Rhodes University — Department of Psychology

Research project cover sheet

To accompany a research project submitted for examination in partial fulfilment of the requirements for the Honours Degree in Psychology / Organisational Psychology

1. Information	
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Type of thesis	Research Project
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2. Declaration by supervisor
Either: This project has been prepared under my supervision. I have read it carefully and believe that it meets the standards set out in the appropriate guidelines booklet in terms of academic content, clarity of research question, description of methodology, quality of analysis and ethical standards, as well as in terms of format, length, structure and referencing. Signature and date:
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Meta-analysis of the Cognitive Rehabilitation of patients living with HIV/AIDS: The case for Executive Functions

Research project submitted by Nicole Joka

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For a dissertation in partial fulfilment of the requirements of the degree of Bachelor of Social Science with Honors in Psychology.

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Date: 29 January 2021

Abstract

In recent years, research has shown that cognitive decline occurs in patients living with HIV and studies have brought into light the different treatment interventions are available to prevent the rapid decline of cognitive functioning in these individuals. Thus, it is crucial that the effect that treatment interventions on the executive function of HIV patients is studied. One such intervention is brain plasticity. Through understanding the model of brain plasticity following traumatic brain injury, and applying cognitive rehabilitation as a method of treatment, researchers believe that it is possible to ameliorate the cognitive deficits. In the present times, access to pharmaceutical treatments like antiretroviral treatment has been more accessible to persons living with HIV, however studies continue to show that as the virus progresses into its severe stages, even with the consistent use of antiretroviral treatment, cognitive domains such the executive function domain continue to become compromised. This means that the individual living with HIV will begin to show deficits in attention levels, memory and important thinking abilities as the virus spreads throughout the central nervous system. This study provides a meta-analysis wherein an array of scholarly articles have been used to measure the efficacy that the model of brain plasticity and the application of cognitive rehabilitation therapy has on the executive function of HIV patients. The findings show improvement in the attention span, cognitive flexibility, processing speed, inhibition, and working memory levels of patients living with HIV after the implementation of cognitive rehabilitation intervention.

Keywords: executive function, cognitive rehabilitation, brain plasticity, cART

Acknowledgements

First and foremost, all glory and praises to God for guiding me through an unbelievably tough year. I am so grateful to have been able to complete my Honours year and this research project despite the unprecedented circumstances that we are currently living through.

Secondly, I would like to express my gratitude to my mom, Dorothy, for her unconditional love, support, care and prayers which is undoubtedly is the reason I have accomplished all that I have today. I am grateful to my family for their unwavering support, and for providing me with the opportunity to continue with my postgraduate studies. Their constant check-ins and care packages when the going become tough are greatly appreciated.

To my postgraduate friends, or rather the 'Bok-boks' Thank you for the laughs, the advice, the chats, (many) cries, late-night study snack runs before curfew and the memes that kept me entertained and going strong through it all.

And finally to my supervisor, Mr. Sizwe Zondo. I have admired his work and his passion for this field of psychology since undergrad. Thank you for your guidance and support throughout this research project, I have learned so much from you throughout the year. It was a great privilege to study under your guidance.

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Chapter 1

Background and Context

Human immunodeficiency virus (HIV) is a growing problem in many parts of the world, and various research has begun to focus on the impact that treatment interventions and the disease itself, has on the neurodevelopment and cognitive abilities of children (Koekkoek, de Sonneville, Wolfs, Licht & Geelen, 2008). As of 2018, the World Health Organization reported that at a global level, 37.9 million infections were reported and 25.7 million of the infection were in Sub-Saharan Africa (World Health Organization, 2018). At a microbiological level, HIV causes inflammation in the central nervous system by reproducing in the microglia, and this progressively causes cognitive and behavioral changes in the individual (Watkin and Treisman, 2015). More particularly, HIV crosses the blood brain barrier where it causes internal brain damage. The blood brain barrier (BBB) is a structural barrier which is made up of endothelial cells, pericytes, astrocytes, microglia and various neurons, and acts as a frontier between the blood and the central nervous system (CNS) in order to prevent infectious toxins and agents from entering the CNS (Haddad-Tovolli, Dragano, Ramalho & Velloso, 2017). Research indicates that HIV can pass through the BBB and this may lead to the onset of HIV associated neurocognitive disorders (Atluri, Hidalgo, Samikkannu, Kurapati, Jayant, Sagar & Nair, 2015). Further, Weber, Blackstone & Woods (2013) report that owing to the limited success from the sole use of pharmaceutical interventions, there is a great need for the implementation of cognitive neurorehabilitation interventions to assist patients with HIV-associated neurocognitive disorders, alongside their regular clinical treatment.

Literature Review

Stages of HIV

Ellis, Calero & Stockin (2009) state that HIV can live undetected in the human body through four stages: the asymptomatic incubation stage, symptomatic acute infection stage, the latency stage and finally, full-blown AIDS. The first two stages of the HIV infection can last for up to four weeks each. In the asymptomatic incubation stage, the person experiences symptoms that can easily be passed off as that of any other viral infection - for example, a common cold or the flu virus (Ellis et al., 2009). During the second stage of the HIV infection the virus actively replicates in the immune system and causes destruction. Ellis et al., (2009) reiterate that even the symptomatic acute infection symptoms can be passed off as another, less alarming sickness; however, it is during this latency stage that the person's CD4+ and CD8+T cell count starts to drop. Ellis et al., (2009) state should the virus go undetected much further, patients will shift into the final stage of the HIV infection, which is then called acquired immune deficiency syndrome (AIDS). In 1992, The Center for Disease Control's released a standardisation criteria which diagnoses an individual with AIDS as including that, the individual should a) have a CD4+ cell count fall below fourteen percent or less than the total lymphocytes; b) have a CD4+ cell count be less than 200 cells; or c) experience an opportunistic infection(s) or neoplasm due to an compromised immune system - these opportunistic infections could be diseases like tuberculosis or pneumonia (CDC, 1992).

To further expand on the stages of the HIV infection mentioned above, Hernandez-Vargas & Middleton (2012) describe the CD4+T cell count and the plasma viral levels as the clinical markers which are used to monitor the progression of the HIV infection in the patient. The four stages that the virus progresses through shows the typical response of the human body to HIV in the absence of pharmaceutical intervention - i.e. antiretroviral treatment (Hernandez-Vargas & Middleton, 2012). During the *acute infection stage* the concentration of circulating CD4+T cells drops as the virus increases its circulation around the body, and this stage can last for a period of 2 to 10 weeks. In addition, during this stage the patient experiences symptoms such as fevers, lymphadenopathy (swollen lymph nodes), pharyngitis (pain or irritation in the throat), headaches and rashes on the skin begin to develop; however as previously mentioned, the symptoms that arise during this stage could be mistaken for that of any other illness (Hernandez-Vargas & Middleton, 2012). Once the virus begins to actively replicate and spread across the body, the *asymptomatic stage* begins and during this stage, the patient does not show any major symptoms and their CD4+T cells return to their 'normal' levels and the viral load decreases once again. Hernandez-Vargas & Middleton (2012) report that this stage can last for a duration of 7 to 10 years, although the progression of the virus as well as the symptoms vary between individuals. Finally, the HIV infection develops into AIDS and this stage is reached when the patients CD4+T cell counts are below 200 cells/mm^3 or when secondary opportunistic infections enter the patient's immune system, and the patients experiences opportunistic infection such as pneumonia and tuberculosis (Hernandez-Vargas & Middleton, 2012).

HIV Treatment and Neurocognitive Effects of HAART

To ameliorate the effects of HIV, highly active antiretroviral therapy (HAART) have aided in prolonging the life expectancy of patients suffering from the disease, diminishing the number of opportunistic infections, as well as increasing the holistic quality of life for these patients. Research has found that early HAART intervention can limit the extent to which the virus penetrates the BBB (Thompson & Jahanshad, 2015). However, Watkins & Treisman (2015), report that despite these advances in interventions, neurocognitive abilities are still compromised owing to the infection attacking the central nervous system. This therefore suggests that there may be a gap in research – treatment aiming to fix the one problem, but also bringing about another in the process (Jeremey et al., 2005).

Joska, Gouse, Paul, Stein & Flisher (2010) conducted a systematic review where they studied the effect of HAART on the neurocognitive functioning of HIV patients. The study spanned for a period of 6 months (Joska et al., 2010). Researchers used fifteen studies for their systematic review, and it was found that eleven of these studies showed a significant improvement in the neurocognitive status of HIV patient's post-HAART treatment. However, it is important to note that although the intervention of HAART improves the neurocognitive functioning, it does not eradicate the neurocognitive impairment of the HIV patient (Joska et al., 2010).

Thus, as a result of the breach in the BBB, Ravindran, Rani & Priya (2014) report that children infected with HIV have shown deficient in various cognitive domains such as attention, language deficits, verbal learning and memory, visuo-motor functions, fine motor performance skills and executive functions when compared to HIV negative child populations. Cognitive deficits that are seen in patients, is linked to the ongoing replication of the virus in the Central Nervous System (CNS). To this effect, HAARTs aim to improve the neurocognitive functioning of HIV patients prior to cells of the CNS dying off, however, there penetration is limited (Robertson, Su, Margolis, Krambrink, Havlir, Evans and Skiest, 2010).

Of interest to my study is the investigation of executive functions and how this cognitive domain is compromised as a result of the HIV/AIDS infection. Moreover, I am interested in investigating the efficacy of adjunct therapies such as cognitive rehabilitative intervention, and how these therapies sustain executive functioning in people living with HIV.

HIV-associated Neurocognitive Disorders

It has been reported that at least 30-50% of individuals living with HIV are at risk for developing HIV-associated neurocognitive disorders (HAND) and the risk factors for HAND include older populations, individual with lower cognitive reserves, those with a history of immunosuppression, and patients living with comorbidities which can be precipitated by substance-use disorders and co-infections such as hepatitis C (Weber, Blackstone & Woods, 2013). Over the years, further advancements in treatment have occurred - i.e. the introduction of combined antiretroviral therapy (cART) and more research has been conducted regarding the co-infections that develop as a result of a patient's seropositive status. Weber et al., (2013) reports that a National Institute of Health group in Frascati, introduced a diagnostic criterion for HAND: Asymptomatic Neuropsychological Impairment (ANI), Mild Neurocognitive Disorder (MND), and HIV-Associated Dementia (HAD). Upon demonstrating mild neuropsychological impairment in at least two cognitive domains that is attributed to the HIV infection (i.e. > 1 Standard Deviation below the normative mean) the patient is diagnosed with ANI, because this cognitive criterion alone comprises of about 50% of HAND diagnoses and affects between 15-30% of HIV-patients overall; yet, a decline in functioning is not directly attributed to ANI (Weber et al., 2013). However, it has been found that when asymptomatic individuals are examined with more sensitive assessment tools - such as performance-based everyday functioning tests - functional impairment is seen (Blackstone et al., 2012) and cognitive neurorehabilitation may be beneficial to these patients. Decline in everyday functioning is a central diagnosis of MND and HAD, with functioning in two or more cognitive domains being > 1 Standard Deviation below the normative mean (i.e. mild-to-moderate) or > 2 Standard Deviations below the demographically-adjusted normative means (i.e. moderate-to-severe). Additional diagnostic criteria for functioning dependence for MND include: decline in at least two instrumental activities of daily living (IADL) - such as financial management; unemployment or reduction of job responsibilities secondary to reduced cognitive abilities; decline in vocational training - more errors, less productivity and efficiency; increased problems in two or more cognitive ability areas in daily life in self-report, in the absence of diagnosed depression; and the mismanagement of medication (Blackstone et al., 2012). Moreover, HAD functional decline diagnostic criteria includes: unemployment owing to cognitive impairment; self-report of dependence in more than two IADL related to cognitive problems; four or more self-report declines in cognitive ability areas of daily-life, in the absence of diagnosed depression; and performance that is > 2 Standard Deviations below the mean on a performance-based laboratory measure of daily functioning (Blackstone et al., 2012).

As previously mentioned, HIV is able to enter into the CNS through infected monocytes and CD4+ lymphocytes. HIV-associated neuropathology is characterized by injury to synapse and dendrite structures, and can later develop into HIV encephalitis - swelling of the brain owing to HIV infection, vasculopathy - inflammation and degeneration of blood vessels, and gliosis, which entails changes to glial cells owing to damage in the CNS (Weber et al., 2013). Just as HIV can affect neural pathways, it can also impact the structure and function of the fronto-striatal-thalamo-cortical circuitry as well as the medial temporal lobe regions (Weber et al., 2013). In the below sections, I detail the impact that HIV has on the fronto-striatal-thalamo-cortical circuitry, with specific reference to executive functions.

Executive Function & HIV Infection

Executive functions encompass a number of cognitive constructs including the processing of working memory, the inhibition of quick responses to stimulus, the ability to shift an individual's mental focus, which gives way to self-regulated behavioral control, and memory retrieval (Blair, 2016, ;Miller & Cohen, 2001). Due to their tertiary functions based on human evolution, executive functions (EF) are defined as the 'higher-order' cognitive functions. Evolutionary, EF are regulated by the prefrontal cortex of the brain which evolved later in homo-sapiens (Berthelsen, Hayes, White & Williams, 2017). Neural cognitive functions flows through various pathways mediated by the prefrontal cortex allowing for high order functions that are regulated by complex frontal pathways Miller & Cohen, 2001). Due to their complex nature and underlying functions, executive functions have been identified as a predictor of cognitive and adaptive functioning capacity, vocational status, risky sexual behavior, and medication adherence among HIV-positive populations (Walker & Brown, 2018).

Executive function is a top-down cognitive process. In the field of psychology, this term has a number of different definitions, however in this instance it means that in order to function successfully in the real-world and in real-world scenarios, one needs to be able to fulfil cognitive tasks from the simplest to the most complex (Faria, Alves & Charchat-Fichman, 2015). Thus, executive functions include problem-solving tasks, planning, manipulating mazes and various other complex tasks where multiple cognitive abilities are required

(Harvey, 2019). Executive functions are made up of six domains, namely: planning, working memory, mental flexibility, inhibitory control, verbal fluency, and processing speed. Working memory for example, is often associated with executive function and it is commonly associated with tasks that are processed in the frontal lobe. Working memory is the system that temporarily stores and manipulates information, and the system is activated during learning processes, language comprehension, reasoning, and consciousness (arousal) (Faria, Alves & Charchat-Fichman, 2015). All in all, the frontal lobes are essential for executive functions and enable humans and animals alike, to follow instructions, ignore irrelevant distractors, divide one's attention in order to process multiple concurrent streams of information and to perform in tasks facilitated by the front striatal brain networks (Harvey, 2019; Walker & Brown, 2018). Below I briefly detail some anatomical structures related to executive functions and outline some neuropsychological tests that measure executive functions. Once I have established these basic features related to executive functions, I will detail how HIV affects executive functions.

Executive Function and Frontal Lobes

Owing to the circularity anatomical link (frontal lobe) and the neuropsychological construct of executive function, there continues to be a debate regarding the regulation of executive functions by the frontal lobes (Alvarez & Emory, 2006). Much research has been done regarding the three-principal frontal-subcortical circuits that are involved in cognitive, emotional, and motivational processes: a) dorsolateral frontal cortex; b) ventromedial; and c) orbitofrontal. Alvarez & Emory (2006) state that the dorsolateral head of the caudate nucleus is linked to a number of EF functions, including verbal and design fluency, the ability to maintain and shift set, planning, inhibition, working memory, organizational skills, reasoning, problem-solving, and abstract thinking. Secondly, the ventromedial circuit starts in the anterior cingulate and projects to the nucleus incumbent and this part of the brain is linked to motivation. According to Alvarez & Emory (2006) lesions in this region can lead to generalized apathy leading to individuals developing may also experience decreased social interaction and psychomotor retardation. Lastly, the orbitofrontal cortex communicates with the ventromedial caudate nucleus and this part of the brain is linked to social behavior. Alvarez & Emory (2006) further state that lesions to this region cause disinhibiting impulsive and anti-social behavior.

Brain structural changes as a result of HIV-infection

Alongside the functional changes that occur, structural changes develop in the brain following the HIV infection. Non-invasive neuroimaging techniques are the gold standard in evaluating brain structural changes due to HIV (Guha, Ortega, Brier & Ances, 2016). Clinically, to investigate these changes, one of two MRI scans is done: (a) an anatomical MRI scan – which will show anything from the degenerative dementias to white matter demyelinating disorders (Thompson & Jahanshad, 2015) and (b) a standard MRI – which shows the structural anatomy of the brain including the major grey matter nuclei, white matter, the gyral and sulcal anatomy of the cortex (Thompson & Jahanshad, 2015).

Neuroimaging indicates that HIV greatly impacts both the structure of the brain, leading to subsequent cognitive findings. A meta-analysis by O' Connor, Zeffiro & Zeffiro (2018) found that early imaging studies of HIV patients indicated showed a decrease in brain parenchyma, white matter, and basal ganglia volume. Interestingly, the authors also noted that after the implementation of combined antiretroviral therapy (cART), patients' cortical, subcortical, gray matter, and white matter atrophy were monitored. It was found that all components (cortical, subcortical and white matter) except gray matter decreased over time. The decrease in volume seen in the tissue components shows a decline in brain function in patients living with HIV. This finding suggests that with the use of cART neurostructural changes occur in the brain (O'Connor et al., 2018). Further, O' Connor et al., (2018) report that the cortical gray matter and brain parenchymal volumes decreased within the first year of acquiring HIV-infection. In addition to the changes of volume seen in the brain regions mentioned above, O'Connor et al., (2018) report that the patient may also experience cortical atrophy. Cortical atrophy is a symptom of sulcal widening and this is the greatest atrophy that is experienced in the basal ganglia (Thompson & Jahanshad, 2015).

To illustrate the effect of HIV in the cortex, the below, Figure 1a compares the cortical grey matter thickness of a group of AIDS patients to a seronegative population (Figure 1b). The seropositive population showed a severe thinning of grey-matter in both brain hemispheres in the anatomic region of the brain where the primary sensory and cortices are found (Figure 1c). Further research was performed which aided to find the correlation between the degree of grey matter deficit and the neurocognitive performance scores of patients. The researchers assessed this relationship using the neuropsychological z-score scale and found that the grey matter deficit was associated with the patients' nadir CD4+T-cell counts. The neuropsychological z-score (NPZ) scales are findings from individual neuropsychological tests which are then converted into z-scores relative to standard norms and finally averaged to form a composite score (Applebaum, Reilly, Gonzalez, Richardson, Leveroni and Safren, 2009). And, the nadir CD4 is defined as the marker of early disease burden, and this is often associated with later losses of tissue that is seen on brain MRIs (Thompson & Jahanshad, 2015: 4)

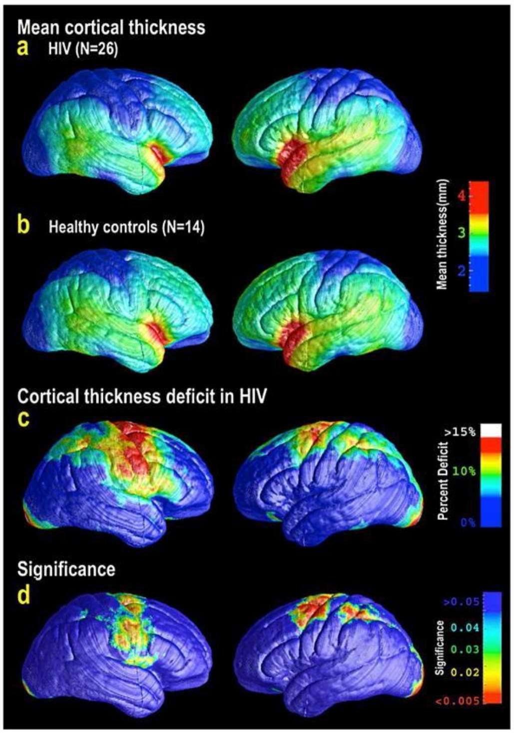


Figure 1: The cortical gray matter thinning on the lateral brain surface in HIV/AIDS. (A) demonstrates the average profile of cortical thickness in AIDS patients. As shown, the right hemisphere of the brain is on the left. (B) represents the mean cortical thickness for seronegative individuals. (C) shows the average percentage of cortex thinning in AIDS in relation to the seronegative control group. (D) the colour-coded map highlights the significance of the group differences at each point, with the colour red representing significant cortical thinning - (Thompson, Dutton, Hayashi, Toga, Lopez, Aizenstein & Becker, 2005).

Further research regarding the structural changes resulting from HIV-infection have been conducted by Kallianpur and colleagues (2013), suggest that patients who have detectable HIV RNA has lower volumes of cerebellar and total subcortical gray matter at -14% and -

10% respectively. Explanation for the above structural anomalies include the inability to clear peripheral blood of HIV RNA, which could be associated with regional brain atrophy. Kallianpur et al. (2013) conclude that peripheral and central viral reservoirs may promote brain dysfunction in HIV positive people.

Executive Function Measures

Wisconsin Card Sorting Test (WCST), Trail Making Test (TMT) Form B, Verbal Fluency Test (VFT) F, A and S and VFT Animal category *verbal fluency*; Clock Drawing Test (CDT) *planning*; Digits Forward and Backward subtests (WAIS-R or WAIS-III) *working memory;* and Stroop Test *inhibitory control* are examples of tests used to measure the various domains of executive functioning in patients (Faria, Alves & Charchat-Fichman, 2015).

Firstly, processing speed is measured in the WCST test. Here, cards need to be classified according to colour, shape or number categories and each time 10 of a maximum of 128 cards have been sorted correctly, the categorization rules change (Forti, Olivelli, Rietti, Maltoni & Ravaglia, 2010). The WCST test also has a number of variations and the variants have fewer cards for the test (Forti *et al.,* 2010).

In the TMT Form B assessment mental flexibility is measured, and here the individual must repeatedly switch their attention between two sequences - numerical and alphabetical sequences. Along with mental flexibility, the use of mental engagement, motor dexterity and working memory is also engaged during this assessment (Faria *et al.,* 2015). Owing to its faster application procedure, researchers prefer to use this variation of assessment as a measurement of mental flexibility (Faria *et al.,* 2015).

Further, the VFT F, A, S and VFT Animal Category are also used to assess an individual's EF abilities, specifically in relation to executive dysfunction owing to aging. These assessments evaluate an individual's verbal fluency and during the assessment, individuals are asked to actively search for information that falls into a specific category (Faria *et al.,* 2015). Thus, language and semantic memory is a secondary measure of this assessment.

Planning is evaluated using the CDT assessment. The objective of this test is to place the twelve numbers that are found on a clock in the correct position as well as to ensure that the placement is equally distributed. Further, the individual will be asked to indicate a requested time “with the minute hand greater than the hour hand” (Faria *et al.,* 2015). In addition to planning, this assessment also evaluates one’s visual constructive skills.

A frequently used assessment, Digits subtest (WAIS-R or WAIS III) measures working memory. Digit subtests is made up of two separate tasks, forward digit subtest and backward digit subtest (Faria *et al.,* 2015). The former, assesses information storing abilities through the application of verbal working memory. In the test, the testing administrator asks the test-taker to repeat a set of numbers back to them in the same order; and in the latter assessment the test-taker repeats the numerical sequence back to the test administrator in the reverse order (Faria *et al.,* 2015). The backward subtest of either WAIS-R or WAIS III also measures verbal content processing in the working memory domain (Faria *et al.,* 2015).

The last assessment, the Stroop test, evaluates inhibitory control. Faria *et al.,* (2015) reports that this test has three conditions: in the first condition, the individual has to quickly say the name of the color that will be presented to them on a card; in the second condition words like “all” and “today” will be printed on certain cards and the individual will be asked to identify the color of those cards. And in the last condition, the name of colors that have words like “yellow” and “green” the participant will have to identify (Faria *et al.,* 2015). Essentially, the Stroop test assesses behaviours that are regarded as automatic and controlled.

Smith et al., (2013) studied the biological, demographic, and psychosocial factors associated with poor cognitive and adaptive functioning in two populations: young adults who are a) prenatally acquired HIV infection and b) young adults who are prenatally HIV- exposed but uninfected. The researchers found that although HIV was diagnosed during early development, the prenatally acquired HIV infected sample group were at an increased risk for showing impairment across all cognitive domains, specifically: Processing Speed, Perceptual Reasoning and in adaptive functioning (Smith et al., 2013). However, following the use of antiretroviral treatment, the central nervous system shows the potential for recovery especially when the patient is diagnosed with HIV and treatment is administered before three years old (Smith et al., 2013). This will further be explained in the brain plasticity section.

HIV/AIDS and Executive Functions

Fellows, Byrd & Morgello (2014) conducted a research study where they looked at the relationship between literacy, ageing and various other neurologic abnormalities and how they relate to cognitive deficits among HIV/AIDS patients. 186 people participated in this study, and all participants underwent comprehensive neurological, neuropsychological, and medical evaluations. The neuropsychological tests that were administered were: a) to assess processing speed: WAIS-III Digit Symbol Coding, WAIS-III Digit Symbol Searching, and Trail Making Test, Part A; b) for executive function: Wisconsin Card Sorting Test - Perseverative Responses, Trail Making Test, Part B, and Controlled Oral Word Association Test c) learning: Hopkins Verbal Learning Test (HVLT)Total Recall and Brief Visuospatial Memory Test (BVMT) Total Recall; and lastly d) memory domain: HVLT-R Delayed Recall and BVMT Delayed Recall (Fellows et al.,2014). Further, Structural equation modeling was used to find the independent effects of age, reading level, motor abnormalities on the cognitive domains mentioned above. Finally, the findings were statistically significant – deficits in information processing speed is related to the cognitive abnormalities that we see in HIV/AIDS populations (Fellows et al., 2014).

Moreover, research has shown that HIV positive persons show a rapid rate of cognitive decline as they get older, in comparison to same-age seronegative populations. Achim, Adame, Dumaop, Everall & Mashliah (2009) analyzed the levels and distribution of amyloid β immunoreactivity in the frontal cortex of 43 patients living with HIV. The participants in this study ranged between 38 and 60 years old. Achim et al., (2009) found that there is an extensive intraneuronal accumulation of amyloid β in older patients living with HIV. Owing to this, as the patient ages, and amyloid β proteins continue to accumulate as a result of HIV infection, neuronal damage worsens, and cognitive impairment worsens. Moreover Achim et al., (2009), suggest that the age-related cognitive decline in executive functions and various other cognitive abilities could also be attributed to the burden of secondary illnesses that occur alongside HIV infection. Secondary illnesses such as cardiovascular disease and cortical amyloid beta pathology are common diseases in aging HIV positive population groups (Achim et al., 2009). Further findings from the Achim et al., (2009) study were that HIV positive males showed higher rates of cognitive deficits in executive function, in the working memory, set-shifting, and inhibition domains specifically, however it is not clear whether this can be attributed to the general biological differences between the sexes or if it is publication bias. Thus, clinical variables can be used in addition to further support the findings from the above-mentioned studies.

Previously it was mentioned that HAND is a key feature of HIV infection, having the cerebral changes resulting from HIV, the subsequent section details the effects that HIV has on executive functions. CD4, cluster of differentiation 4 cells help to predict the cognitive impairment in HIV patients. In a study conducted by Forti et al., (2010) the clinical variables from the studies revealed that nadir CD4 count is inversely associated with performance in all domains of executive function. In other words, a decrease in the CD4 cell count leads to an increase in the likelihood of experiencing cognitive decline. Due to the virus affecting the frontal systems of the brain, this leads to damage in both cognitive and limbic aspects of executive function. For example, the measure of inhibitory control of an HIV+ individual shows a pattern of hypo-activation in the right and left putamen. Furthermore, reduced inhibitory control is correlated to decreased glial functioning within the frontal white matter of the brain, and this can play an etiological role in striatal abnormalities (Forti et al., 2010). It is also worth adding that, the low performance of patients in set-shifting and inhibition subtests of executive function coincides with the model of addiction, which proposes that "poor inhibitory control may constitute an endophenotype associated with increased vulnerability for substance use behaviors" (Forti et al., 2010: 10).

In another study, the effect of HIV on executive function Nichlos and colleagues (2016), compared the levels of executive function between (1) perinatally acquired HIV participants (PHIV) (Mean age = 14.5 years), (2) PHIV/C (Prevention Class) (Mean age = of 15.5 years) and (3) perinatally acquired HIV-exposed (PHEU) but not infected, (Mean age = 12.9 years). Findings indicated that the PHEU groups scored significantly slower on Inhibition and Colour Naming/Reading Combined task and made more errors on Inhibition. Furthermore, the three groups showed no differences in fluency and problem-solving. Nichlos et al., (2016) observed that the outcomes of EF measures were also associated with demographic variables. The researchers explain that participants who performed better on verbal tasks (Verbal fluency, Colour-Word Interference and Twenty Questions tests) had caregivers with a higher educational background, and the measures from these assessments were associated with female sex, being younger in age, stemming from an upper class background, having a biological parents as the primary caregiver and being of non-black race. Further, Nichlos et al., (2016) report that the performance on the Design Fluency was associated with younger age, having biological parent as the primary caregiver and higher household income. In conclusion, it was found that PHIV youth with previously AIDS-defining conditions have more compromised EF functioning abilities.

Similarly, a study aimed at predicting the long-term EF deficit between perinatal HIV infection, HIV-exposed uninfected in comparison to HIV-unexposed status of Ugandan children of school-going age was conducted by Ezeamama and colleagues (2016). These researchers used eight subtests to measure three executive function domains. The tests that were conducted included: the behavioral regulatory index (BRI) which made up of the shift, inhibit and emotional control subtests; metacognition index (MCI) which comprises the initiation, planning, working memory, material organization/monitoring subscales; and lastly the global executive composite (GEC) which represents the sum of subtests. The findings from the studies suggest that all EF subtest results showed significant differences between the groups, with the PHIV sample group showing more executive dysfunction than the other groups. Moreover, Ezeamama et al., (2016) notes that the PHEU and PHIV groups used in the study were exposed to similar socio-demographic, environmental, nutritional, and other caregiver factors that are known to have an impact on the child's neurodevelopment, thus affecting the overall outcome of the research - i.e. PHIV and PHEU status having a long-term effect on a child of school-going ages' performance at school owing to their compromised executive functioning abilities.

All in all, with regard to executive function differences between HIV positive and HIV negative samples, research seems to indicate that individuals living with HIV tend to show significant deficits in EF compared to controls (Walker & Brown, 2018). An emerging theme from the above cited studies is that in spite of the intervention of highly active antiretroviral therapy (HAART) to ameliorate the effect of HIV, children with HIV continue to experience executive function deficits. As such, other non-pharmaceutical interventions are required. Based in this observation, the objective of my study is to investigate the efficacy of cognitive rehabilitation therapy (CRT) to mitigate the effects of EF, in people living with HIV, given the limitations of ARTs. I will use a meta-analysis to investigate this effect.

Theoretical Framework

The theoretical framework that will guide my study is brain plasticity. Brain plasticity or also termed neuroplasticity, is the nervous system's ability to change its activity in response to intrinsic or extrinsic stimuli by rearranging its structure, functions, or neural connections (Mateos-Aparicio & Rodriguez-Moreno, 2019). Cognitive deficits can occur in patients as a result of traumatic brain injury, the reason for the cognitive disturbances is owing to the damage that happens in white-matter connections and thus, diffuse axonal injury occurs. HIV causes cognitive disturbances, and as we have previously explained progression of the virus results in impairment in mainly the domains of attention, memory, and executive function (Galetto & Sacco, 2017). Studies have shown that cognitive rehabilitation has helped improve patients' autonomy and quality of life following TBI. Thus, cognitive rehabilitation will further be explained as an application of the framework of brain plasticity.

Secondary to the brain plasticity framework is cognitive rehabilitation. Cognitive Rehabilitation Therapy (CRT) is essentially the treatment given to patients that have experienced brain injury (Brown, 2012). According to Mecacci (2005) this form of therapy attempts to restore impaired cognitive function and improve overall functioning for the completion of daily activities, after cognitive function has been compromised. CRT can be broken down into two approaches: compensatory and restorative (Barman, Chatterjee & Bhide, 2016). The compensatory approach or behavioral intervention teaches patients skills to compensate for the cognitive deficit. This can be done by giving a patient a notebook or electronic aid such as an alarm or reminder on their cell phone – these apparatus work to prompt the person to complete certain tasks and thus aims to assist with memory function. However, it is important to note that this approach uses external aids to improve activities of daily life, it does not treat the impairment itself (Sohlberg, 2006). The restorative approach on the other hand, is aimed directly at working towards reinstating the impaired functioning (Barman, Chatterjee & Bhide, 2016). An example of such an intervention, is having the patient complete tasks repetitively in order to improve memory function. In a study conducted by Sohlberg & Mateer (1987) it was found that patients who have suffered traumatic brain injury performed better the in the Paced Auditory Serial Addition Test, Stroop Test and the Trail Making Test, after receiving cognitive rehabilitation therapy. These tests are administered to patients who have undergone Attention Process Training - a rehabilitation programme aimed at improving the visual and auditory attention of patients with acquired brain injury (Barman et al., 2016). Moreover, CRT usually combines these two approaches in order to achieve the best results in patients.

Cognitive Rehabilitation and HIV

There is emerging literature on the use of cognitive rehabilitation therapy (CRT) of HIV-patients' executive function. Research by Boivin, Nakasujja, Sikorskii, Opoka & Giordani (2016) aimed to evaluate the neuropsychological and behavioral benefits of a computer-based rehabilitation training intervention on 159 Ugandan children living with HIV (6-12 years; 77

boys, 82 girls). The rehabilitation intervention that was applied in this study was the Captain's Log programme that sought to rehabilitate working memory, attention and visual-spatial analysis. It was found that participants who received the rehabilitation showed improved EF scores following the intervention (Boivin et al., 2016). Findings emerging from the study were that the intervention was an effective method for neurocognitive rehabilitation for children living with HIV, especially for those with low-resource socioeconomic backgrounds who are receiving antiretroviral treatment prior to starting the programme.

Another study by Becker and colleagues (2012) researched the feasibility of a cognitive stimulation program to improve neuropsychological test performance in individuals living with HIV. The study had two outcomes: the primary outcome was the change in neuropsychological test performance as indexed by the Global Impairment Rating, and the secondary outcome was to improve the mood and overall quality of life rating of the patients - these factors will be measured using the Brief Symptom Inventory subscales and Medical Outcomes Survey-HIV scales, respectively. Becker et al., (2012) used the SmartBrain computer-based intervention, and it was found that participants showed improvements in cognitive functioning after a 24-week period. This study has a number of limitations, and the key components for measuring the success of cognitive rehabilitation programs was access to the internet, thus implying that accessibility to the internet, and the speed of the internet connection can greatly affect the consistency of the participants and thus impacting the overall success of the intervention (Becker et al., 2012). The study found that cognitive stimulation can help to improve the cognitive functioning of HIV patients, thus disease severity is lessened and there is the potential rehabilitation (Becker et al., 2012).

Subsequently, Eaton et al., (2019) proposed a study on the feasibility and acceptability of cognitive mediation group therapy compared to mutual aid group therapy for ageing persons with HAND. Two interventions were applied in the study, : (a) combined remediation group therapy that involved mindfulness-based stress reduction - e.g. meditation, body scans, deep breathing, with a BrainHQ computer programme with activities to train EF. The control group was exposed to a procedure similar to the one used by the Alcoholics Anonymous, where group facilitators facilitate the discussion and participants essentially assist in helping one another overcome the problem at hand (Eaton et al., 2019). The research by Eaton and colleagues (2019) was an experimental design and the outcomes of this intervention are yet to be reported.

Ezeamama et al., (2020) recently published a study investigating participants who were in the intervention group at the Midway Uganda Hospital received cognitive training through one of two rehabilitation interventions, *Brain Powered Games* and *Spatial Navigation Training*. The participants in the study were inpatients living with HIV admitted at the hospital mentioned above, they received ART treatment as well as standard healthcare. Of note, the participants in this study showed neurocognitive decline owing to both their age and HIV status.. These interventions are both computer-based rehabilitation programmes which follow the restorative approach to CRT (Ezeamama et al., 2020). Similar to previously mentioned studies, participants in this study continued to receive standard medical treatment and as is the case of Ezeamama (2020) patients received combination antiretroviral therapy in the form of either abacavir or zidovudine (AZT) or tenofovir (TDF) and lamivudine (3TC) and efavirenz (EFV) or nevirapine (NVP). Findings from the study showed statistically significant score on executive function domains and that CCRT training was beneficial to patients, as it improved not only their EF (verbal fluency) domain, but also other cognitive functions such as verbal learning/memory (immediate and delayed recall tests), short-term working memory (digit span backwards), and processing speed, to mention a few.

Iannuzzi et al., (2016) conducted a study the cognitive neurorehabilitation of executive function using a computer-based restorative approach on a sample size of three HIV positive cART treated patients. Although, the sample size was small and no control group was used with which to measure any statistical differences that may come about in the study, Iannuzzi et al., (2016) report that satisfactory improvement was shown in the EF, attention and working memory and memory and motor skills domains of patients. Subsequent to the intervention, researchers observed an improvement in the IADL and reduced anxiety in patients receiving the intervention. Suggestions emanating from the study included further research with larger sample sizes, in the experimental and control conditions.

Lastly, Livelli et al., (2015) reported that in their study there was a significant interaction between the paper-based CRT intervention and the EF outcomes of participants. To measure executive function, the researchers used the Tower of London simplified version, Stroop Colour Test-Errors, Trail Making Test Part B, Frontal Assessment Battery and the Rey Oesterreich complex figure copy assessments. there were 32 participants in the sample ground. The mean scores of their experimental group increased from *M = 50.41* at baseline to *M = 54.51* at post-assessment, in comparison to the control group which report *M = 49.6* at baseline and *M = 47.48* at post-assessment for EF; thus, indicating a significant improvement in EF outcomes after the CRT intervention (Livelli et al., 2015).

In spite of the above cited studies, there continues to be a dearth of research indicating the efficacy of cognitive rehabilitation of executive functions, in both children and adolescents living with HIV (Livelli et al., 2015). With research indicating that South Africa has a high rate of HIV infections, particularly in child and adolescent statistics, further research on the effectiveness of HAART coupled with cognitive rehabilitation as a treatment intervention is believed to offer wider ranging quality of life and functioning needs to children living with HIV/AIDS.

My aim is thus to conduct a meta-analysis in order to collate data on the empirical evidence to support the cognitive rehabilitation of executive functions following HIV/AIDS.

Chapter 2 Methodology

2.1 Research Objectives

This research study aims to answer the following research question: *Does Cognitive Rehabilitation Therapy aid in the treatment of impaired executive functioning of patients living with HIV?* Research presently exists that indicates has shown that a positive relationship exists between cognitive rehabilitation and the improved functioning across cognitive domains (Boivin et al., 2016 ; Livelli et al., 2015). However, the effects of cognitive rehabilitation specifically on the rehabilitation of executive functions in people living with HIV is limited. To address this limitation, my study seeks to contribute to the HIV cognitive rehabilitation literature by conducting a meta-analysis that collates evidence on the efficacy of CRT to ameliorate deficits in executive functions in people living with HIV. The achievement of my research objectives will lead to further discourse on: (a) the role of non-pharmaceutical, alongside HAART, to contribute to the cognitive functioning of persons living with HIV, (b) the differences between restorative and compensatory approaches of CRT and its effect on the EF domain of HIV persons and c) the application of

CRT interventions into communal health care, into low-resources settings. My research questions and subsequent hypothesis are as follows:

2.2 Methodology

2.2.1 Research Design

My research study employed a meta-analytic research design, which is a quantitative procedure. According to Haidich (2010) the meta-analysis uses an epidemiological study design and it uses previous research studies to create conclusions about a particular area of research. Haidich (2010) explains that among the outcomes that are obtained from the meta-analysis it provides an estimation of the effect that the treatment has or the risk that it poses for the disease. Further the meta-analysis also examines the variability or heterogeneity in the study results (Haidich, 2010). In this context of this study, previous studies on HIV and cognitive rehabilitation interventions will be used to measure the success that it has on ameliorating executive function in persons living with HIV. The strengths of the meta-analysis design are that it overcomes the issue of small sample sizes – large sample sizes increase the cost of research and it also difficult to generalize from such studies (Haidich, 2010). In addition, meta-analysis designs improve the reliability of information owing to the statistical significance that we find in the data (Haidich, 2010).

2.2.4 Inclusion Criteria

The eligibility criteria used for this quantitative study is based on the PICO approach - population, intervention, comparison and outcome (Tawfik, Dila, Mohamed, Tam, Kien, Ahmed & Huy, 2019). For the topic that I have chosen, I have made the following inclusion criteria: (1) cognitive rehabilitation intervention following either a restorative or compensatory approach on the EF domain of HIV patients, (2) HIV patients have already been on cART or HAART prior to the commencement of study and (3) no restriction to the country that the research was conducted in, no exception to race, age, gender, language that the research was conducted in and date published. Furthermore, studies were excluded if (1) the full-text was not available as open access journals or easily accessible through the use of Rhodes University credentials, (2) if no control groups were used to monitor the statistical success of the intervention, and while conducting the search, many protocol studies were found where the use of intervention was hypothesized, thus these studies were also excluded owing to the lack of data.

In order to conduct the meta-analysis, I had to complete a search in order to find the relevant studies. Computer searches were primarily conducted using various databases. The initial search for studies was conducted using Google Scholar, which later led to the PubMed database and further to the specific databases as the search terminology was modified. The search included terms such as “executive (dys)function”, “cognitive rehabilitation (therapy)”, “hiv-patients”.

2.2.5 Identification of Trials

After applying the above-mentioned eligibility criteria and many rounds of refining the search terminology, five studies were retained for this meta-analysis. The year of publication of these studies ranged from 2012 to 2020. The studies were conducted in a number of different countries: Italy (Livelli *et al.*, 2015 & Iannuzzi *et al.*, 2016); Uganda (Boivin *et al.*, 2016 & Ezeamama, *et al.*, 2020); and the United States of America (Becker *et al.*, 2012). In addition, the studies used showed different measures to assess the success of patients' reaction to the cognitive rehabilitation interventions. Iannuzzi *et al.*, (2016) used a computer-based rehabilitation program which is available at https://dynamicbrain.brainhq.com/ , while Livelli *et al.*, (2015) had patients administer two paper-based tasks Metacognitive Strategy Training - a five minute paper-and-pencil based exercise to help improve daily problem-solving abilities - and Goal Management Training - a five minute paper-and-pencil based exercise to improve the ability to stop and thinking about what one is doing, being able to identify a specific goal, delineating the steps needed to achieve the goals and evaluating the outcomes. Further, Becker *et al.*, (2012) used a computer-based program called *SmartBrain*, the program comprises fourteen activities for participants to complete and adjusts the level of the stimulation exercise according to how the participant is performing. Similarly, a computer-based training called *Captain’s Log* was used by Boivin *et al.*, (2016) and Ezeamama *et al.*, (2020) where all participants started off with the simplest program level for each task, with training becoming more difficult as they progressed. In Ezeamama *et al.*, (2020) the intervention had two components - culturally adopted Brain Powered Games and Spatial Navigational Training - taking up 20 and 25 minutes to complete respectively. Both Becker *et al.*, (2012) and Boivin *et al.*, (2016) computerized program automatically audited the progress of participants as they completed each exercise, at each session.

2.2.6 Procedure

Lastly, the statistical significance was analyzed, as well as the sizes of samples in each study, and the homogeneity of the estimated effect sizes for each component of EF using the Comprehensive Meta-Analysis software to conduct a weighted analysis of the data. The following table shows the main statistical data that was extracted from the studies mentioned above:

Source	**Sample Size Experimental**	**Sample Size Control**	**Mean Experimental**	**Mean Control**	**Standard Deviation Experimental**	**Standard Deviation Control**
Becker et al., (2012)	**46**	**14**	**3.6**	**3.1**	**1.6**	**0.9**
Boivin et al., (2016)	**52**	**54**	**42.9**	**45.8**	**0.8**	**0.8**
Ezeamama et al., (2020)	**41**	**40**	**52.5**	**51.8**	**54.4**	**46.6**
Vance et al., (2012)	**22**	**24**	**162.2**	**216.1**	**82.4**	**96.1**
Livelli et al., (2015)	**16**	**16**	**54.5**	**47.8**	**1.9**	**1.4**

Chapter 3 Results

Results

As previously mentioned, the hypothesis for my research is as follows: The group of HIV patients that receive cognitive rehabilitation intervention will score higher on neuropsychological tests which test for EF compared to HIV patients who have not received cognitive rehabilitation intervention.

I ran a fixed effect meta-analysis on the data to determine the relationship between cognitive rehabilitation and executive functioning in HIV patients. The fixed effect meta-analysis was used because this model assumes that all the studies used in the meta-analysis equally contribute to the overall outcome of the intervention and that the differences in the observed effects are a result of sample error (Borenstein, Hedges & Rothstein, 2007). The range of the sample sizes was between 32 (Livelli et al., 2015) to 106 (Boivin et al., 2015). The upper limits of the studies fell within various ranges as well. The upper limits ranged between 0, 36 (Vance et al., 2012) and 5, 43 (Livelli et al., 2015). Further ranges indicate that the lower limits of the data fell between -0, 80 (Vance et al., 2012) and 2, 96 (Livelli et al., 2015). The overall effect size lower and upper limits from the meta-analysis were 0, 28 and 0, 76, respectively. In addition, the z-values of the studies, using a confidence level of 95% were as follows: 1, 02 (Becker et al., 2012); -0, 74 (Vance et al., 2012); 6, 63 (Livelli et al., 2015); 4, 68 Boivin et al., (2016) and 0, 34 (Ezeamama et al., 2020). The overall z-value from the meta-analysis reported at 4, 31. Moreover, the p-values also with a confidence level of 95% for the studies were reported at: 0, 31 (Becker et al., 2012); 0, 46 (Vance et al., 2012); 0, 00 (Livelli et al., 2015); 0, 00 (Boivin et al., 2016); and 0, 73 (Ezeamama et al., 2020). The overall p-value from the meta-analysis was 0, 00. Consequently, of the five studies used for this meta-analysis, the overall effect size was 0, 52. Cohen's d describes the overall difference between two means (Lakens, 2013). Although the Cohen's d score is medium, it still has a significant effect. This means that the cognitive rehabilitation intervention is effective on the executive functioning of HIV patients.

Table 1: Sample sizes, upper and lower limits, p-value and z-value of studies used in meta-analysis showing the effectiveness of cognitive rehabilitation interventions on HIv patients.

Studies	Sample Size	Upper Limit	Lower Limit	p-value	z-value
Becker et al., (2012)	60	0, 91	-0,29	0, 31	1, 02
Vance et al., (2012)	46	0, 36	-0, 80	0, 46	-0, 74
Livelli et al., (2015)	32	5, 43	2, 96	0, 00	6, 63
Boivin et al., (2016)	106	1, 36	0, 56	0, 00	4, 68
Ezeamama et al., (2020)	81	0, 51	-0, 36	0, 73	0, 34

The fixed relative weights indicate how much each individual study used in the meta-analysis contributes to the effect (Borenstein *et al.*, 2007). Boivin *et al.*, (2016) weighted 34, 66 and Ezeamama *et al.*, (2020) relative weight was 29, 52, and these two studies contributed the most to the overall effect. Vance *et al.*, (2012) and Becker *et al.*, (2012) had a medium contribution to the overall effect size, weighing 16, 65 and 15, 52 respectively. And lastly, Livelli *et al.*, (2015) contributed the least to the overall effect size, with a relative weight of 3, 65. The effects of the fixed relative weights can be attributed to the varied sample size in each study (Borenstein *et al.*, 2007). Boivin *et al.*, (2016) had the biggest total sample size of all the studies used in the analysis, with 106 participants in the study and Ezeamama *et al.*, (2020) had a total number of 81 participants in their study. The lowest number of participants which also contributed the least to the relative fixed weights, had only 32 total participants in their study (Livelli *et al.*, 2015). In addition, the studies which had a moderate contribution to the overall fixed relative weight had a sample size of 46 (Vance *et al.*, 2012) and 60 (Becker *et al.*, 2012).

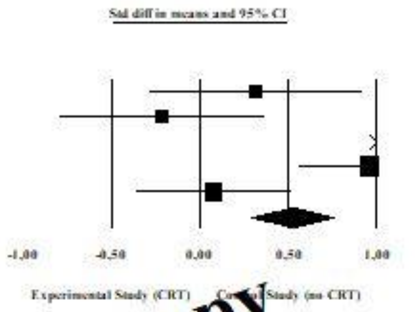
The heterogeneity measure of the data gives us an indication as to whether or not the intervention is effective (Borenstein *et al.*, 2007). The meta-analysis gave us a significant p-value of 0, 00 and this means that the treatment intervention, cognitive rehabilitation therapy, is an effective form of treatment for remedying the executive functioning of HIV patients. The variation that is a result of heterogeneity is described by the I-squared value. This value is expressed as a percentage (Borenstein *et al.*, 2007). The i-squared value was 91%.

Lastly, a high-resolution plot was formulated using the Comprehensive Meta-Analysis Software and the overall Cohen's *d* score of 0, 52 reflects the significant interaction between cognitive rehabilitation intervention and executive function. The individual effect sizes of each study scored as follows: 0, 31 (Becker *et al.*, 2012); -0, 23 (Vance *et al.*, 2012); 4, 20 (Livelli *et al.*, 2015); 0, 96 (Boivin *et al.*, 2016); and 0, 08 (Ezeamama *et al.*, 2020).

Figure 2: Table showing the statistics yielded from each study in the meta-analysis indicating: the standard differences in means, the standard error, variant, lower and upper limits, z-values and p-values. Plot showing the standard differences between the experimental group - which received CRT and the control group - which did not receive CRT.

HIV Treatment and Control

Study name	Std diff in means	Standard error	Variance	Lower limit	Upper limit	Z-Value	p-Value	Relative weight	Relative weight
Becker et al. (2012)	0,312	0,307	0,094	-0,288	0,913	1,019	0,308	15,52	
Vance et al. (2012)	-0,219	0,296	0,088	-0,799	0,361	-0,740	0,459	16,65	
Livelli et al. (2015)	4,195	0,632	0,400	2,955	5,434	6,633	0,000	3,65	
Boivin et al. (2016)	0,959	0,205	0,042	0,557	1,361	4,675	0,000	34,66	
Ezeamama et al. (2016	0,076	0,222	0,049	-0,359	0,512	0,344	0,731	29,52	
	0,520	0,121	0,015	0,283	0,757	4,306	0,000		



Meta Analysis

Chapter 4 Discussion & Conclusion

Context

HIV/AIDS is known to cause a number of serious effects on one's health and neurocognitive functioning. This meta-analysis used statistics from studies that were conducted in a number of different countries. The studies varied from developed countries such as Italy (Livelli et al., 2015; Iannuzzi et al., 2016) to developing countries like Uganda (Boivin et al., 2016; Ezeamama et al., 2020). In addition to this, the patients that were enrolled in the various treatment intervention programmes were both young and old. All the participants in each study had HIV infection and were actively receiving HAART treatment prior to participating in the study.

Summary of Results

The initial aim of this study was to determine if cognitive rehabilitation therapy helps in improving the deficiency of executive functioning in patients living with HIV. The results from the meta-analysis aims to provide support for the effects of this intervention on the compromised cognitive domain. After running the meta-analysis on the Comprehensive Meta-Analysis software, it was found that the effect size data fell in the medium range which scored at 0, 52. This indicates that although a small result, there is a significant interaction between the treatment intervention and the performance in the executive function domain.

With regards to the individual results that were obtained, the only study that showed a insignificant interaction between the two variables was Vance et al., (2012) which scored -0, 22 on the standard difference in means. Although each study had a very different range of samples used and the lengths of each study also differed, the effects of the cognitive rehabilitation intervention was remarkably similar across the studies that were included in this analysis.

In the initial hypothesis it was stated that the different types of cognitive rehabilitation intervention - whether it was a computerized intervention or paper-based intervention - would impact the outcome of the analysis. Majority of the studies that were included in this meta-analysis had patients use computerized intervention programmes in an attempt to improve their executive functioning. These variables were not separated and it may have caused the results to skew. A particular point of interest here is how the studies that involved a computer-based cognitive rehabilitation intervention contributed the most to the overall effect size of the data. This gives the indication that the patients living with HIV who received a computerized intervention showed better executive function at post-assessment than the patients who received paper-and-pencil based intervention. The weightings will be discussed further in the next section.

In addition, each study had different timeframes in which their study was done. Becker et al., (2012) had participants spend twenty-four weeks working on the SmartBrain programme. While the participants in the Vance et al., (2012) completed self-administered ten hours of the INSIGHT computer program. Moreover, the participants in the Livelli et al., (2015) study spent: four months completing eight paper-and-pencil based exercises, and eight computerized exercises that were repeated over a period of thirty-six sessions, with each session being fifty minutes long. Moreover, the participants in the Boivin et al., (2016) study received twenty-four sessions which were each one-hour in length which were administered over two months. And lastly, Ezeamama et al., (2020) …. Interestingly, the fixed relative weighting showed that the study conducted by Boivin et al., (2016) contributed the most to overall effect size of the study. The weighting for this study was 34, 66 and the fixed relative weighting for Livelli et al., (2015) scored at 3, 65. Previously in the interpretation of the results section, it was highlighted that the weights can reflect the sample sizes used in the studies. Yet, with regards to the timeframes that each study was conducted in it is unclear as to whether or not the amount of time spent on the cognitive rehabilitation interventions had an impact on the overall success of the treatment intervention and the effect size. The impact of the amount of cognitive rehabilitation on the maintenance of treatment could not be evaluated as not all the studies used in this meta-analysis followed up on the effects of the intervention. Thus, we are uncertain of the long-term effects of this intervention on patients. More research is needed in this regard.

Design Limitations and Weaknesses

This meta-analysis has a number of limitations that are important to mention. The first limitation concerns the availability of research on the executive function domain. Very little research has been conducted on solely the executive functioning domain of HIV patients. Most research combines the different cognitive domains, owing to the way that all the cognitive domains work together. For example, in the study conducted by Kanmogne et al., (2018) both the executive function and verbal fluency domains were assessed. In the study various executive function and verbal fluency assessments were used. Halstead Category Test (HCT), Wisconsin Card Sorting Test (WCST), Colour Trails-II test (CTT2), and Stroop Colour-Word Interference Test (SCWT) were used to measure executive function in seronegative and seropositive sample groups (Kanmogne et al., 2018). And, Category Fluency, Action Fluency, and Letter Fluency assessments were used to measure verbal fluency in seronegative and seropositive sample groups (Kanmogne et al., 2018). Another instance where the executive function domain was assessed alongside another cognitive domain is in the study by Haase, Nicolau, Viana, Barreto & Pinto (2014). This study measured the processing speed and executive functioning of Brazilian children and adolescents living with HIV after performing a series of neurocognitive tasks (Haase et al., 2014). Thus, in order to validate the data obtained from this meta-analysis, it is imperative that broader research is conducted solely on the executive function domain of HIV patients, and that the research has greater sample sizes from different cultural populations.

Cofounding Variables and Possible Threats to Internal Validity

Other than the HIV virus worsening the executive functioning of seropositive individuals, the presence of a confounding factor could also have impacted the weaking seen in this cognitive domain. Schillerstrom, Horton & Royall (2005) have observed that should the individual have another previously diagnosed chronic disorder, regardless of the nature of the disease, it is known to cause dysfunction in a number of cognitive tasks and executive functioning. In the studies conducted by Becker et al., (2012) and Vance et al., (2012) it was reported that the sample group did not show a history of any neurological diseases, however participants in the Livelli et al., (2015) study had HIV-associated neurocognitive disorders. Though the participants had HIV-associated neurocognitive disorders, researchers never stipulated what these HIV-associated neurocognitive disorders were.

Another variable that may have influenced the course of the results from the meta-analysis is the progress of the HIV infection in relation to their executive function abilities. Previously, it was mentioned that the CD+4 cell counts and the viral load of individuals are used as an indication of how much the virus has progressed in the person's body (Hernandez-Vargas & Middleton, 2012). In the study conducted by Becker et al., (2012) it was reported that sixty percent of the participants had AIDS, in addition their mean CD4+ cell count was 523, 3 and the mean viral load was 2, 05 log10. The participants in the Livelli et al., (2015) study had a CD4+ cell count above 350 and nothing was reported regarding their viral load. Moreover, there were no reports of the CD4+ cell counts and viral loads of the sample in the Vance et al., (2012), Boivin et al., (2016) and Ezeamama et al., (2020) studies.

A further limitation to the study is the distribution of resources in the countries that were used in the meta-analysis - developing and developed countries. The majority of studies used in this meta-analysis were computerized rehabilitation programme (Becker et al., 2012; Vance et al., 2012; Boivin et al., 2016; Ezeamama et al., 2020), with one exception in Livelli et al., (2015) where they administered both pencil-and-paper based and computerized rehabilitation exercises. According to Ge, Zhu, Wu & McConnell (2018) technology-based cognitive training programme are fast developing as suitable rehabilitation interventions for individuals with various cognitive impairments. However, we cannot ignore the disadvantages that we have certain studies (Ezeamama et al., 2020 & Boivin et al., 2016) where participants dropped out of the study before the post-intervention assessment, owing to them not being able to keep up with the pace of the study - because of the lack of computers, or not knowing how to operate the rehabilitation programme that has been prescribed for them (Ge et al., 2018). Thus, this cofounding variable could have impacted the outcomes of this study.

In addition to resource limitation, one of the inclusion criteria for this meta-analysis was that all participants were actively on HAART prior to commencing the cognitive rehabilitative intervention. The sample sizes were fairly small across the board, and in particular studies the samples were small because patients were dropped from the study owing to the lack of adherence to their HAART treatment. I want to highlight to studies in particular: Ezeamama et al., (2020) and Boivin et al., (2016) where the participants were all from Uganda, a developing African country. Tuller, Bangsberg, Senkungu, Ware, Emenyonu & Weiser (2010) looked at the various reasons why there was a lack of adherence to HAART treatment in Southwestern Uganda. One of the issues that patients encountered was the cost of transportation to the clinic to fetch their monthly prescriptions. Tuller et al., (2010) reported that these individuals had to priorities the little income that they do receive and money for food, shelter and education was much higher on their list of monthly expenses. In addition to the lack of transport, many participants reported that owing to the far distances they have to travel, they have to take time off work and this negatively affects their already low earnings (Tuller et al., 2010). Although this research is not directly attributed to the lack of adherence to HAART treatment that we saw in Boivin et al., (2016) and Ezeamama et al., (2020), it does however help to provide context to the possible reasons for the small sample size owing to participants being scrapped because of their lack of adherence to HAART treatment.

Recommendations for Future Research

The discussion section of this dissertation has already covered a large scope of areas that should be taken into consideration should this research study be replicated. The recommendations aimed to account for internal and external validity issues that may have been present in this meta-analysis. Replication of this study with a greater sample size is imperative. In addition to the sample size, having a sample that is reflective of our population will also positively impact the reliability of the data. Moreover, considering that all the studies used in the meta-analysis used different pencil-and-paper and computer-based rehabilitation interventions it may be of interest to measure the effectiveness of a standardized paper-based or computerized programme in order to measure the effectiveness of cognitive rehabilitation intervention on HIV patients.

In conclusion, it would be beneficial if a specific battery of standardized tests for HIV populations were to be developed with the South African context in mind - the variety of education and socioeconomic backgrounds, and the resource availability and literacy abilities in our country. This will not only help to achieve more reliable findings on the success of cognitive rehabilitation interventions for our own population, but it will also make South African research more generalizable to other countries. Finally, it would be of interest to include the effect that cognitive rehabilitation intervention has on the overall activities of daily living and the functioning capabilities of HIV persons in their various careers.

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