21.55	-1.60
Work	107.31 (11.26)	91.71 (14.65)	3.34	***.003*** **	6.01	25.19
Leisure	106.09 (14.03)	93.09 (13.31)	2.69	***.012*** *	3.12	22.88
Age (yrs)	41.88 (11.41)	40.27 (6.55)	0.50	.623	-5.05	8.28
Estimated duration of HIV infection (mos)	109.59 (71.29)	85.60 (58.87)	1.04	.306	-23.04	71.01
Adherence[b]	3.71 (0.588)	3.60 (0.632)	0.49	.629	-0.34	0.55

Note. Columns 2 and 3 present data for *M*(*SD*). Equal variance not assumed. CRIq = Cognitive Reserve Index questionnaire; CI = confidence interval; LL = lower limit; UL = upper limit. Statistically significant between-group differences are highlighted in boldface font in the *p* column. Statistically significant associations prior to the Bonferroni correction applied are highlighted in bold italicized font [a]All CRIq scores are age-standardized. [b]Scored out of 4 on the Morisky Green Levine Medicine Adherence Scale (Morisky et al., 1986). *$p < .05$. **$p < .01$. ***$p < .001$. ***†$p < .0026$.

Regression Models

As Table 12 shows, age accounted for a significant proportion of the variance in global *T*-score (18.1%), motor function (18.3%), and executive function (14.7%). It was not a significant predictor of performance within the other cognitive domains.

Table 12

Regression Models, Set I: Age as a predictor of cognitive function (N = 32)

Outcome Variable	*b*	*SE b*	*β*	*F*	*df*	*p*	ΔR^2
Global *T*-score	-.426	.165	-.425	6.63	1,30	**.015***	.181
Motor function	-1.051	.412	-.428	6.51	1,29	**.016***	.183
Attention and working memory	-.576	.421	-.242	1.87	1,30	.181	.059
Information processing speed	-.234	.264	-.160	0.79	1,30	.383	.025
Language	-.310	.167	-.321	3.45	1,30	.073	.103
Memory: Audio-verbal	-.091	.178	-.093	0.26	1,30	.614	.009
Memory: Visual-spatial	.134	.191	.127	0.49	1,30	.490	.016
Executive function	-.682	.300	-.383	5.17	1,30	**.030***	.147

Note. Age (in years) as a statistically significant predictor is highlighted in boldface font in the *p* column.

*$p < .05$.

The second set of regression models examined the degree to which cognitive reserve (as indexed by the age-standardised CRIq total score) predicted cognitive function, either globally or in one of the domains. As Table 13 shows, cognitive reserve indexed in this way was not significantly predictive of any cognitive outcome variable, explaining less than 8% of the variance in each case.

Table 13

Regression Models, Set II: Cognitive reserve (CRIq score) as a predictor of cognitive function (N = 32)

Outcome variable	*b*	*SE b*	*β*	*F*	*df*	*p*	ΔR^2
Global *T*-score	-.098	.112	-.157	0.76	1,30	.391	.025
Motor function	-.425	.269	-.281	2.49	1,29	.125	.079
Attention and working memory	-.124	.269	-.084	0.21	1,30	.211	.007
Information processing speed	.000	.167	.000	< .001	1,30	.998	< .001
Language	.062	.109	.102	.318	1,30	.577	.010
Memory: Audio-verbal	-.064	.111	-.104	.330	1,30	.570	.011
Memory: Visual-spatial	-.096	.119	-.146	.653	1,30	.425	.021
Executive function	-.069	.202	-.062	.116	1,30	.736	.004

Note. In each model, the predictor under examination was cognitive reserve, as indexed by the age-standardized score on the Cognitive Reserve Index questionnaire (CRIq).

The third and final set of regression models examined the degree to which cognitive reserve (as indexed by either education, IQ, white matter volume, or gray matter volume) predicted cognitive function, either globally or in one of the domains. As Table 14 shows again, cognitive reserve indexed in these ways was also not significantly predictive of any cognitive outcome variable, explaining less than 29% of the variance in each case.

Table 14

Regression Models, Set III: Cognitive reserve (proxy measures) as predictors of cognitive function (N = 32)

Outcome / Predictor	*b*	*SE b*	*β*	Δ*F*	*df*	*p*	ΔR^2
Global *T*-score				0.592	4,27	.671	.081
Education (yrs)	.071	.861	.017				
Performance IQ	.130	.105	.251				
White matter volume	-1.746E-5	< .001	-.081				
Gray matter volume	1.848E-5	< .001	.106				
Motor function				2.59	4,26	.060	.285
Education (yrs)	1.609	1.871	.162				
Performance IQ	.130	.229	.104				
White matter volume	< .001	< .001	-.527				
Gray matter volume	< .001	< .001	.608				
Attention and working memory				0.961	4,27	.445	.125
Education (yrs)	-1.547	1.993	-.159				
Performance IQ	.467	.244	.379				
White matter volume	-6.669E-5	< .001	-.131				
Gray matter volume	3.999E-6	< .001	.010				
Information processing speed				1.229	4,27	.322	.154
Education (yrs)	0.068	1.210	.011				
Performance IQ	0.296	0.148	.389				
White matter volume	5.014E-5	< .001	.160				
Gray matter volume	-3.449E-5	< .001	-.135				
Language				0.389	4,27	.814	.055
Education (yrs)	-0.731	0.843	-.185				
Performance IQ	-0.043	0.103	-.086				
White matter volume	5.109E-6	< .001	.025				
Gray matter volume	4.019E-6	< .001	.024				
Memory: Audio-verbal				1.941	4,27	.132	.223
Education (yrs)	0.895	0.773	.224				
Performance IQ	0.109	0.095	.215				
White matter volume	< .001	< .001	.595				
Gray matter volume	< .001	< .001	-.635				
Memory: Visual-spatial				0.617	4,27	.654	.084
Education (yrs)	0.303	0.904	.070				
Performance IQ	0.139	0.111	.255				
White matter volume	1.687E-5	< .001	.075				
Gray matter volume	-3.943E-5	< .001	-.215				
Executive function				0.791	4,27	.541	.105
Education (yrs)	-1.053	1.509	-.154				
Performance IQ	0.235	0.184	.255				
White matter volume	-2.495E-5	< .001	-.065				
Gray matter volume	6.522E-5	< .001	.211				

Note. In each model, the predictor under examination was cognitive reserve, as indexed by the age-standardized score on the Cognitive Reserve Index questionnaire (CRIq).

CHAPTER 6

Discussion

This study aimed to investigate whether age and cognitive reserve have an impact on the cognitive function of people living with HIV (PLWH). To answer this question of interest, I gathered cognitive data across several domains and took multiple measures of cognitive reserve from a sample of South African HIV-infected adults. Correlational analyses, independent sample *t*-tests, and regression analyses tested the three hypotheses that guided the investigation. The first hypothesis stated that cognitive reserve is a significant predictor of cognitive test performance in PLWH. The second hypothesis stated that age is a significant predictor of cognitive test performance in PLWH. The third hypothesis stated that the interaction of cognitive reserve and age is a significant predictor of cognitive test performance; specifically, older individuals with lower cognitive reserve will display poorest cognitive performance.

The abovementioned analyses indicated that age, but not cognitive reserve, was a significant predictor of cognitive function (specifically in the domains of motor function and executive function). Hence, this set of results confirmed the first, but not the second, hypothesis. Cognitive reserve, measured in both a standardised scale and through proxy measures, was found to have no significant effect on cognitive functioning, neither globally nor in separate domains, hence the second hypothesis was rejected.

Influence of Cognitive Reserve on Cognitive Function

Analyses (correlational, *t*-test, and regression) of the current data indicated that, in this sample of HIV-infected adults, cognitive reserve was not a statistically significant influence on cognitive function as assessed by performance on a battery of standard neuropsychological tests.

Bivariate correlational analyses detected a weak negative correlation between global *T*-score and the standardised CRIq total score, $r = -.157$, $p = .391$. Other proxy measures of cognitive reserve (fractional anisotropy, total white and gray matter brain volume, Performance IQ [PIQ], highest level of education) also bore no statistically significant relationship with the global *T*-score.

The independent-sample *t*-tests divided the study sample ($N = 32$) into two groups based on their standardised CRIq total score. The division point between the groups (higher cognitive reserve, lower cognitive reserve) was set at a score of 100, which is set mean of the CRIq in the published literature on the instrument (see. e.g., Nucci et al., 2012).

The *t*-tests detected no significant between-group differences with regard to global *T*-score, MRI measures, and PIQ). They did, however, detect a significant between-group difference with regard to highest level of education, $p = .006$, with the higher cognitive reserve group having completed more years of formal education than the lower cognitive reserve group. This result is expected because highest level of education is used in calculating the CRIq total score. So, although it could lend some support to the CRIq as a measure of cognitive reserve, it may also be regarded as a confounded and incidental finding.

When investigating individual cognitive domains, the *t*-tests detected a significant between-group difference for motor function, $p = .008$. Upon further investigation of the test scores that constituted that domain, only performance by the non-dominant hand on the Grooved Pegboard Test was significantly different across groups, $p = .003$. This finding is not altogether surprising because some previously published studies have reported significant associations between motor function and cognitive reserve. For instance, Guzzetti et al. (2019) reported that higher CRIq scores (not age-standardized) were significantly associated with reduced motor impairment (measured subjectively, using the Unifying Parkinson's Disease Rating Scale) in Parkinson's disease patients. Similarly, Bonner-Jackson et al. (2013)

reported higher cognitive reserve (as measured using a hybrid composite score of four IQ, vocabulary, and reading tests) was significantly associated with motor function (determined by volume loss in motor areas of the brain) in prodromal Huntington's disease patients. Moreover, Umarova et al. (2019) reported that cognitive reserve (as measured by a vocabulary test) was significantly associated with neurological motor functions (as measured by years of education) in TBI patients. The variability in measures and in patient populations makes it difficult to draw direct comparisons with this study's results. Nonetheless, the possibility of cognitive reserve affecting motor function specifically is a possibility that should be investigated further.

Two separate sets of regression models tested the predictive power of cognitive reserve regarding cognitive performance. The first set used the standardised CRIq total score as predictor; global *T*-score and score for each independent cognitive domain investigated separately as outcomes. The outcome variables were the same for the second set of models; in those models, the four proxy measures of cognitive reserve (highest level of education, PIQ, total white matter volume, and total gray matter volume) were predictors.

The first set of models consistently reported very low proportions of explained variance in cognitive outcomes, with R^2 values ranging from < .001 to .079. The strongest of these models was that with motor function as the outcome variable, $ß$ = -.281, R^2 = .079, p = .125.

The second set of models also delivered no statistically significant results. They did, however, yield a higher range of explained variance, R^2 = .055 to .285. Again, the model for motor function stood out, $ß$ = -.527 - .608, R^2 = .285, p = .060. This result, although not statistically significant, seems to again suggest that cognitive reserve may have some relationship with motor function in HIV-infected adults.

Measuring Cognitive Reserve

Because there is no universally accepted standard measure of cognitive reserve, comparison of findings across investigations into the construct is fraught with difficulty. This is as true of the comparisons I make here as it is of any other study of cognitive reserve.

To alleviate that problem at least partially, I used two different measures of cognitive reserve: (1) the standardised CRIq total score, which is the only measure developed to measure cognitive reserve (which I standardised to account for the effects of age), and (2) a collection of four commonly used proxy measure (two passive and two active aspects of cognitive reserve). Unfortunately, the regression models highlighted how each could deliver (slightly) different results. Although both indices of cognitive reserve were not significantly predictive of cognitive test performance, the difference in the amount of variance each explained reserve was statistically significant (as demonstrated by a t-test comparing the two outcome values, $p = .002$). The combination of the four proxy measures explained a much higher amount of variance in each cognitive test outcome than the standardised CRIq total score. Because the combination variable is comprised of two measures of the 'passive aspects' (i.e., white matter volume and gray matter volume) and two measures of the 'active aspect' (i.e., highest level of education and an IQ score) of cognitive reserve, one might argue that the current data lend support to the passive and active conceptualization of cognitive reserve. Although a counterargument could be that more variables would naturally increase the amount of variance explained, it must be kept in mind that the standardised CRIq total score is comprised of educational and occupational attainment, as well as leisure pursuit variables.

Influence of Age on Cognitive function

The results of this study lend support to and are consistent with previously published research in this field in suggesting that aging often exacerbates other disease processes and has compounding negative effects on the afflicted individual (see e.g., Babu et al., 2019; Levin et al., 2019). In this study, correlational, *t*-test, and regression analyses all found that age was a significant factor regarding cognitive outcomes. The quantity of significant results across different types of analyses speaks to the importance of this factor as a predictor of cognitive function.

Bivariate correlational analyses detected a moderate negative correlation between age and global *T*-score, the primary cognitive outcome variable and a measure of global cognitive function, $r = -.425$, $p = .015$. This finding suggests overall cognitive function declines as age increases.

The *t*-tests detected significant between-group differences with regard to global *T*-score, $p = .012$, with younger participants ($M = 47.58$, $SD = 6.49$) outperforming older participants ($M = 38.84$, $SD = 10.35$). However, when investigating individual cognitive domains the *t*-tests detected only one statistically significant between-group difference for executive functioning ($p = .012$). Analyses of performance in two other domains (motor function and language) detected strong trends toward such between-group differences ($p = .061$ and .070, respectively). These results confirm that some cognitive domains (executive function most strongly, motor function and language perhaps more weakly) are more likely to be affected by the aging process. They also highlight the ways in which analyses of global cognitive scores are incomplete, if not misleading.

Regression modelling indicated that age remained a significant predictor of global cognitive function, explaining 18.1% of variance in the outcome, $p = .015$. These regression results must be interpreted cautiously because the distribution of global *T*-scores failed one of

the three normality assumptions. Great care was taken in investigation these normality assumptions, especially in post-hoc review and although the distribution of the residuals was marginally outside of the acceptable range, values for Cook's distance, collinearity tolerance, and variance inflation factors were found to be acceptably low. These marginal violations of some assumptions underlying the integrity of regression modelling are not unexpected because the sample is composed entirely of HIV-infected individuals. That is to say, because more than half of the 32 participants (n = 19; 59%) showed some degree of cognitive impairment based on their global deficits scores (GDS), data from neuropsychological tests are unlikely to be normally distributed as they would in the general population.

Similar regression models predicting scores on individual cognitive domains indicated that, even after accounting for the other factors listed above, age remained a significant predictor of performance on tests of motor function (R^2 = .183, p = .016) and of executive function (R^2 = .147, p = .030). The influence of age on language test performance was only marginally non-significant, (R^2 = .103, p = .073). Although caution is required when interpreting the motor function results because one assumption (the normal distribution of the sample's cognitive performance) was violated, the assumptions for executive function and language were all met.

Taken together, these analyses provide support for the hypothesis that age is a significant predictor of global cognitive function in HIV-infected samples. Perhaps more usefully, age appears to significantly predict performance by HIV-infected adults on tests of executive function, and, to a lesser degree, motor function and language. Although it must be kept in mind that this particular sample was somewhat skewed towards younger adults, the fact that statistically significant results were found consistently across different means of analysis and even after controlling for other possibly influential factors is an indication of how substantially age affects cognitive performance. The value of these results goes beyond

corroborating existing literature, it also raises the question as to when the negative effects of age on cognitive function in HIV begin to have significant effect as this population was skewed towards younger ages, yet 59% were found to have some form of cognitive impairment.

It should be noted that because the concept of cognitive reserve, and particularly the way it is measured, is so intertwined with and influenced by age, analyses investigating their interaction and the resulting effect on cognitive function could not be done. Hence the third hypothesis could not be tested.

Cognitive Profile of this Study Population

The most widely cited study investigating HIV-associated cognitive impairment in South Africa (Joska et al., 2011) reports that in a sample of 283 HIV-infected participants 23.5% were cognitively normal, 8.8% presented with asymptomatic cognitive impairment (ANI), 42.4% presented with mild cognitive disorder (MND) and 25.3% presented with HIV-associated dementia (HAD), based on the Gisslén criteria. The current findings are, broadly speaking, consistent with those reported in that study.

Specifically, analyses of GDS taken from performance on the 13 test outcome variables detected some form of overall cognitive impairment in 19 of the 32 participants in this study (59.38%; i.e., 13 participants, or 40.62% of the sample, were cognitively intact.) At a more granular level, 14 of the 32 participants (43.75% of the sample) showed mild cognitive impairment while 5 (15.63%) showed mild-to-moderate impairment, based on the deficit score criteria classification taken from Carey et al. (2004). One of the study's eligibility criteria specified that no individual with severe cognitive impairment could be included, and analysis of GDS scores confirmed that that criterion had been applied successfully.

Limitations and Directions for Future Research

Five specific limitations of the study design must be borne in mind when interpreting its findings.

First, and perhaps most importantly, the sample size (N = 32) was quite small and was statistically underpowered (especially with regard to the independent-samples *t*-test, when the overall N was split into two groups of 16) to investigate the questions of interest. A post-hoc power analysis showed that the statistical power this study achieved based on the sample size is 0.13. This is lower than desired and does limit the strength of the results. The reason the study concluded with the sample size (N = 32) was: (1) unforeseeable attrition of parent studies' participant pool, and (2) an a priori power analysis showed 32 participants would provide an acceptable effect size (β = .5) to conduct analyses. The parent studies from which this study emerged initially had a much larger participant poor, however due to abnormally high rates of attrition roughly 70% of that initial participant pool were unreachable and could not be recruited. The parameters of this study's approval by the Research Ethics Committee of the UCT Faculty of Health Sciences would not allow for the recruitment of participants outside of the parent studies' participant pool and the time restrictions of the Master's degree this study was for would not allow for reapplication to the Research Ethics Committee.

Despite these mitigating factors, the fact is that the study was underpowered and hence its results must be interpreted with caution, especially when evaluating whether they can be generalized to the population of South African PLWH.

A second limitation is the marked gender and ethnic biases of the sample (84.3% of participants were women and 96.6% were Xhosa-speaking). These biases are a consequence of the sampling method, which was non-random and opportunistic, and they mean that the sample is not representative of the demographics of either the population of PLWH in the Western Cape province or in South Africa. In mitigation of this limitation is the fact that

there is no substantial evidence that ethnicity should impact on cognitive functioning, Moreover, the existence of sex differences in HIV-associated cognitive impairment is controversial and further research is needed to establish its effect (Burlacu et al., 2018; Sundermann et al., 2018).

A third limitation is the lack of a demographically-matched HIV seronegative control group. The addition of this design element would have bolstered the findings and helped mitigate the limitation of the small sample size. In addition, the use of such a control group would have been helped differentiate more clearly the influence of HIV-associated cognitive impairment from the influence of age and cognitive reserve in cognitive impairment. Although this role of an HIV seronegative control group was recognised and discussed, in practicality collecting especially MRI data for such a control group was impossible given the temporal and financial restrictions of this Master's study.

A fourth limitation relates to ways in which the possible presence of unmeasured vascular pathology may have influenced the results. Approximately 75% of participants had a body mass index (BMI) that categorized them as being at least overweight (and, in some cases, obese). The sample's average BMI was 30 and was skewed significantly towards higher values, with the highest being 48. These data raise questions about the sample's cardiovascular risk factors. Taken together with the fact self-reported co-morbidities of hypertension, diabetes, and high cholesterol were quite low (15.63%, 6.25%, and 6.25%, respectively), it is possible that many participants had undiagnosed and untreated cardiovascular co-morbidities. In a neuropsychological study, this is an issue of major concern because cardiovascular pathology has independent effects on cognitive functioning (Cysique & Brew, 2019; Rodriguez-Penney et al., 2013).

A fifth limitation was that the study could have significantly benefitted from the collection of new blood cultures instead of relying on archival and self-report data regarding

ART adherence and estimated duration of infection. This new collection would have allowed analysis of more accurate clinical data regarding HIV-associated variables (e.g., CD4 and viral load counts) as well as co-morbid medical conditions, hence providing much more clarity on the influence of the independent and interactional effects of HIV, age, and cognitive reserve on cognitive functioning.

Summary and Conclusion

The primary aim of this study was to investigate the influence of age and cognitive reserve (both independently and in interaction) on cognitive functioning in a sample of HIV-infected South African adults.

Despite some methodological limitations, results suggested that age plays a significant role in the cognitive test performance on PLWH, with older adults likely to show significantly more deficits than younger adults. This finding is consistent with a large body of extant literature, although it is notable that much of that literature emerges from high-income countries of the global north.

Although it is clear that age is just one among a complex network of variables contributing to cognitive, affective, and behavioural function in PLWH, knowing that the aging process does affect those outcomes and describing and understanding age-related effects is valuable for clinicians, researchers, and policy makers. These individuals can incorporate that knowledge into interpreting results of cognitive screens, planning for and anticipating decline severity and trajectory, knowing where to most effectively allocate resources, and timing interventions and management plans so that the most important areas of need are covered throughout the disease process.

The current analyses did not support the hypothesis that cognitive reserve would have a significant influence on cognitive test performance. In contrast to the literature describing age-related effects on cognition in PLWH, published research on cognitive reserve in HIV is

sparse. One possible reason for this scarcity may be publication bias (i.e., non-significant results not being published). I argue that the current finding, suggesting that despite measuring cognitive reserve in multiple theoretically defensible ways there were no detectable effects on cognitive test performance, should be reported in the literature because it provides (at least) some guidance for future research in this field.

Regarding measures of cognitive reserve, as noted in earlier chapters the construct lacks a universally-applied definition and hence different studies tend to assess it in different ways, thus making cross-study comparisons difficult. Clearly, more research is needed into defining the construct clearly and designing appropriate measures that will be accepted and applied widely. One way to proceed, in the interim, is to use multiple different estimates of cognitive reserve as was done here.

In conclusion, this study provided evidence for the influence of age on cognitive function in PLWH but did not find evidence for the influence of cognitive reserve. Although neuroscience research attaches increasing importance to the construct of cognitive reserve it is crucial that only factors which significantly impact cognitive function are identified and investigated to maximise the efficiency of resource allocation of intervention efforts. This is especially imperative in countries such as South Africa that are characterized by high HIV disease burden and limited clinical and infrastructural resources.

CHAPTER 7

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Appendixes

Appendix A

Screening questionnaire and the Morisky Green Levine Medicine Adherence Scale

Age and Cognitive Reserve Study Participant #: _____ Initials: _____

Checklist ☑		
5	Medicine adherence scale (MGLs)	
5	Self-report Questionnaire	
15	Lawton IADLs	
30	MINI	

Morisky Green Levine Medicine Adherence Scale (MGLs)		
1) Do you ever forget to take your medicines?	0 Yes / No 1	0 1 2 3 4
2) Are you ever careless about taking medicine	0 Yes / No 1	0 1 2 3 4
3) Do you stop taking your medicines when you are feeling better?	0 Yes / No 1	0 1 2 3 4
4) Do you stop taking your medicines if you feel worse?	0 Yes / No 1	0 1 2 3 4
Total		

Date of Diagnosis	
Current ART Regiment	

	Date	Successful regiment	Failed regiment
Date of ART started			
D4T			
AZT			
3TC			
EFV			
NVP			
TDF			
FTC			

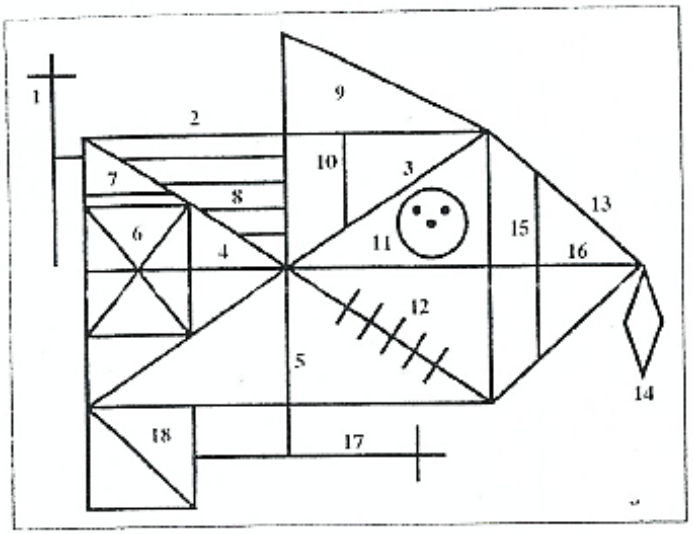
Self-report Questionnaire							
Use history : Have you ever used							
Alcohol	N | Y	Start date		End date		Units/week	
Smoked (cigarettes)	N | Y	Start date		End date		Units/week	
Substance (drug) use	N | Y	Start date		End date		Units/week	

Medical History	Self	Parents	Siblings	Other family	None
High blood pressure					
	Notes:				
Diabetes					
	Notes:				
High cholesterol					
	Notes:				
Migraine headaches					
	Notes:				
Stroke					
	Notes:				
TB infection					
	Notes:				
Dementias (i.e. Alzheimer's, Vascular or other)					
	Notes:				
Traumatic brain injury					
	Notes:				
Surgeries					
	Notes:				

Appendix B

The Rey-Osterrieth Complex figure

Scoring Sheet



Scoring Criteria for RCFT Drawings

Score	Accuracy	Placement
2	Accurately drawn	Correctly placed
1	Accurately drawn	Incorrectly placed
1	Inaccurately drawn	Correctly placed
0.5	Inaccurately drawn, but recognizable	Incorrectly placed
0	Inaccurately drawn and unrecognizable, or omitted	Incorrectly placed

S ing Element	Copy	Immediate Recall	Delayed Recall
1. Vertical Cross	2 1 0.5 0	2 1 0.5 0	2 1 0.5 0
2. Large Rectangle	2 1 0.5 0	2 1 0.5 0	2 1 0.5 0
3. Diagonal Cross	2 1 0.5 0	2 1 0.5 0	2 1 0.5 0
4. Horizontal Midline of Large Rectangle (2)	2 1 0.5 0	2 1 0.5 0	2 1 0.5 0
5. Vertical Midline of Large Rectangle (2)	2 1 0.5 0	2 1 0.5 0	2 1 0.5 0
6. Small Rectangle	2 1 0.5 0	2 1 0.5 0	2 1 0.5 0
7. Small Horizontal Line above Small Rectangle (6)	2 1 0.5 0	2 1 0.5 0	2 1 0.5 0
8. Four Parallel Lines	2 1 0.5 0	2 1 0.5 0	2 1 0.5 0
9. Small Triangle above Large Rectangle (2)	2 1 0.5 0	2 1 0.5 0	2 1 0.5 0
10. Small Vertical Line within Large Rectangle (2)	2 1 0.5 0	2 1 0.5 0	2 1 0.5 0
11. Circle with Three Dots	2 1 0.5 0	2 1 0.5 0	2 1 0.5 0
12. Five Parallel Lines	2 1 0.5 0	2 1 0.5 0	2 1 0.5 0
13. Sides of Large Triangle attached to Large Rectangle (2)	2 1 0.5 0	2 1 0.5 0	2 1 0.5 0
14. Diamond	2 1 0.5 0	2 1 0.5 0	2 1 0.5 0
15. Vertical Line within Sides of Large Triangle (13)	2 1 0.5 0	2 1 0.5 0	2 1 0.5 0
. Horizontal Line within Sides of Large Triangle (13)	2 1 0.5 0	2 1 0.5 0	2 1 0.5 0
17. Horizontal Cross	2 1 0.5 0	2 1 0.5 0	2 1 0.5 0
18. Square attached to Large Rectangle (2)	2 1 0.5 0	2 1 0.5 0	2 1 0.5 0
	_____	_____	_____
	Raw score	Raw score	Raw score

Recognition Trial Worksheet

_____ Recognition True Positives = Sum of items 2, 5, 7, 8, 9, 12, 13, 15, 19, 20, 22, and 24 that were circled.

_____ Recognition False Positives = Sum of items 1, 3, 4, 6, 10, 11, 14, 16, 17, 18, 21, and 23 that were circled.

_____ Recognition True Negatives = 12 minus Recognition False Positives.

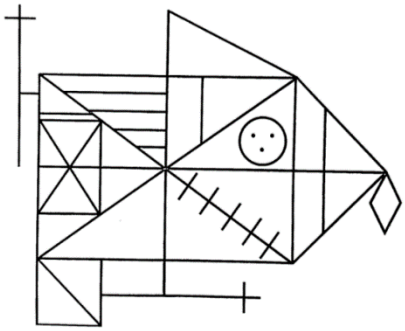
_____ Recognition False Negatives = 12 minus Recognition True Positives.

_____ Recognition Total Correct = Recognition True Positives plus Recognition True Negatives.

Appendix C

the Rey Complex Figure Organizational Strategy Score (RFC-OSS)

The RCF Organizational Strategy Score.



RCF-OSS Instructions

Level 7 – excellent organization. Configural elements, the rectangle and centerlines, are completed first
Criteria: (a) rectangle is drawn first (may include the left hand cross);
(b) both vertical and horizontal centerlines are drawn directly after the rectangle;
(c) **all** of the internal sections, outside attachments and the diagonals aligned with centerlines.

Level 6 – conceptual organization. Vertical and horizontal centerlines are drawn early.
Criteria: (a) either rectangle, contour, an internal section or outside attachments is drawn first;
(b) both centerlines are drawn as whole single lines and completed prior to drawing diagonals and internals sections;
(c) diagonals are aligned with centerlines (i.e., meet at the midpoint junction);
(d) **majority** of internal sections and outside attachments are aligned with centerlines.

Level 5 – part-configural organization. Vertical and horizontal centerlines are present.
Criteria: (a) either rectangle, contour, an internal section or outside attachment is drawn first;
(b) both centerlines are present;
(c) **at least one** internal section or outside attachment is aligned with vertical centerline, and **at least one** internal section or outside attachment is aligned with horizontal centerline;
(d) at least one centerline is drawn as a whole single line, whilst remaining centerline can be completed fragmentally (i.e., in segments), although portions must connect.
(e) a piecemeal approach is not adopted.

Level 4 – piecemeal / fragmented organization. Piecemeal, fragmented or part-whole approach (subunits/ sections are drawn sequentially piece by piece).
Criteria: (a) either rectangle, contour, an internal section or outside attachment is drawn first;
(b) only **one** centerline is completed as a whole single line unless the contour or rectangle is completed first, in which case, neither centerline can be completed as a whole;
(c) remaining internal sections and outside attachments are completed one at a time in a piecemeal manner (subsequent sections of drawing can be aligned with segments of centerlines).

Level 3 – random organization. Only one complete centerline is used for alignment.
Criteria: (a) either rectangle, contour, an inside section or outside attachment is drawn first;
(b) one complete centerline aligned with **at least one** internal section/outside attachment is present (centerline can be completed fragmentally, i.e., in segments, although segments must connect);
(c) remaining centerline, if present, is not utilized for alignment of other components;
(d) if present, segments of an incomplete centerline can be utilized to align sections of drawing;
(e) piecemeal approach is not adopted.

Level 2 – poor organization. Criteria for levels 3 to 7 have not been satisfied.
Criteria: (a) any attempt to draw figure;
(b) any part of figure is drawn first;
(c) if present centerlines are not aligned to any of internal sections or outside attachments;
(d) piecemeal approach is not adopted.

Level 1 – unrecognizable or substitution. No attempt is made to draw figure. Child may draw a substitution or an unrecognizable scrawl.

Appendix D

The Cognitive Reserve Index Questionnaire

Cognitive Reserve Index

CRIq

questionnaire

M. Nucci, D. Mapelli & S. Mondini (2012)

Instructions: The CRIq can be administered by a family member or the caregiver when the participant cannot be interviewed due to attested or suspected cognitive decline. Check the appropriate box at the bottom of the questionnaire.

Surname: ..... Name: .....

Date of birth: ...../...../..... Place of birth: ..... Age: .....

Place of residence: ..... Nationality: :.....

Civil status: single ☐ married ☐ divorced ☐ widowed ☐

CRI-Education

Instructions: Count 1 for each year of education. Count 0.5 for every 6-month period of vocational training courses taken.

	Years
1. Years of education (including postgraduate studies and any specialization)	.....
2. Vocational training (0.5 for every 6 months)	.....

CRI-WorkingActivity

Instruction: Indicate working years rounded off on a five-year scale (0-5-10-15-20, etc.; e.g., if a person has been working for 17 years, write down 20). The degree of intellectual involvement and personal responsibility discriminates between the 5 levels of working activity. Report on all working activities, even in the case of simultaneously held multiple jobs.

	Years
1. Low skilled manual work (farm work, gardener, housemaid, caregiver, waiter, driver, mechanic, plumber, call center operator, babysitter, etc.)	.....
2. Skilled manual work (craftsman, cook, store clerk, tailor, representative, serviceman/servicewoman, hairdresser, clerical worker, nurse, etc.)	.....
3. Skilled non manual work (business owner, white-collar employee, sales agent, priest or monk/nun, real estate agent, nursery school teacher, musician, etc.)	.....
4. Professional occupation (Managing director of a small company, lawyer, qualified freelance professional, contractor, doctor, teacher, engineer, etc.)	.....
5. Highly responsible or intellectual occupation (Managing director of a big company, senior manager, judge, university professor, surgeon, politician, etc.)	.....

CRI-LeisureTime

Instructions:

- Each item refers to activities carried out regularly throughout adult life (i.e. from 18 years onwards).
- All paid activities are excluded from this section (for paid activities, return to CRI-WorkingActivity).
- Register answers according to the frequency mentioned for each activity (e.g., weakly, monthly, annual).
- The column Years refers to the number of years in which the mentioned activity has been carried out Often/Always, overstating according to a scale of 5 to 5 years (5-10-15-20, etc.). For example, whether a person regularly reads a newspaper for 27 years, will be registered Often/Always for 30 years, even if he/she has stopped reading for many years.
- If the activity has never or seldomly been carried out (option Never/Rarely) the number of years need not be indicated.
- If over the participants lifespan the activity changed in frequency in a significant manner, only the period (in number of years) of the highest frequency is to be considered. For example, if a person drove a car every day for 40 years, but in the following 15 years he/she did so only once or twice a week, than the answer is Often/Always for 40 years.

1. ACTIVITIES WITH WEEKLY FREQUENCY

	less or equal then 2 times in a week	more or equal then 3 times in a week	Years
1. Reading newspapers and magazines	☐ Never/Rarely	☐ Often/Always	.....
2. Domestic chores (cooking, washing, grocery shopping, ironing, etc.)	☐ Never/Rarely	☐ Often/Always	.....
3. Driving (not biking)	☐ Never/Rarely	☐ Often/Always	.....
4. Leisure activities (sports, hunting, dancing, chess, coin collecting, etc.)	☐ Never/Rarely	☐ Often/Always	.....
5. Using new technologies (digital cameras, computer, Internet etc.)	☐ Never/Rarely	☐ Often/Always	.....

2. ACTIVITIES WITH MONTHLY FREQUENCY

	less or equal then 2 times in a month	more or equal then 3 times in a month	Years
1. Social activities (political parties, recreational clubs, associations, etc.)	☐ Never/Rarely	☐ Often/Always	.....
2. Cinema, theater	☐ Never/Rarely	☐ Often/Always	.....
3. Gardening, DIY, small-scale operations such as knitting, etc.	☐ Never/Rarely	☐ Often/Always	.....
4. Looking after grandchildren/nieces/ nephews or elderly parents	☐ Never/Rarely	☐ Often/Always	.....
5. Voluntary work	☐ Never/Rarely	☐ Often/Always	.....
6. Artistic activities (music, singing, performance, painting, writing, etc.)	☐ Never/Rarely	☐ Often/Always	.....

3. ACTIVITIES WITH ANNUAL FREQUENCY

	less or equal then 2 times in a year	more or equal then 3 times in a year	Years
1. Exhibitions, concerts, conferences	☐ Never/Rarely	☐ Often/Always	.....
2. Journeys lasting several days	☐ Never/Rarely	☐ Often/Always	.....
3. Reading books	☐ Never/Rarely	☐ Often/Always	.....

4. ACTIVITIES WITH FIXED FREQUENCY

1. Children	☐ No	☐ Yes	number .....

			Years
2. Pet care	☐ Never/Rarely	☐ Often/Always	.....
3. Managing one's current account	☐ Never/Rarely	☐ Often/Always	.....

Questionnaire administered to: interested party ☐ family/caregiver ☐ .....

Date: ...../...../..... Interviewer: .....

RESULTS

CRI-Education .....

CRI-WorkingActivity .....

CRI-LeisureTime .....

CRI .....

☐	☐	☐	☐	☐
low	medium-low	medium	medium-high	high
≤ 70	70 : 84	85 : 114	115 : 130	≥ 130

South African - Amended version of the CRIq

Cognitive Reserve Index questionnaire (CRIq) – South African amended (SAa) [Pilot]																	
Surname:						Name:								Age:			
Date of birth:	D	D	M	M	Y	Y	Y	Y	Date of interview:	D	D	M	M	Y	Y	Y	Y
Place of birth:									Place of residence:								
Nationality:				Civil status:	single		married		divorced		widowed						

CRI - Education					
1. Highest level of education					
Cannot read / write	0	Grade 6 / Standard 4	6	FET College	13
Can read / write	0.5	Grade 7 / Standard 5	7	Diploma	
Grade 1	1	Grade 8 / Standard 6	8	Certificate	
Grade 2	2	Grade 9 / Standard 7	9	University undergrad	14
Grade 3 / Standard 1	3	Grade 10 / Standard 8	10	University postgrad	15
Grade 4 / Standard 2	4	Grade 11 / Standard 9	11	Other:	
Grade 5 / Standard 3	5	Grade 12 (Matric)	12		

Name of primary school:		Private	Public	Rural	Urban
Name of secondary school:		Private	Public	Rural	Urban
Name of tertiary school:		Private	Public	Rural	Urban
2. Total years of education (including postgraduate studies and any specializations)					
3. Vocational training (0.5 for every 6 months)					

CRI – Working Activity					
1. Source of income					
None	0	Old age grant	2	Pension	4
Disability grant	1	Veteran grant	3	Private/Occupational	5
2. Income range					
None	0	R1 000 – R1 999	3	R10 000 – R15 000	6
R1 – R499	1	R2 000 – R4 999	4	R15 000 – R20 000	7
R500 – R999	2	R5 000 – R9 999	5	R20 000 +	8

3. Work activity		Years
1	Low skilled manual work (farm worker, gardener, housekeeping, caregiver, waiter, driver, mechanic, plumber, call centre operator, electrician, babysitter etc.)	
2	Skilled manual work (craftsman, cook, store clerk, tailor, representative, serviceman/woman, hair dresser, clerical worker, nurse, etc.)	
3	Skilled non manual work (business owner, white-collar employee, sales agent, priest or monk/nun, real estate agent, nursery school teacher, musician, etc.)	
4	Professional occupation (Managing director of a small company, lawyer, qualified freelance professional, contractor, doctor, teacher, engineer, etc.)	
5	Highly responsible or intellectual occupation (Managing director of a big company, senior manager, judge, university professor, surgeon, politician, etc.)	

CRI – Leisure time

Instructions:

- Each item refers to activities carried out regularly throughout adult life (i.e. from 18 years onwards)
- All paid activities are excluded from this section (for paid activities, return to CRI – Working)
- Register answers according to the frequency mentioned for each activity (i.e. weekly, monthly, annually)
- The years column refers to the number of years in which the mentioned activity has been carried out Often/Always, overstanding according to a scale of 5 to 5 years (5-10-15-20, etc.). For example, whether a person regularly reads a newspaper for 27 years, will be registered Often/Always for 30 years, even if he/she has stopped reading for many years.
- If the activity has never or seldomly been carried out (option Never/Rarely) the number of years need not be indicated.
- If over the participants lifespan the activity changed in frequency in a significant manner, only the period (in number of years) of the highest frequency is to be considered. For example, if a person drove a car every day for 40 years, but in the following 15 years he/she did so only once or twice a week, than the answer is Often/Always for 40 years.

1. Activities with weekly frequency		Less or equal than 2 times in a week	More or equal than 3 times in a week	Years
1	Reading newspapers and magazines	Never/Rarely	Often/Always	
2	Domestic chores (cooking, washing, grocery shopping, ironing, etc.)	Never/Rarely	Often/Always	
3	Driving (not biking), use public transport (independently)	Never/Rarely	Often/Always	
4	Leisure activities (sports, hunting, dancing, chess, coin collecting, etc.)	Never/Rarely	Often/Always	
5	Using new technologies (digital camera, computer, internet, smart phone, etc.)	Never/Rarely	Often/Always	

2. Activities with monthly frequency		Less or equal than 2 times in a week	More or equal than 3 times in a week	Years
1	Social activities (political parties, recreational clubs, associations, etc.)	Never/Rarely	Often/Always	
2	Cinema, theatre, movies	Never/Rarely	Often/Always	
3	Gardening, DIY, small-scale operations such as knitting, etc.	Never/Rarely	Often/Always	
4	Looking after grandchildren/ nieces/ nephews or elderly parents	Never/Rarely	Often/Always	
5	Voluntary work	Never/Rarely	Often/Always	
6	Artistic activities (music, singing, performances, painting, writing, etc.)	Never/Rarely	Often/Always	
3. Activities with annual frequency		Less or equal than 2 times in a week	More or equal than 3 times in a week	Years
1	Exhibitions, concerts, conferences	Never/Rarely	Often/Always	
2	Journeys lasting several days	Never/Rarely	Often/Always	
3	Reading books	Never/Rarely	Often/Always	
4. Activities with fixed frequency				Number
1	Children	Never/Rarely	Often/Always	
				Years
2	Pet care	Never/Rarely	Often/Always	
3	Managing one's current account	Never/Rarely	Often/Always	

Note: The CRIq can be administered by a family member or caregiver when the participant cannot be interviewed due to suspected cognitive decline. Check appropriate box at the end of the questionnaire.

Questionnaire administered by:

Participant		Family/Caregiver		Clinician	

Date:	D	D	M	M	Y	Y	Y	Y	Interviewer:	

Appendix E

Consent Form

Informed Consent Form

Informed Consent to Participate in Research and Authorisation for Collection, Use, and Disclosure of Protected Health Information

Participant number: _____
Participant initials: _____

Study title:

A Model of Age and Neuro-cognitive Reserves' Influence on Neuro-ognitive Function and Activities of Daily Living in HIV

Investigators

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021-650-4608
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Hello!
Thank you for being here today and for your willingness to listen about this study.

This form is to give you information about the study that you have been asked to take part in and to ask your permission to use the information we collect from you. The reason for all of this is so that we can learn more about HIV and how it affects people, so that we can help people with HIV in better ways. The researcher (Marcelle Boshoff), and the translator, (Primrose) will explain and describe everything about the study for you and answer any questions you may have

Please know that ALL the information collected from you will remain completely and strictly confidential, i.e. it won't be shared with anyone outside of this study.

It is completely up to you if you want to take part in this study. You only take part if you want to and if you agree to take part, you can stop at any time without any penalties.

Before you decide whether you want to take part in this study or not, everything will be explained to you, in the language you choose, and you can read this form which also explains everything about the study. Please ask as many questions as you want/need to and we will gladly answer them.

What is a research study?
A research study is a very careful way of looking at something and collecting information about what is being looked at. It can be as simple as asking a few questions such as in a survey or in an interview. Or it can be more difficult and may look at a particular sickness or testing new treatments for a particular sickness.

What is this study about?
This study asks questions about the HIV virus and how it affects people's brains, specifically the way people think and do everyday things. We will be looking specifically at how HIV affects all the ways in which people think, for example how they learn, remember, concentrate and solve problems. We will also be using MRI (Magnetic Resonance Imaging) scans to take pictures of people's brains to see how the HIV has physically affected their brain.

Why is this study being done?
We hope that getting more information specifically about how HIV affects people's brains will help make advances in treatment and intervention programs to help people with HIV live better lives. If we better understand how HIV affects the brain, we can better understand how to deal with it, i.e. if we find that HIV affects memory more than concentration for example, we can tell doctors and other medical practitioners so that they are aware of this and can treat people with HIV accordingly.

What is my role in the study?
Your role in this research study, should you agree to take part, is to be a research participant. A research participant is a person who agrees to take part in a research study. This is completely voluntary. As a research participant you will be helping the researcher to answer the questions in the study. You can decide you no longer want to be in the study at any time. We will ask you to give us information in the

form of the MRI scan (brain picture), different thinking tests and other questions about how you feel and experience having HIV.

What are my responsibilities in the study?
It is your responsibility to obey the safety instructions of the researcher and the staff at Groote Schuur Hospital. It is also your responsibility to ask questions and indicate when you do not fully understand something being said to you. A translator will be present during the whole study to help explain everything in the language of your choice.

Why are you being asked to take part?
We are asking you to take part in this study because you were in the previous study at Groote Schuur Hospital with Dr Heckmann and Dr Megan, and we would like to get more information from you about how you experience being HIV-positive and how feel about it and how you experience it.

How does this research study work?
This research study will follow a specific protocol that will be set out below:

What is a protocol?
A research protocols helps a researcher to carry-out the research. A protocol is like a cookbook. It tells the researcher what can and cannot happen during the research. It includes information the researcher must follow to protect participants from harm. This protocol must be reviewed by a Human Research Ethics Committee before the research can begin.

The research protocol
This study's research protocol has 3 steps.

Step1. The MRI scan. The first part of this study will be to prepare you for the MRI scan. Your safety and health are the main priority. That is why everything will be explained to you in detail and you will be given an information form (included in this pack). Then the researcher, translator and the MRI staff will ask you detailed questions from the MRI screening from (also included in this pack) to make sure it is safe for you to get the MRI scan. After all the preparations are made you will get the MRI scan. The scan will take about 30-40 minutes.

Step 2. After the MRI scan we'll take a break and you can have some light refreshments. Then the researcher and translator will do the thinking tests with you. These tests are very much like the ones that you have previously done with Dr

Heckmann and Dr Megan. These tests should take about 60 minutes, and you can have breaks in between when you need to.

Step 3. After the thinking tests we'll take another break with some refreshments. Then finally the researcher and the translator will ask you some easy questions about how you are feeling, the kinds of things you do every day, what kind of medicine you take, etc. This should take about 30 minutes. After this is done, the study will be done and you will be given transport back home.

Can anyone be in a research study?
Each study has a list of who can and cannot be in the research. This is written in the protocol. In order to protect research participants, only people who qualify can be in a study. This study aims to collect information from about 70 to 100 participants.

How long will the study last?
The study should take about 2 to 3 hours, including breaks with light refreshments.

Are there any benefits to you for being in the study?
If you decide to take part in the study we will collect the information from you. You are allowed to stop taking part, i.e. change your mind at any time. We will provide you with the transport to Groote Schuur Hospital and back, as well as R150 for your time.

What are the risks and discomforts of this study?
There are no risks when you take part in this research study. The tests and questions we ask do not hold any foreseen harm to you. We make every effort to make sure that the MRI scan is safe for you to get. The MRI scan may be uncomfortable for you due to the loud noises it makes. To make sure that this loud noise is not too uncomfortable for you, we give you ear plugs to help with the loud noises and we take you through a 'mock' or 'fake' scan first to make sure that you are comfortable with it before we start.
What happens if I get hurt taking part in this study?
The research study has taken out **insurance from [the University of Cape Town** in the event of a research/trial-related injury, i.e. harm suffered as a result of participation in the trial. We agree to pay **all reasonable medical expenses in keeping with the Association of the British Pharmaceutical Industry Guidelines** (ABPI) if you get **an injury directly because you took part** in the trial.
The ABPI guidelines recommend **that we should compensate (pay) you, without you having to prove that it was our fault,** for any injury from the study that was part of the protocol for this study.

We **will not be liable** for any loss, injuries and/or harm that you may sustain where the loss is caused by

- The use of unauthorised medicine or substances during the study
- Any injury due to you not following the protocol requirements or the instructions that the study doctor may give you
- Any injury that comes from poor action or lack of action to deal poorly with a side effect or reaction to the study medication
- An injury that results from negligence on your part

What other choices do you have?
Taking part in this research study is completely YOUR CHOICE. If you do not want to take part in the study you do not have to. No one can force you to take part in this study.

What is informed consent?
If you decide you would like to be in a research study, the facts about the research will be given to you in an information sheet or consent form. This is to help you understand what will happen to you in the research study. It will explain the kinds of things that you can expect will happen at each visit so that you can make up your mind. You will be told about all the risks, if there are any benefits and any other options to the study. You will be able to ask any questions about the study and you may be able to speak to your family or friends before making your decision. You are also able to ask questions during the study.

What will happen when the study is over?
After the study we will take all the information we collected from you and the other participants and do analyses on them, i.e. we will look at everything together and see what patterns are there and what we can learn from all the information.

Will your test results be shared with you?
Informing you about your test results are not part of the protocol, but if something is found, like a medical condition (a problem) that may affect you, you will be called and informed as soon as possible and we will give you advice if you need to see a doctor.

Will the results of the research be shared with you?
If you are interested in the results (what we find out) after we have looked at and analysed all the information we can call you and sent you the information. Please indicate below if you would be interested in knowing about the results of the

research study. Please note that collecting and looking at all the information can take a long time, usually around 12 months after your participation.

Who will see the information which is collected about you during the study?
The information collected from you is kept confidential and private. All the information gained from you is entered under a code to guarantee your privacy. Only the researcher will know what your information is. Once the information is taken together it is all under the code, so your name does not appear anywhere. All the information taken together will be seen by the researcher and her supervisors (teachers). Your information will not be seen by anyone outside of this study.

Who do I speak to (or contact) if I have any questions about the study?
You can contact the researcher directly if you have any questions about the study. There is a tear off slip at the end of this form with her information for you.

Please state your name: _____

☐ I give my consent that the researchers may use the data already collected should I choose to stop participating

☐ I do not give my consent that the researchers may use the data already collected should I choose to stop participating and the researchers must please discard all data related to me

Signatures

As the researcher of this study, I have explained to the purpose, the procedures, the possible benefits, and the risks of this research study to the prospective participant; the alternatives to being in the study; and how the participant's protected health information will be collected, used, and shared with others:

_____ _____

Signature of Person Obtaining Consent Date

_____ _____

Witness Date

You have been told about this study's purpose, procedures, and risks; how your protected health information will be collected, used and shared with others. You have received a copy of this form. You have been given the opportunity to ask questions before you sign, and you have been told that you can ask other questions at any time.

You voluntarily agree to participate in this study. You hereby authorize the collection, use and sharing of your protected health information. By signing this form, you are not waiving any of your legal rights.

_____ _____

Signature of Person Consenting Date

Please state below if you would like to be informed of the results of this research study:

_____ (initial) Yes, I would like to be informed of the research findings.

Please state below if you would like to be notified of future research projects conducted by our research group:

_____ (initial) Yes, I would like to be added to your research participation pool and be notified of research projects in which I might participate in the future.

Method of contact:

Phone number: _____

E-mail address: _____

Mailing address: _____

Participant number: _____

Participant initials: _____

Study title:

A Model of Age and Cognitive Reserves' Influence on Neuro-cognitive Function and Activities of Daily Living in HIV

If you would like to contact the researcher with any question please feel free to contact us:

Ms Marcelle Boshoff cell: 083 961 4265 email: boshoff717@gmail.com

Ms Marcelle boshoff holds a BSocSci Honours degree in Psychology and has sufficient previous experience to conduct clinic research. She is a candidate for a Master of Arts in Neuropsychology degree and is currently completing her internship to qualify for the degree (2018-2019).

Appendix F

CUBIC's standard MRI screening form

Cape Universities Body Imaging Centre (CUBIC)

University of Cape Town

MRI Participant Screening Form

Study:	CR4H		
Participant Code:	C12		
Date Of Birth:	1/01/1962	Weight:	58,9 kg
		Height:	150 cm

The following information is very important to ensure your safety and to prevent any interference during the MR procedure.

Please answer the following questions (mark with a X):

		Yes	No	Don't Know
1.	Do you have a cardiac pacemaker/defibrillator?		X	
2.	Do you have a neuro-stimulator?		X	
3.	Do you have a cochlea implant/surgery to your ears? (If yes, please specify)		X	
4.	Have you ever had heart surgery such as a valve replacement? (If yes, please specify)		X	
5.	Have you ever had any type of electronic, mechanical, or magnetic implant? (If yes, please specify)		X	
6.	Do you have any foreign body in your eyes or body? (Bullet fragments etc..)		X	
7.	Do you have a vena cava filter?		X	
8.	Do you have a prosthetic limb, eye or other artificial device not already mentioned? (If yes, please specify)		X	
9.	Are you pregnant or breast feeding?		X	
10.	Are you claustrophobic?		X	
11.	Do you have aneurism clips?		X	
12.	Do you have renal impairment?		X	
13.	Do you have asthma?		X	
14.	Do you have allergies? (If yes, please specify)		X	
15.	Do you have any other implants? (e.g. screws, plates, joint replacements)		X	
18.	Other		X	

I hereby acknowledge that the potential risks of the examination have been explained to me and that during the course of the investigation it may for the intravenous injection of a contrast agent.

Attention: It is the policy of this institution not to discuss results of the MR Investigation with the patients for ethical reasons. All enquiries in this regard should be directed to the referring physician.

Participant Signature: _____ **Date:** 23/08/2019

Consented by: _____ Signatures Removed

Please remove all loose metallic objects, including metallic body piercings, hearing aids and

Appendix G

REC REF 236/2018

UNIVERSITY OF CAPE TOWN
Faculty of Health Sciences
Human Research Ethics Committee

Room E53-46 Old Main Building
Groote Schuur Hospital
Observatory 7925
Telephone [021] 406 6492
Email: sumayah.ariefdien@uct.ac.za
Website: www.health.uct.ac.za/fhs/research/humanethics/forms

22 November 2018

HREC REF: 236/2018

A/Prof K Thomas
Psychology
Room 2.17, PD Hahn Building
Upper Campus-

Dear A/Prof Thomas

PROJECT TITLE: INFLUENCE OF AGE AND COGNITIVE RESERVE ON COGNITIVE FUNCTION AND ACTIVITIES OF DAILY LIVING IN HIV (Master's candidate-M Boshoff) sub-study linked to 221/2008

Thank you for your response letter, addressing the issues raised by the Human Research Ethics Committee (HREC).

It is a pleasure to inform you that the HREC has **formally approved** the above-mentioned study.

Approval is granted for one year until the 30 November 2019.

Please submit a progress form, using the standardised Annual Report Form if the study continues beyond the approval period. Please submit a Standard Closure form if the study is completed within the approval period.
(Forms can be found on our website: www.health.uct.ac.za/fhs/research/humanethics/forms)

We acknowledge that the student: Ms Marcelle Boshoff will also be involved in this study.

Please quote the HREC REF in all your correspondence.

Please note that the ongoing ethical conduct of the study remains the responsibility of the principal investigator.

Please note that for all studies approved by the HREC, the principal investigator **must** obtain appropriate institutional approval, where necessary, before the research may occur.

Yours sincerely

Signature Removed

PROFESSOR M BLOCKMAN
CHAIRPERSON, FHS HUMAN RESEARCH ETHICS COMMITTEE

Federal Wide Assurance Number: FWA00001637.
Institutional Review Board (IRB) number: IRB00001625

REF 397/2014

HUMAN RESEARCH ETHICS COMMITTEE
11 MAY 2015
HEALTH SCIENCES FACULTY
UNIVERSITY OF CAPE TOWN

UNIVERSITY OF CAPE TOWN
IYUNIVESITHI YASEKAPA • UNIVERSITEIT VAN KAAPSTAD

FACULTY OF HEALTH SCIENCES
Human Research Ethics Committee

FHS016: Annual Progress Report / Renewal

HREC office use only (FWA00001637; IRB00001938) This serves as notification of annual approval, including any documentation described below.			
☑ Approved	Annual progress report	Approved until/next renewal date	30.6.2016
☐ Not approved	See attached comments		
Signature Chairperson of the HREC	Signature Removed	Date Signed	11/5/2015

Comments to PI from the HREC

Principal Investigator to complete the following:

1. Protocol information

Date form submitted	24th of June 2014		
HREC REF Number	397/2014	Current Ethics Approval was granted until	**30th of June 2015**
Protocol title	Understanding the role of inflammation and the metabolic syndrome in promoting the morbidity of accelerated acing in a South African HIV-infected Community based cohort { linked to 221/2008; 084/2010 & 227/2006}		
Protocol number (if applicable)			
Are there any sub-studies linked to this study?	X Yes No		
If yes, could you please provide the HREC Ref's for all sub-studies? **Note:** A separate FHS016 must be submitted for each sub-study. This study is linked to to 221/2008; 084/2010 & 227/2006			
Principal Investigator	Dr Nicola Wearne		
Department / Office Internal Mail Address	Department of Nephrology and Hypertension – Groote Schuur hospital E13		

REF 241/2018

UNIVERSITY OF CAPE TOWN

HUMAN RESEARCH ETHICS COMMITTEE
11 OCT 2018
HEALTH SCIENCES FACULTY

FACULTY OF HEALTH SCIENCES
Human Research Ethics Committee

Form FHS006: Protocol Amendment

HREC office use only (FWA00001637; IRB00001938)		
☑ Approved	☐ Type of review: Expedited	☐ Full committee
This serves as notification that all changes and documentation described below are approved.		
Signature Chairperson of the HREC	Signature Removed	Date 11/10/2018

Note: All major amendments must include a local **PI Synopsis** justifying the changes for the amendment. Please note that incomplete amendment submissions will not be reviewed.

Comments from the HREC to the Principal Investigator:
Note: The approval of this protocol amendment does not grant annual approval. Please complete the FHS016 / FHS017 form for annual approval at least one month before study expiration.

Principal Investigator to complete the following:

1. Protocol information

Date (when submitting this form)	30 Sept 2018
HREC REF Number	241/2018
Protocol title	The relationship between HIV-associated neurocognitive disorders, ART adherence and CSF discordance in an ART-experienced cohort in Cape Town
Protocol number (if applicable)	
Principal Investigator	Prof John Joska
Department / Office Internal Mail Address	Dept of Psychiatry.

1.1 Is this a major or a minor amendment? (see FHS006hlp) Major (tick box) Minor (tick box)	☐ Major	☐ **Minor**
1.2 Does this protocol receive US Federal funding?	☐ Yes	☐ **No**

Appendix H

Missing data and set upper limit input

Main data set – Missing data variables

Neuro-cognitive test	**Upper limit**	**Number of cases corrected**
Grooved Pegboard Test-time	300 seconds	1
Color Trails Test-time	240 seconds	3

Main data set – Multiple imputations limits

Variable	**Lower limit (minimum)**	**Upper limit (maximum)**
HVLT learning total	0	36
HVLT Delay	0	12
GPT non-dominant hand	0	300

Appendix I

Assumptions of normality, independence and homoscedasticity for regression models.

Assumptions for Regression Models, Set I: Age as a predictor of cognitive function (N = 32)

Predicted by Age	Correlation(sig)	Std residual range		Cook's distance maximum	Collinearity	
		Minimum	Maximum		Tolerance	VIF
Global T-score	-.425(.008)	-3.550	1.502	.431	1.000	1.000
Motor function	-.428(.008)	-4.204	.981	.509	1.000	1.000
Attention and Working memory	-.242(.091)	-4.019	1.202	.032	1.000	1.000
Information processing speed	-.160(.191)	-2.241	1.183	.139	1.000	1.000
Language	-.321(.037)	-1.634	1.752	.219	1.000	1.000
Audio-verbal memory	-.093(.307)	-2.020	1.694	.236	1.000	1.000
Visual-spatial memory	.127(.245)	-1.987	1.899	.259	1.000	1.000
Executive function	-.383(.015)	-2.017	1.945	.112	1.000	1.000

Assumptions for Regression Models, Set II: Cognitive reserve (CRIq score) as a predictor of cognitive function (N = 32)

Predicted by CRIq-T-Std	Correlation(sig)	Std residual range		Cook's distance maximum	Collinearity	
		Minimum	Maximum		Tolerance	VIF
Global T-score	-.157(.195)	-3.728	1.333	.288	1.000	1.000
Motor function	-.281(.063)	-4.201	1.185	.340	1.000	1.000
Attention and Working memory	-.084(.325)	-4.179	.969	.362	1.000	1.000
Information processing speed	.000(.499)	-2.092	1.304	.227	1.000	1.000
Language	.102(.289)	-1.609	1.870	.176	1.000	1.000
Audio-verbal memory	-.104(.285)	-2.112	1.722	.267	1.000	1.000
Visual-spatial memory	-.146(.213)	-2.221	1.932	.334	1.000	1.000
Executive function	-.062(.368)	-2.065	1.786	.177	1.000	1.000

Assumptions for Regression Models, Set III: Cognitive reserve (proxy measures) as predictors of cognitive function (N = 32)

Predicted by CRIq-T-Std	Correlation(sig)	Std residual range		Cook's distance maximum	Collinearity	
		Minimum	Maximum		Tolerance	VIF
Global T-score	.274-.022	-3.750	1.333	.562	.401-.827	1.209-2.494
Motor function	-.098-.334	-3.520	1.481	1.871	.398-8.32	1.202-2.515
Attention and Working memory	-.047-.312	-4.295	1.041	.251	.401-.827	1.209-2.494
Information processing speed	.079-.378	-2.071	1.270	.672	.401-8.27	1.209-2.494
Language	-.218-.071	-1.521	1.930	.163	.401-8.27	1.209-2.494
Audio-verbal memory	-.134-.202	-1.882	1.231	.713	.401-8.27	1.209-2.494
Visual-spatial memory	-.093-.234	-2.046	1.605	.333	.401-8.27	1.209-2.494
Executive function	-.032-.250	-2.139	2.357	.574	.401-8.27	1.209-2.494