

**THE COGNITIVE REHABILITATION OF A SAMPLE OF CHILDREN LIVING  
WITH HIV: A SPECIFIC FOCUS ON THE COGNITIVE REHABILITATION OF  
SUSTAINED ATTENTION**

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## ABSTRACT

Pharmacological interventions to treat Human Immunodeficiency Virus (HIV) with antiretrovirals (ARVs), have dramatically improved the survival rates of HIV positive children maturing into adulthood. However, HIV-associated neurocognitive decline still persists in the era of ARVs. Within the framework of brain plasticity, a number of researchers have begun to assess the feasibility of cognitive rehabilitation therapy as a complement to ARVs to reverse neurocognitive decline as a result of HIV (e.g., Becker et al., 2012). Only one study has been conducted in South Africa, by Zondo & Mulder (2014), assessing the efficacy of cognitive rehabilitation in a paediatric sample. The current research builds on the above mentioned study by implementing an experimental approach to examine the effect of cognitive rehabilitation in a sample of both HIV positive and HIV negative children. Five HIV positive and six HIV negative children were assigned to either an experimental or control group. The experimental group underwent two months of cognitive rehabilitation therapy remediating sustained attention, whereas the control group took part in placebo activities. Sustained attention measures were taken before and after the intervention training sessions, using a sustained attention subtest from the Test of Everyday Attention for Children (TEA-CH). A *Mann Whitney U Test* revealed that the experimental group ( $Mdn=38.50$ ) did not differ significantly from the control group ( $Mdn = 37.00$ ) after the cognitive rehabilitation intervention,  $U=12.00$ ,  $z= -.55$ ,  $p= .66$ ,  $r= -.17$ . But a *Wilcoxon Signed Rank Test* found that there was a significant improvement from pretest scores ( $Mdn=31.00$ ) to posttest scores ( $Mdn=38.00$ ) following the rehabilitation for HIV positive participants in the sample,  $T=15.00$ ,  $z = -2.02$ ,  $p= .04$ ,  $r= -.90$ . This raises the possibility that cognitive rehabilitation could be used as a low cost intervention in underdeveloped contexts.

*Keywords:* HIV, ARVs, Neurocognition, Brain Plasticity, Rehabilitation

### **Declaration of Originality**

I, the undersigned, hereby declare that the work contained in this thesis is my own work, unless otherwise referenced. It has not been previously submitted at any other university for the purposes of fulfilment of a degree.

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## LIST OF ACRONYMS

AIDS: Acquired Immune Deficiency Syndrome

ANI: Asymptomatic Neurocognitive Impairment

APT: Attention Processing Training

ARVs: Antiretrovirals

BBB: Blood Brain Barrier

cART: Combination Antiretroviral Therapy

CD4+ T cells: Cluster of Differentiation 4 T-helper cells

CNS: Central Nervous System

HAART: Highly Active Antiretroviral Therapy

HAD: HIV-Associated Dementia

HAND: HIV-Associated Neurocognitive disorders

HIV: Human Immunodeficiency Virus

HIV+: Human Immunodeficiency Virus positive

HIV- : Human Immunodeficiency Virus negative

MND: Mild Neurocognitive Impairment

RNA: Ribonucleic Acid

ARVs

cART

HAART



Different terms to describe antiretrovirals

“Some men see things as they are and ask why. Others dream things that never were and ask why not”. George Bernard Shaw

## **CONTEXT AND LITERATURE REVIEW**

### **1.1 *HIV/AIDS AND COGNITIVE REHABILITATION***

HIV-related Central Nervous System (CNS) dysfunction which is linked to neuronal ribonucleic acid (RNA), as a result of HIV infection, is ultimately linked to HIV-related neurocognitive disorders (Bell, 2004; Hauser et al., 2007). Researchers have found that HIV-associated neurocognitive dysfunction can be summarily categorised into four distinct categories: a) Asymptomatic Neurocognitive Impairment (ANI); b) Mild Cognitive Impairment (MND); c) HIV Associated Dementia (HAD); and d) HIV Encephalopathy (Joska, Fincham, Stein, Paul, & Seedat, 2010). Studies on the neurocognitive outcomes have shown that children diagnosed with an early HIV infection are at a greater risk for encephalopathy which includes developmental delays and cognitive impairments across multiple domains (Armstrong, Seidel, & Swales, 1993; Van Rie, Harrington, Dow, & Robertson, 2007). HIV resultant cognitive defects, which are often progressive, are frequently characterised by learning disabilities, decreased attention and deficits in visuo-spatial abilities in children (Armstrong et al., 1993; Joska et al., 2010). Although much progress has been made in the pharmacological sciences with ARV therapy to counteract the effects of HIV on cognition, the literature on HIV is replete with studies that indicate that ARV therapy does not improve HIV-related neurocognitive decline (Boivin et al., 2010; Koekkoek, de Sonnevill, Wolfs, Licht, & Geelen, 2008). The treatment of HIV changed with the introduction ARV therapies. These drugs are effective in suppressing plasma HIV-1 RNA (viral load) (Department of Health and Human Services, 2012) and as a result mortalities and opportunistic infections have declined (Centre for Disease Control and Prevention, 2010 [CDC]). However, the effectiveness of ARV drugs on neurocognitive functioning remains variable (Weber, Blackstone, & Woods, 2013). This may be due to the

fact that the CNS may be able to contain a reservoir of the virus that can remain untouched by ARVs (Iglesias-ussel & Romerio, 2011). It is palpable that ARVs vary in their ability to cross the blood brain barrier (BBB) and in their ability to act upon the CNS viral reservoir (Weber et al., 2013). A handful of non-ARV pharmacotherapy procedures have generated mixed results and most of these non-ARV medications have shown initial promise in pilot trials but have not maintained the observed results in larger clinical trials (Weber et al., 2013). HIV stem cell transplantation has also shown early signs in reversing the effect of HIV (Allers et al., 2011), but the replicability of stem cell research in Sub-Saharan Africa remains in the distant future. Thus, there is a dearth of rigorous experimental studies on alternative methods to complement ARV therapy such as cognitive rehabilitation for the remediation of HIV-associated neurocognitive impairment.

A number of researchers have suggested that ARV therapy is beneficial and is best when accompanied by enhanced cognitive modifiability programs to help stem the effects of HIV/AIDS on the brain (Weber et al., 2013). Evidence based cognitive rehabilitation is the process of relearning cognitive skills that have been lost or altered as a result of damage to brain cells (Malia et al., 2004). Cognitive rehabilitation has been defined as "efforts to promote maximal adaptive cognitive functioning in patients with neurologically induced cognitive deficits" (Eslinger, 2002, p. 17). In this instance, cognition, refers to a complex collection of mental skills such as: attention, perception, learning, comprehension, remembering, and problem solving skills (Malia et al., 2004). Cognitive rehabilitation aims to reinforce, strengthen, and establish new patterns of cognitive activity to compensate for impaired neurological systems, through brain plasticity. The process of cognitive rehabilitation involves, extensive and repeated exercises that each targets the cognitive impairment in a different way (Malia et al., 2004). For the purpose of this study, the focus will be on rehabilitating children in terms of remediating sustained attention loss as a result of HIV/AIDS. Sustained attention skills are understood to be the underlying foundations of all other cognitive skills such as executive functions and problem solving skills (Malia et al., 2004).

## ***1.2 Aims and Objectives of my Research***

The first study in Sub-Saharan Africa to investigate the potential benefits of cognitive rehabilitation on neuropsychological functioning of children on ARVs, demonstrated the credible neurocognitive benefit of cognitive rehabilitation therapy in aspects of attention and executive functioning (Boivin et al., 2010). Although the study by Boivin et al. (2010) showed improved performance of attention and executive function in children, the authors have stressed the need for more evidenced based experimental studies to investigate cognitive rehabilitation in HIV/AIDS children over a prolonged intervention period. The aim of my research was to investigate neurocognitive remediation of sustained attention loss in a sample of HIV positive (HIV+) children. Although extensive research has been conducted on the use of cognitive rehabilitation on attention impairment (Cicerone et al., 2011), no experimental studies have been conducted in South Africa with special focus on HIV cognitive rehabilitation. The objective of my research, is against the backdrop that South Africa has the highest number of people living with HIV (UNAIDS, 2012). It is therefore necessary to examine the effectiveness of cognitive rehabilitation in a sample of HIV/AIDS children on ARV therapy in the Eastern Cape, South Africa given the findings that ARVs have a limited effect in reversing neurocognitive decline in children and adults alike (Boivin et al., 2010; Weber et al., 2013). Insights gained from the present study will extend the existing body of knowledge around HIV infected children's psychological functioning in a South African context.

### **1.3 Introduction**

In order to reverse HIV-related cognitive decline it is important to understand brain plasticity, thus in Section 1.4, I explore the notion of brain plasticity and show how the brain changes in response to learning. In Section 1.5, I show how brain plasticity through cognitive rehabilitation techniques can be used to compensate for damaged brain functions. In order to understand how HIV causes cognitive decline, it is important to understand how HIV functions biologically. In Section 1.6, the thesis will briefly outline the effects of HIV in South Africa and explain the biology of HIV infection and how it impacts on the CNS, and how it causes cognitive decline. In Section 1.7, I discuss how HIV-associated neurocognitive disorders are classified within the HIV literature. This will be followed by Section 1.8, which discusses the effects of HIV on cognition, e.g., motor skills, memory, and executive functions. Since attention is the focus of this thesis and also forms the foundation of cognitive processes, it is important to discuss it in more detail. Therefore, in section 1.9, I will discuss the neurology of sustained, selective and divided attention and show how this cognitive process is negatively affected by HIV. In light of these negative cognitive affects, the question of whether it can be stabilized or reversed becomes particularly important. In section 1.10, I outline some evidence that ARVs can sometimes improve cognitive decline. However, as shown by section 1.7 and 1.8 medical interventions are not necessarily effective in reversing cognitive decline. This leaves some space for rehabilitation therapies to utilize the brains plasticity to fix cognitive decline when ARVs cannot. Therefore, in section 1.11, I will discuss the approaches to cognitive rehabilitation. The research shows that these types of rehabilitation therapies are particularly effective as a complement to ARV therapy. If these conclusions are valid they could be important for combating HIV-associated cognitive impairment in South Africa in a cost effective way.

## 1.4 *Neural Plasticity*

Scientists accept that the ability of the brain to be able to change its structure and function in response to experience and damage is one of the fundamental properties of the CNS (Doidge, 2007). It is accepted that if brain connections never altered their structure, individuals would be stuck in the present, since one would not be able to hold onto any new memories or experiences that they have learnt throughout the day. The fact that thoughts, memories and experiences, leave traces on the structure of the human brain is an example of plasticity (Doidge, 2007). The term plasticity has since been used to refer to the ability of the cortex to change its neural connections and code experiences involved in processing information and learning.

The concept of neural plasticity is not a new phenomenon, William James in 1890 proposed the term in his book *Principles of Psychology* that the habits of living beings are due to the plasticity of the brain. William James in 1890 wrote on the subject of plasticity: "Plasticity, then, in the wide sense of the word, means the possession of a structure weak enough to yield an influence, but strong enough not to yield all at once. Organic matter, especially nervous tissue, seems endowed with a very extraordinary degree of plasticity" (James, 1890, p.11). James (1890) believed that if enough pressure and force is applied to a piece of metal it will bend and mold with the direction of the force, he proposed that similar changes could occur to the CNS in response to external behavioural training or internal changes brought on by disease or injury (James, 1890). Around the same period Ramon Y Cajal went against the putatively held belief that the CNS was made of a net of neurons, and instead suggested that it was composed of individual units called neurons (Kolb & Whishaw, 2009). Charles Sherrington confirmed Cajal and James's discoveries by showing that neurons were connected by junctions called synapses, evidence for the pathways in the CNS capable of plasticity (Kolb & Whishaw, 2009). Over half a century later, Donald Hebb, postulated a basic mechanism for plasticity, wherein an increase in synaptic strength arises when presynaptic cells repeatedly takes part in the firing of the postsynaptic cells, then the connections between the presynaptic neuron and the postsynaptic neuron will be strengthened

and some growth process takes place in one or both cells (Hebb, 1949). This theory is commonly summarized as “cells that fire together, wire together” (Doidge, 2007). Therefore, learning and memory for an event is triggered by the repetitive firing of two cells which means that the memory or learned event would be stored in the brain as the connection between the synapses would be strengthened (Hebb, 1949).

To date there is no universally agreed upon definition of neural plasticity in physical medicine and rehabilitation (Warrach & Kleim, 2010). More generally, the term plasticity is used to denote changes in brain organization which correlates to behaviour modifiability. This change in brain structure is believed to translate to changes in neurons and synapses and their ability to alter their structure and function in response to external pressure like behavioural or cognitive training. Suffice to say, neural plasticity is the process by which the brain encodes experience and learns new behaviour. It is the process whereby the damaged brain re-learns behaviour and cognitive skills. The ability of the brain to structurally and functionally change is one of the CNS most basic characteristics and this can even be seen in rudimentary life forms such as *Caenorhabditis elegans* which has 302 neurons (Kolb & Whishaw, 2009). *Caenorhabditis elegans* are able to make associations between sensory experiences such as smell, and as such, have the capacity to learn the association between consequences like mild shocks (Morrison & Kooy, 2001). In order for an animal to make associations between sensory events, the nervous system has to undergo change in order to code the sensory events (Kolb & Whishaw, 2009).

The previous section discussed the historical background of neural plasticity. The next section will provide evidence which suggests that throughout life the brain is remodelling its neural circuitry in order to encode new experiences. It follows that for each new memory or learning experience, there is some structural and functional change in the nervous system (i.e., at the level of synapses, neurons, neuronal networks and cortical reorganization) in order to support the learning.

## ***1.5 Structural and Functional Plasticity due to Learning and Experience***

A fundamental characteristic of the human CNS is that learning new skills or injury to the nervous system can induce structural and functional reorganization (Pascual-Leone, Amedi, Fregni, & Merabet, 2005). Structural and functional plasticity affect different levels of cerebral organisation. At the structural level, scientists note morphological changes in brain structure. For example, rats reared in enriched environments allows them to perform more complex activities and show a more complex synaptic structure with more synapses per neuron than rats reared in less stimulating environments (Rosenzweig, 1996). In a related vein, functional plasticity refers to physiological changes such as reorganization in neural circuitry (Berlucchi, 2011). For example, functional reorganization has been evidenced in blind people when they develop a larger representation in the sensorimotor cortex due to Braille-reading (Kujala, Alho, & Näätänen, 2000); and in deaf people, where visual processing takes over parts of the cortex involved in hearing (Neville & Lawson, 1987).

### **1.5.1 Learning and Experience**

The idea of environmental influences on brain functioning has been widely used to study learning induced plasticity. A number of examples exist in the literature which illustrates the influence of learning and experience on brain structural change. For instance, an increase in gray matter volume in either motor, auditory or visuo-spatial brain regions has been correlated with musical proficiency (Bengtsson et al., 2005; Gaser & Schlaug, 2003a, 2003b; Hänggi, Koeneke, Bezzola, & Jäncke, 2010; Sluming et al., 2002); complex visuomotor skills like juggling (Draganski et al., 2004); and with extensive learning of abstract information (Draganski et al., 2006). These morphological brain differences point to structural adaptations in response to the repetitive nature of learning a skill (Gaser & Schlaug, 2003). Similarly, other activities such as, learning a new language has been shown to change brain structure

with enhanced left inferior frontal gyrus activation (Stein et al., 2012). These examples illustrate the brain's ability to change its structure as results of experience, learning and physical activity. Of specific interest to this project is the discovery over the years that show the interplay between cortical reorganisation of the brain and rehabilitative medicine, where the damaged brain relearns lost behaviour. The following section will briefly outline two examples of research that illustrate the interplay between neural plasticity and rehabilitative medicine.

### **1.5.2 Plasticity in cortical maps**

Bach Y Rita performed a ground-breaking experiment involving a patient with a balance problem who felt as though she was continuously falling. This falling sensation was the result of an overdose of the antibiotic gentamicin which destroyed 97% of her vestibular apparatus (Doidge, 2007). This apparatus includes semicircular canals in the ear that are connected to the brainstem and helps us orient our movements in space (Guskiewicz & Perrin, 1996). The physician and neuroscientist Paul Bach-Y Rita treated the patient with a sensory substitution device which he developed to provide corrective sensory feedback from a motion sensor through electrodes to the patient's tongue. The sensory device placed on the patient's tongue helped the patient to walk properly without continually falling. After wearing the device for a period of time, the patient experienced residual effects and could maintain her balance even after removing the device. This example shows that the brain established new pathways for the corrected sensory information in spite of damage to the vestibular circuit (Doidge, 2007).

In another experiment the neuroscientist Vilayanur Ramachandran found that a loss of afferent sensory inputs is followed by the functional reorganisation of the primary somatosensory cortex. Science has shown that when a patient loses an arm to amputation, they may continue to feel the presence of their arm that is no longer there. Moreover, the vivid presence of a phantom limb can cause the individual a lot irritation as they feel as though their arm is itchy but they cannot scratch it since it is non-existent. Ramachandran explored this with a patient who had his left arm amputated and was experiencing phantom

limb pain. He started by touching various parts of the patient's body with a Q-tip and found that the left phantom arm responded to tactile stimulation on the left side of his face. The discovery of the virtual missing arm on his face made it easier for the patient to relieve the itching phantom arm (Ramachandran, 2011).

Ramachandran reasoned that the answer to this phenomenon lies in brain's anatomy. Neuroscience has shown that the entire skin surface of the left side of the body is mapped onto a strip of the cortex running down the right side of the brain, this has been illustrated by the Penfield map (Ramachandran, 2011). Ramachandran found that the map of the face was located next to the map of the hand, therefore, when an arm is amputated, although there is no longer an arm, there is still a map of the arm in the brain. Moreover, the map of the arm in the brain continues to represent the non-existent arm, this explains the presence of the phantom arm. Ramachandran concluded that the tactile stimulation the patient felt on his phantom arm from stimulation to his face was that the sensory input flowing from the facial skin to the face map in the brain begins to invade the vacated territory of the arm map in the brain which is in need of sensory stimulation (Ramachandran, 2011). Therefore, the nerve fibres from the facial skin that project to the face extend neural tendrils into the arm map and establish new synapses. This study demonstrated that a loss of afferent sensory inputs is followed by the functional reorganisation of the primary somatosensory cortex.

In conclusion, the somatosensory cortex is capable of cortical reorganisation as a result of injury. In each of the cases discussed, there is an increase in representation of the relevant somatosensory task as a result of stimulation. What the above sections on learning, brain plasticity, and cortical reorganisation allude to is that plasticity is the biological mechanism in which learning, memory, addiction, maturation, and adaptation correspond to changes in the CNS. Plasticity is also the same biological mechanism in which the damaged brain can adapt its neural circuitry as a result of injury or functional losses. For example, this is seen in the above two cases. I will now proceed to present the key theoretical framework underpinning my research, cognitive rehabilitation

## **1.6 Cognitive Rehabilitation**

The previous section showed that plasticity is a fundamental property of the brain; which is continually modified by experience, and that the term plasticity has been used to denote the changes in brain modifiability as a result of brain injury. The next section, will introduce cognitive rehabilitation. Cognitive rehabilitation uses brain plasticity to induce functional reorganization to compensate for lost cognitive functions resulting from brain damage.

### **1.6.1 Historical Background**

The first recorded case of cognitive rehabilitation according to Bercker and colleagues (Berker, Berker, & Smith, 1986) began in 1865 with the work of Paul Broca in an attempt to teach an aphasiac patient to read. World War One further sparked a number of comprehensive programs devoted to treating brain damage, as a result of improvements seen in the survival rates of head-injured soldiers due to early attempts at cognitive rehabilitation (Goldstein, 1942).

During and after World War Two, a neuropsychologist called Alexandar Luria was involved in neuropsychological rehabilitation and responsible for organizing a hospital for brain-injured soldiers (Luria, 1979). Luria (1963) believed that the brain's neurons cannot regenerate; he concluded that, once a particular function is lost, that function could not be recovered. Luria's emphasis was on compensation known as functional reorganisation, through which undamaged neural circuits take over a lost function (Sohlberg & Mateer, 2001). Luria demonstrated that this was possible with supporting clinical evidence (Luria, 1962). According to Luria (1963) reorganization of function occurred through new learned connections in the brain, this was the result of direct training exercises targeting the cognitive deficit. Luria (1963) postulated that through direct training exercises, different parts of the brain would reinforce and take over the damaged cognitive function. Luria's emphasis was

on compensation of function rather than restitution of damaged brain functions. According to Luria, restitution of function involves a spontaneous recovery, whereby damaged brain functions are healed and cognitive functions are restored. On the other hand, compensation refers to a transfer of cognitive functions from damaged brain functions to healthy brain tissue (Sohlberg & Mateer, 2001).

In his seminal work on *Higher Cortical Functions in Man* (1962) Luria outlined higher brain function and cerebral organization and how the localization of brain lesions results in specific pathological symptoms (Luria, 1962). Luria's notion that the brain is hierarchically organized as an integrated system continues to remain popular within the neuropsychological approach. Luria was the first to introduce the idea that the brain was hierarchically organized into building blocks which correlate with anatomical areas in the brain: a) the Attentional system (comprised of the brain stem and is necessary for gathering information to the brain for survival); b) Information processing (the second layer, dedicated to organizing and making sense of information gathered by the attentional system); and c) Executive functions (control our higher order functions like planning, organizing and problem solving) (Luria, 1963). According to Luria (1963) cognitive rehabilitation needed a strong neuropsychological theoretical basis in order to understand the cognitive deficit. A theoretical understanding of higher brain functions could then be used to plan rehabilitation techniques based on the use of intact brain systems to compensate for the cognitive deficit. I will now move on to discuss the different terminologies used in the cognitive rehabilitation literature.

## **1.6.2 Nomenclature in Cognitive Rehabilitation Literature**

Arising from the above theories, cognitive rehabilitation is defined by the American Congress of Rehabilitation Medicine, Brain Injury Special Interest Group (1997) as: "a systematic, functionally oriented service of therapeutic cognitive activities and an understanding of the person's behavioural deficits. Services are directed to achieve functional changes by: reinforcing, strengthening or establishing previously learned patterns of behaviour, or,

establishing new patterns of cognitive activity or mechanisms to compensate for impaired neurological systems" (Bergquist & Malec, 1997, p. 49).

Within the domain of cognitive neuropsychology, the key theories underlying cognitive rehabilitation are restoration or compensation (Kolb & Whishaw, 2009). Recovery at the behavioural level involves restoring the ability to perform the action in exactly the same manner before the injury. Similarly, recovery at a neural level involves restoring function in brain tissue that was lost as a result of brain injury (Levin, Kleim, & Wolf, 2009). On the other hand, compensation at a behavioural level involves performing the movement in a different manner as one did before the injury. As such, compensation at a neural level, involves the reorganization of functions whereby neural tissue takes on a function it did not have prior to the injury (Levin et al., 2009). My study used a compensatory approach which is premised on drill-and-practice of cognitive skills which allows for neural organization so that other neural circuits can take over the lost cognitive functions.

In spite of the seemingly clear definitions of restoration and compensation described above, there continues to be some heuristic debate over the above terms in the cognitive rehabilitation literature. A major problem in the literature is the conceptual definition of what constitutes recovery (Kolb & Whishaw, 2009; Levin et al., 2009). The term recovery is used to define clinical improvements in brain functions regardless whether these clinical improvements have been through restoration or compensation (Levine et al., 2009). For example, recovery could mean a complete recovery in that the effected individual could regain their previously lost function. The term can also be used to indicate that the individual has seen some marked degree of improvement of the lost function. Most neuroscientists argue that true recovery is never possible because once neural tissue is damaged it does not completely recover to its original morphology and function, hence any improvements would be compensational in nature. In spite of this, other therapists believe that functional improvements, in any case, are representative of recovery of function since the patients can now perform tasks they were previously unable to perform (Warrach & Kleim, 2010). The key challenge in the cognitive rehabilitation literature arises when functional recovery is

often used without making a distinction between recovery at a neural level or at a behavioural level.

In conclusion, although neuroscience has flourished in the last few decades and has demonstrated that the CNS is capable of structurally and functionally adapting in response to learning and injury. Neuroscience is far from restoring brain tissue to place new neurons in damaged brain circuits to restore its function. Instead, neuroscientists recognize that the rules governing how the brain processes information may help with how the damaged brain adapts to injury. Following this logic, it is possible that brain plasticity can be used to induce functional reorganization in the cognitively impaired brain as a result of HIV damage.

## **1.7 *Biological Substrate of HIV***

In order to understand why cognitive rehabilitation is necessary to reverse HIV-associated cognitive impairment it is important to understand the microbiological profile of HIV and how the virus affects the immune system and CNS. In section 1.6.1, I will discuss the epidemiology of HIV which will focus on the causes, subtypes and routes of transmission of HIV; in section 1.6.2, I will discuss the microbiological profile of HIV and how the virus affects the immune system and CNS; and lastly, in section 1.6.3, I will introduce the emerging discourses around HIV and ARVs and discuss the limitations of ARVs. I will conclude that the CNS acts as a viral reservoir for HIV, which ARVs cannot easily eradicate and which therefore, causes cognitive decline.

### **1.7.1 *Epidemiology of HIV***

The insidious medical effects caused by a number of viral infections have been well documented throughout history and these include amongst Cholera; Malaria; Avian influenza, Severe Acute Respiratory Syndrome, and more recently, Ebola. HIV has burgeoned to pandemic status having infected millions of people across the globe. HIV is a health threat of global proportions which poses significant challenges to child and adolescent

psychology. This section outlines the HIV statistics in South Africa and extent of the HIV/AIDS epidemic in South Africa.

HIV remains one of the world's most serious health challenges (Joint United Nations Programme on HIV/AIDS [UNAIDS], 2012). Globally, 34.0 million people were living with HIV at the end of 2011 (UNAIDS, 2012). It is estimated that around 0.8% of adults between the ages of 15-49 years of age worldwide are living with HIV. Of this population, Sub-Saharan Africa remains the most severely affected region, with nearly 1 in every 20 adults (4.9%) living with HIV, which accounts for 69% of people living with HIV across the globe (UNAIDS, 2012). In spite of the above statistics, Sub-Saharan Africa has had steep declines in the number of people acquiring HIV. New HIV infections have fallen by 33% since 2001. Worldwide the number of people acquiring HIV in 2012 was 2.3 million (1.9 million-2.7 million) down from 3.4 million (3.1 million-3.7 million) in 2001. As such, new infections have declined by 52% since 2001 (UNAIDS, 2012).

Worldwide 260 000 (230 000-320 000) children became newly infected with HIV in 2012 which came down from 550 000 (500 000-620 000) in 2001 (UNAIDS, 2012). However, Sub-Saharan Africa still accounted for 71% of newly infected children in 2011. The number of adults and children living with HIV in sub-Saharan Africa in 2011 was 23.5 million and the number of newly infected adults and children with HIV in 2011 was 1.8 million (UNAIDS, 2012). Recent statistics from 2012 reveal a similar trend, in that there are estimated to be 5.58 million people living with HIV in South Africa, which accounts for 11% of the population (South African Institute of Race Relations [SAIRR], 2012). According to the South African Institute of Race Relations survey, five million (89%) were adults aged 20-64, and 2.93 million (53%) are women of a child bearing age between the ages of 15-24 years of age. The youth between the ages of 15-24 years accounted for 731 000 (13%) and children under the age of 14 years accounted for 454 000 (8%) of HIV/AIDS infections (SAIRR, 2012).

### ***1.7.1.1 HIV Subtypes***

There are two distinct types of HIV that have been identified and these are named HIV-1 and HIV-2 (Gao et al., 1999). The acquired immunodeficiency syndrome (AIDS) is the result of HIV-1 which is the predominant form that is found throughout the world and is categorized into three distinct groups: M (major), O (outlier), and N (non M/non O, new) (Requejo, 2006). The M, N and O viruses are members of the lentivirus lineage which also includes the simian immunodeficiency virus strains which is able to infect non-human primates (Requejo, 2006). In the lentivirus lineage groups M and N are more closely related than group O, which is distant from the other strains (Gao et al., 1999). It is believed that group M has spread worldwide and is the cause of the global AIDS pandemic, this group is further divided into different 11 subtypes named A through to K (Gao et al., 1999; Requejo, 2006). The 11 subtypes of group M are geographically distinct, and predominate in North America whereas clade B predominates in Europe (Requejo, 2006). It is believed that clade C is linked to an estimated 50% of infections around the world and is ubiquitous in South Africa with 90% of South Africans being infected with this clade (Liner, Hall, & Robertson, 2007; Shankar et al., 2005; Singh et al., 2010). HIV-2 is also classified into five subtypes which are named from A to E, these are all equidistant from each other (Yamaguchi et al., 2004).

### ***1.7.1.2 Transmission of HIV***

In adults the main route of transmission of HIV-1 is predominantly through heterosexual coital transmission. More insidiously, around 33% of the people currently affected by HIV/AIDS are aged between 15-24 years of age, and are unaware of their status, which has resulted in a high seroprevalence rates among women (UNAIDS, 2012).

Among children, vertical transmission of HIV is the primary routes of transmission in which infants become infected with the virus (UNAIDS, 2012). Vertical infection occurs when HIV

is transmitted from mother to child when HIV crosses the placenta (Coutsoudis et al., 2004). This in utero transmission usually occurs between the second and the third trimester of pregnancy (Chakraborty, 2008). Of great concern is that, in utero transmission may be associated with accelerated disease progression in infected infants (Chakraborty, 2008). Intrapartum transmission can also occur through maternofetal transfusion, through infected blood or vaginal fluids during labour or delivery or contact of the infant's skin or mucous membranes with the infected blood or maternal secretions during infancy (Chakraborty, 2008). HIV is also present in breast milk and can be vertically transmitted through breast feeding which involves frequent exposure of infants' oral and gastrointestinal tracts to infected milk (Chakraborty, 2008). In a randomized trial undertaken in Kenya, breastfeeding versus formula feeding showed that 44% of transmission of HIV was the result of breast milk transmission (Coutsoudis et al., 2004). Furthermore, a meta-analysis of nine trials showed a cumulative risk for breast feeding which remains constant from 1-18 months of age (Coutsoudis et al., 2004).

### ***1.7.1.3 Mother to Child Infection and HIV Progression***

Vertically infected children with HIV have accelerated disease progression as the paediatric CNS is still developing and contains less differentiated cell types (Chakraborty, 2008). The reason for this accelerated progress in children has been explained as the result of a) a higher viral load of HIV in the blood (i.e., the measure of severity of an infection), b) an active thymus with a larger pool of cells which are susceptible to HIV infection, c) immature CNS during infancy (Hilburn, Potterton, & Stewart, 2010), d) human leukocyte antigen class sharing between mother and infant (i.e., white blood cells with the same genetic markers) and lastly e) cluster of Differentiation 4 T cells (CD4+) with an impaired functional phenotype that are unable to process pathogens effectively (Chakraborty, 2008). From the above, most noteworthy is that CD4+ T cells arise from the immune systems production of new cells in the bone marrow and are activated to generate an immune response to newly encountered diseases. Once a disease has been eliminated from the immune system, a portion of the T cell population give rise to a reservoir of memory cells, which then respond to a recurrence of the disease (Cichocki, 2011).

In this respect, HIV related symptoms and CD4+ T cell depletion, occurs in most untreated children within the first few years of life (Chakraborty, 2008). As a result of the above process, children infected through vertical transmission are more likely to suffer severe neurodevelopmental problems in infancy as this is a significant period of brain development compared with those infected later in life (Willen, 2006). In terms of brain development, the most rapid brain growth occurs in the first four years of life; therefore HIV infection that occurs later in childhood, is less likely associated with the major neurocognitive impairment seen among vertically infected infants (Hilburn et al., 2010).

In spite of the above disease progression, the risk for vertical transmission can be greatly reduced by the use of ARVs (Barron et al., 2013). South Africa has made great strides in the prevention of mother-to-child transmission since its inception in 2002 (Barron et al., 2013). Despite the success of the prevention of mother-to-child transmission programme in South Africa, a number of challenges still persist and these include a) the cost of antiretroviral medications b) lack of adherence to medication c) limited access to ARVs, d) confusing government and media messages regarding ARV therapy and e) socio-cultural issues around the beliefs of disease and causes of HIV which have made the treatment of HIV difficult (Joska, Hoare, Stein, & Flisher, 2011).

The previous section discussed the route of HIV transmission. In the subsequent section, the discussion will be largely based on the microbiological profile of HIV and how the virus affects the CNS.

### **1.7.2 Microbiology of HIV infection**

HIV is a retrovirus in that it needs cells from a host in order to make more copies of itself and is different from other infectious diseases by its systematic attack on CD4 T cells (Cichocki, 2011). CD4 T cells are used as a vital defence by the body to protect it from viruses (Belman

et al., 1988). Two major types T cells have been identified: (1) CD4 (helper) and (2) CD8 cells (suppressor).

HIV uses CD4 cells as a host cells that help HIV replicate (Cichocki, 2011). CD4 cells initiate the body's response to infectious disease. When HIV attaches to CD4 cells, these cells become damaged and depleted, possibly through an initial depletion of memory T-cells (Cichocki, 2011). It is through the depletion of these cells that leads to progressive immune deficiency, which results in a compromised immune system to fight the HIV virus, leading to opportunistic infections and illness (McArthur, Brew, & Nath, 2005). After the HIV provirus attaches to the host-cell genome (CD4 T cells), it can remain latent for many years without causing cellular damage (McArthur, Steiner, Sacktor, & Nath, 2010). However, when cell activation occurs, this produces retroviruses (RNA) (McArthur et al., 2005). Plasma HIV RNA level (viral load) is an indicator of the number of copies of HIV in the blood. Moreover, CD4 cell count and plasma HIV RNA viral load are important predictors of the sequela of HIV disease progression.

In the case of HIV, fewer CD4 cells account for a weaker immune system, therefore, HIV attacks and concomitantly weakens the infected person's immune system thereby making the person more vulnerable to illness and infections (Burns, Hernandez-Reif, & Jessee, 2008). The stages of HIV infection are widely understood to progress in a progressive pattern: a) Firstly, once an individual has been exposed to the virus, the subject will display flu-like symptoms such as fever, headache, sore throat, rash and diarrhoea (National Institute of Allergy and Infectious Diseases [NIAID], 2006). Once the HIV virus progresses, the second stage leads to a decrease of CD4 T cells resulting in a weakened immune system (NIAID, 2006). As the body of the infected individual becomes weak and fragile, the body becomes unable to fight off infections which results in AIDS (Burns et al., 2008).

Within the paediatric population, the HIV RNA retrovirus replicate at an exponential rate in which infected blood circulates the organs and lymph nodes of the infected child leading the

CNS to become entrenched with the HIV virus (Burns et al. 2008). To counteract the effects of viral RNA replication, antibodies are produced to reduce the levels of HIV (Burns et al. 2008). A review of the literature shows that the progression of HIV to AIDS in children occurs in four stages: 1) at stage one the virus occurs when the child's symptomatology displays 0-1 symptoms of the infection; 2) stage two is known as a mildly symptomatic category whereby the child displays two or more symptoms such as infections, skin infections, or infections in the liver or spleen; 3) stage three occurs when moderate symptoms of HIV appear such as prolonged fever, fatigue, diarrhoea, pneumonia or mouth and skin disorders, although at this stage, the child may not have developed any life threatening infections that can be characterized as AIDS (Burns et al., 2008).

AIDS usually develops when the child becomes vulnerable to opportunistic infections, this usually occurs for children under the age of 5 when the CD4+ cells fall below 500 per cubic millimetre of blood (Burns et al., 2008). When the child reaches this last stage (stage 4) of AIDS the individual's health will become depleted and the child is vulnerable to opportunistic infections (Burns et al., 2008). The AIDS stage ostensibly occurs during immunosuppression, the disease at this stage is defined by infections in the brain such as neurological conditions, infections in the eyes, infection on the vital body organs and cancers (NIAD, 2006).

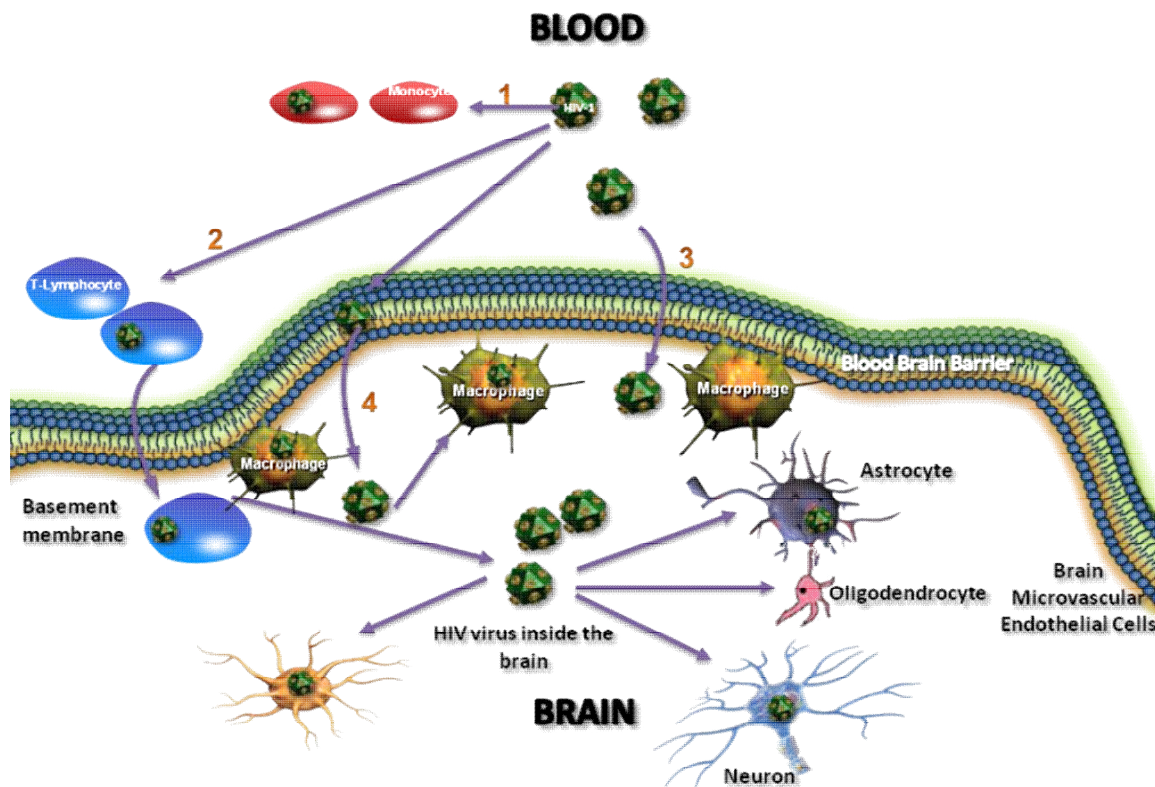
#### ***1.7.2.1 HIV and the Central Nervous System***

I will now move on to briefly discuss the effect of HIV on the CNS. Studies have identified dysfunction at the CNS as invariably the route by which HIV affects motor and cognitive development (McArthur & Brew, 2010). HIV-associated neurocognitive impairment is characterized by synaptodendritic injury; this injury disrupts the integrated functioning of neural systems, which are required to process information, thereby leading to HIV-associated neurocognitive disorders (Ellis, Calero, & Stockin, 2009). Therefore, HIV causes damage to many different neural pathways, such as the structure of white matter and the functioning of

the fronto-striatal-thalamo-cortical neural circuitry (Ellis et al., 2009; Thompson et al., 2005; Woods, Moore, Weber, & Grant, 2009).

HIV is understood to enter the brain and to do this it must cross the BBB (Buckner, Luers, Calderon, Eugenin, & Berman, 2006; Eugenin, Gaskill, & Berman, 2009). The CNS is separated from the rest of the body by the BBB. The BBB is a selectively permeable, continuous cellular layer that is made up of brain microvascular endothelial cells linked to each other by tight junctions, which regulate the entry of substances from the bloodstream to the CNS (González-Scarano & Martín-García, 2005). The BBB provides anatomical and physiological protection for the CNS. More importantly, it separates the brain and spinal cord from circulating blood and restricts the entry of harmful substances like bacteria and viruses into the CNS (González-Scarano & Martín-García, 2005; McArthur et al., 2005). Therefore, cells that cross the BBB are carefully regulated as not to affect the CNS. Besides this protective layer, HIV has been shown to bridge the BBB and enter in cells that are trafficking nutrients to the brain, this phenomenon is known as the Trojan horse hypothesis (Haase, 1968).

According to the Trojan horse hypothesis, HIV is carried across the BBB by infected monocytes, which differentiate into macrophages (Clay et al., 2007). Cell free viruses can also enter the CNS by infecting endothelial cells of the BBB (Argyris et al., 2003). Macrophages infect other cells in the CNS like microglia and astrocytes by direct contact (Rackstraw, 2011). Microglia and macrophages become cellular reservoirs for further replication within the CNS (Gonzalez-Scarano & Martin-Garcia, 2005; McArthur, 2005). This lends credence to the idea that the CNS is a sanctuary site for viral replication. For HIV, which infects several types of CD4 + cells such as monocytes, the Trojan horse hypothesis is most intuitively appealing and is generally accepted. (Please See Figure 1.1). The subsequent section will now move on to discuss these different cells affected by HIV in more detail.



*Figure 1.1* The Trojan Horse Effect and the Blood Brain Barrier (Shailendra, Saxena, Tiwari, & Nair, 2013). 1) HIV is carried across the BBB by infected monocytes, which differentiate into macrophages, 2) CD4<sup>+</sup> T cells can be infected and, 3) Another probable cause is the direct entry of HIV through the BBB into the brain, 4) Entry of HIV through endothelial cells can pose another threat of HIV infection in the brain. The infection of astrocytes is limited and whether neurons and oligodendrocytes are infected is still unclear (Shailendra et al., 2013).

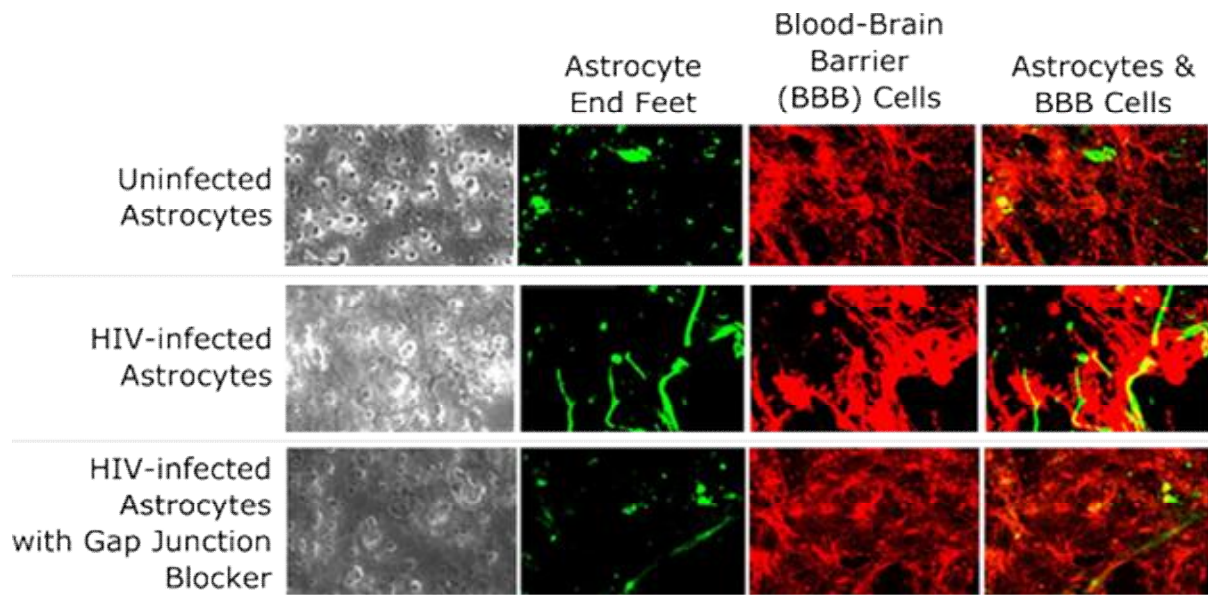
### **1.7.2.2 Cells implicated in HIV neuroinvasion**

HIV is a highly neurotropic virus and is able to gain entry and infiltrate the CNS (Hult, Chana, Masliah, & Everall, 2008). This, according to McArthur (2005) leads HIV to directly induce distinct neurological syndromes like that of HIV-associated neurocognitive disorders (HAND). Due to HIV crossing the BBB and entering the brain early in the course of

infection, there are a number of key cells that are affected and these include: macrophages, astrocytes, neurons, and oligodendrocytes. These white and gray cells will in turn be briefly discussed.

Microglia and brain macrophages constitute the resident cells of the brain (Shaked, Porat, Gersner, Kipnis, & Schwartz, 2004). Macrophages and their precursors, monocytes, are critical effectors of inflammation thereby providing a supporting structure of the CNS to defend the brain from injuries caused by disease (Geissmann, Manz, Jung, Sieweke, & Ley, 2011; Shaked et al., 2004). More importantly, it is believed that damage to microglia cells and monocytes/macrophages as a result of HIV infection is directly linked to neurocognitive decline in children as well as in adults (Koekkoek et al., 2008).

Unlike microglia which expresses the CD4 co-receptor HIV needs in order to replicate, the mechanism of HIV entry into astrocytes is unknown since astrocytes do not express CD4 cells (Iglesias-ussel & Romero, 2011). However, it has been suggested that the mannose receptor which is found on the surface of macrophages and dendritic cells may serve as a CD4 co-receptor (Liu et al., 2004). Astrocytes are support cells in the brain and are found in abundance throughout the CNS. These cells are thought to be responsible for maintaining homeostasis in the CNS and establishing as well as maintaining CNS boundaries like the BBB (Eugenin, Clements, Zink, & Berman, 2011; González-Scarano & Martín-García, 2005; McArthur et al., 2005). For example, astrocytes help maintain the BBB through their "end feet" thereby interacting with structural components of the BBB (Eugenin et al. 2011). It is believed that only a small fraction of astrocytes become infected with HIV. In vitro research shows that when astrocytes become infected the BBB structure weakens and becomes more permeable thereby disrupting its function by developing abnormal foot connections which resulted in necrosis of uninfected cells on the other side of the filter (Please see Figure 1.2) (Eugenin et al., 2011). This disruption of the BBB may be responsible for neurological disorders experienced by 40-60% of people infected with HIV (Eugenin et al., 2011). In terms of the paediatric population, astrocytes may be more susceptible to viral infection as the CNS is still developing (Tornatore, Chandra, Berger, & Major, 1994).



*Figure 1.2* Microscopic view of HIV-infected and uninfected astrocytes. The middle row shows a staining technique which demonstrates how HIV interferes with the development of astrocyte end feet (green), disrupts the growth of cells in the BBB (red), and shows abnormal connections between astrocytes and the BBB (yellow and red) (Eugenin et al., 2011).

Neurons are the main effectors of cognitive and motor functioning and empirical evidence has supported the finding that there is significant neuronal cell death in HIV infected brains (Petito & Roberts, 1995). However, neurons do not express CD4 (Gonzalez-Scarano & Martin-Garcia, 2005; McArthur, 2005). This has led researchers to conclude that the virus does not directly infect neurons. However, it may cause damage to neural tissue either through direct means (e.g., viral proteins) or through indirect means by inflammation (Hult et al., 2008), which can result in damage to a variety of neural systems. Different subsets of neurons and astrocytes express some of the chemokine receptors that are co-receptors for HIV infection (Asensio & Campbell, 1999; Meucci et al., 1998; van der Meer, Ulrich, González-Scarano, & Lavi, 2000). The possibility of neuronal infection would be an important factor in HIV neuropathology and infected neurons, like that of astrocytes, may provide reservoirs for the virus, as neurons are the main effectors of cognitive and motor function (Gonzalez-Scarano & Martin-Garcia, 2005).

In the brain, oligodendrocytes are a type of white matter cell with their main functions to provide structural support to neurons. Oligodendrocytes also play a role in producing myelin sheath which insulates axons for the purpose of protection and promotes fast axonal conduction of nerve impulses (Gonzalez-Scarano & Martin-Garcia, 2005; McArthur, 2005). The mechanism in which HIV gains entry into oligodendrocytes is still unknown as they do not express CD4 co-receptors (Kramer-Hämmerle, Rothenaigner, Wolff, Bell, & Brack-Werner, 2005). Therefore, it is believed that oligodendrocytes are believed to be minimally involved in HIV-related cognitive decline (Kramer-Hammerle et al. 2005). However, they express high levels of galactosyl ceramide (i.e., myelin components and play a role in myelin function) which may mediate HIV infection of astrocytes (Harouse et al., 1991).

The previous section dealt with how HIV transmigrates across the BBB and infects resident cells in the CNS. In the subsequent section, I will introduce the use of ARV therapy to treat HIV and outline some complications that arise from its use.

### **1.7.3 Emerging Discourses on the Limitations of ARVs**

Despite the effectiveness of ARV regimes in prolonging survival, HIV-associated neurocognitive decline still occurs in an estimate of 30-50% of people (Heaton et al., 2010). However, the majority of cases of HIV-associated neurocognitive decline are less severe in the ARV era, with a mild-to-moderate and clinically relevant neurocognitive dysfunction (Heaton et al., 2010). The causes of milder forms of HAND in the ARV era are not well understood. A number of hypothesis have been put forward as to why ARVs are ineffective in reducing cognitive decline. Potential factors may include CNS viral reservoirs and neurotoxicity of ARVs.

#### ***1.7.3.1 Viral Reservoirs***

ARVs are effective in managing HIV by controlling viral replication and restoring immune functioning (CDC, 2010). However, the complete eradication of HIV is currently impossible.

One of the major obstacles in treating HIV is the ability of the CNS to function as a viral reservoir and for the virus to remain latent in subpopulations of infected cells which can persist for long periods of time despite ARV therapy (Iglesias-ussel & Romerio, 2011). Latent reservoirs consist of cells harbouring latent proviruses (i.e., a copy of the HIV genome) which persist in CD4<sup>+</sup> T cells and monocytes. These latently infected cells represent a stable reservoir for HIV and transcribe HIV at low levels and produce transcripts which stay in the nucleus of cells (Lassen, Ramyar, Bailey, Zhou, & Siliciano, 2006). HIV that is present in a subpopulation of infected cells can persist for long periods of time in the CNS, and can re-emerge after a period of immunosuppression despite ARV therapy. (Blankson, Persaud, & Siliciano, 2002; Iglesias-ussel & Romerio, 2011; Lassen et al., 2006). Therefore, it follows that HIV which is present in these latent reservoirs is a barrier to viral eradication and can escape immune surveillance (Lassen et al., 2006).

The above constitutes a major hurdle in treating HIV since ARVs do not eradicate HIV despite intensified treatment. This is because current ARVs main purpose is to interfere with the generation of new virions (HIV RNA), but do not eliminate the virus from already infected cells in the CNS. Research suggests that in most patients on ARVs, CD4<sup>+</sup> T cells decay very slowly, with an approximate half-life of three years (Chun et al., 1997). In terms of the approximate figure of cells in the latent reservoir which is believed to be  $10^6$ , it would take 73 years of ARV treatment to eliminate these latent cells (Siliciano & Siliciano, 2000).

### ***1.7.3.2 Neurotoxicity***

Recent studies have suggested that ARV therapy may have neurotoxic effects that may have an adverse effect on neurocognitive functioning. In a longitudinal observational study inclusive of 101 patients with advanced HIV disease, stronger ARV regimes with a high CNS penetration-effectiveness score of 2.0 were found to be associated with having an undetectable cerebrospinal fluid viral load (Marra et al., 2009). However, this was also associated with poorer neurocognitive performance which points to ARVs neurotoxicity in

the CNS leading to compromised brain functioning (Marra et al., 2009). In another study, Robertson et al (2010) found that HIV+ participants who discontinued their ARV regimes showed improved cognitive functioning. The authors point to ARVs neurotoxic side effects on cognition.

Similarly, in a Ugandan study conducted by Sacktor et al. (2009), it was found that HIV+ participants who started ARV therapy improved on verbal memory, motor and psychomotor speed and executive functioning. In spite of these improvements, it was found that, peripheral neurotoxicity occurred in 30 of the participants, presumably due to the ARV stavudine (Sacktor et al., 2009). It has been evidenced that patients taking stavudine and didanosine had decreases in frontal white matter compared to HIV- controls (Schweinsburg et al., 2005). In another study, it was found that ARVs affected the function of dendritic cells, T-cells and the differentiation of a variety of cells (Piccinini, Rinaudo, Anselmino, Buccinnà, & Ramondetti, 2005). These findings suggest that certain ARV regimes may have neurotoxic effects on cellular functioning and subsequent CNS and cognitive functioning.

In conclusion, there are major debates emerging from the literature surrounding HIV, ARVs, and neurocognitive functioning. Major debates include a) whether ARV treatment will protect the CNS over the long term (McPhail & Robertson, 2011), b), whether stronger ARV regimes will offer neuropsychological protection for children (Van Rie et al., 2007), and c) whether stronger ARV regimes that offer better CNS penetration may cause neurotoxicity remains an open question. Till this point, the thesis has discussed the material and biological nature of HIV and the conflicting nature of ARVs and their role in cognition. The subsequent sections discuss the nomenclature of HAND which persists in the era of ARV therapies. After this section, the thesis discusses the neuropsychology of HIV in children. Once this has been discussed, the aspect of attention and HIV will be further explored, the key focus of this thesis.

## **1.8 Nomenclature of HIV-associated neurocognitive disorders**

The previous sections discussed the biological profile of HIV and how it invades the resident cells in the CNS and causes neurocognitive decline. ARVs work by controlling the replication process of HIV; however, the physiological characteristics of the CNS allow the HIV virus to harbour a reservoir of viral replication which causes neurocognitive damage. This has meant that HIV-associated neurocognitive decline continues to persist in the face of ARV therapy.

Terms to define HIV associated neurocognitive impairment prior to ARV therapy included: HIV Dementia, AIDS dementia complex, HIV associated cognitive motor complex, and AIDS related Dementia to explain neurocognitive impairment (Singh, 2012). Different terms have been used to describe HIV-associated neurocognitive impairment in the ARV era. Any significant neurocognitive impairment is described under the umbrella term HAND. This is an umbrella term, which describes a spectrum of neurocognitive impairment seen in HIV such as ANI, MND, and HAD and HIV encephalopathy. The above distinctions of HIV neurocognitive decline will now be discussed in turn.

### **1.8.1 Clinical features of HIV-associated Neurocognitive disorders**

HIV has been shown to directly invade the brain and cause several neurological disorders collectively known as HAND (Joska et al., 2011). The adult literature on HIV-related neurocognitive impairment supports a spectrum of progressively more severe cognitive disorders caused by HIV known as HAND. The HAND criteria provide clinical support as they allow for a spectrum of functional impairment which is helpful for ARV management plans for individuals with HIV-associated neurocognitive impairment (Hoare et al., 2014). A group of clinicians formed by the National Institutes of Health updated the research nosology taking into account the advances in ARV therapy. The outcome of the National Institutes of Health meeting was a new case definition of HAND (Antinori et al., 2007).

Three broad subdivisions were included to represent HAND, which are based on criteria depending on the degree of cognitive impairment and associated changes in everyday functioning. HAND allows for three diagnostic categories: ANI; MND; and HAD (Antinori et al., 2007). The ANI, MND, and HAD categories are used when an individual's performance on a range of neuropsychological tests falls below age and education defined norms in at least two domains of function (Antinori et al., 2007). The diagnosis of all three forms of HAND requires that neurocognitive impairment cannot be explained by a co-morbid condition, and that the cognitive impairment is caused, with the greatest likelihood by HIV infection. The diagnosis of HAND is predicated on assessing at least five areas of neurocognitive functioning that are known to be affected by HIV infection: verbal/language, attention/working memory, abstraction/executive, memory (learning and recall), and speed of information processing, sensory-perceptual, and motor skills (Antinori et al., 2007).

HAND remains prevalent in the ARV era, it is claimed that up to 50% of HAND cases have been reported (Grant, 2008). The epidemiology of HAND in the era of ARV therapy was represented in the CNS HIV Antiretroviral Therapy Effects Research project study during the years 2003-2007 (Heaton et al., 2010). The results come from a battery of comprehensive neuropsychological evaluations on a cohort of 1 500 HIV+ individuals from the United States. Results from this study revealed that over 45% of the cohort was found to have a HAND diagnosis, with about half of these fulfilling the diagnosis of ANI. ANI is the mildest form of HAND. It is a new pathological entity that is characterized by asymptomatic or unrecognized impairment. ANI represents the majority of HAND cases (Heaton et al., 2010).

#### ***1.8.1.1 Asymptomatic Neurocognitive Impairment***

ANI refers to slowing in mental skills and a loss of concentration that is quantified as less than one standard deviation below the mean in at least two cognitive areas among at least five domains, but without any apparent changes in everyday functioning (Woods et al., 2009). ANI has become a controversial entity in that it does not require the presence of everyday functional decline like that of MND and HAD (Gisslén, Price, & Nilsson, 2011).

Therefore, the clinical outcomes of ANI have yet to be defined. From a clinical point of view it is important to note that being 'asymptomatic' is not a disease since there is no biological substrate as yet attached to the entity (Torti, Focà, Cesana, & Lescure, 2011).

Gisslen et al. (2011), claim that there is an overestimation of the problem since patients are being classified as cognitively impaired without any real impact on everyday functioning. This may cause HIV+ individuals to worry unnecessarily in light of no reported symptoms and functional impairment and few treatment options (Gisslen et al., 2011). However, Heaton et al. (2010) believes that an ANI diagnosis may identify individuals who are unaware of impairment and thus are at risk for neurocognitive decline. In recent study, Blackstone et al. (2012) measured functional decline with a performance based measure and via self-reports. Individuals who were classified as functionally impaired by the performance based measure were more likely to be unemployed than those who were defined as functionally impaired by self-report (Blackstone et al., 2012). Interestingly, in this study self-reports classified more participants as having neurocognitive impairment, however, with the performance based measure only a small portion of the sample were classified as impaired (Blackstone et al., 2012). This raises questions about meta-cognition and how much insight an individual may have regarding their cognitive functioning. In the case of cognitive impairment, self-reports may limit the validity of the test. It may be premature to treat ANI as a real entity as there is no set biological substrate that is clearly established in this case ANI might be more theoretical than pathological.

### ***1.8.1.2 Mild Neurocognitive Impairment***

The CNS HIV Antiretroviral Therapy Effects Research project classified 180 (12%) fulfilled the diagnosis of MND (Heaton et al., 2010). MND requires mild to moderate neurocognitive impairment and is defined as acquired impairment in two or more of the cognitive domains, and with marked impairments in activities in daily living (Antinori et al., 2009). The neurocognitive impairment needs to represent at least one standard deviation below the mean. A diagnosis of MND is satisfied when two or more of the following criteria are met and

which are not attributable to a co-morbid condition: 1) the patient or informant report declines in at least two instrumental activities of daily living (e.g., financial management, social functioning or dressing); 2) unemployment or a significant reduction in job responsibilities secondary to reduced cognitive abilities; 3) decline in vocational functioning (e.g., increased errors, decreased productivity); 4) patient or an informant report of increased problems in at least two cognitive ability areas in day to day functioning (this criterion cannot be used if based on self-report of the individual with depression, as this may increase the likelihood of a biased self-report); 5) scores that are one standard deviation below the mean on a performance-based laboratory of everyday functioning (e.g., medication management) (Antinori et al., 2007).

### ***1.8.1.3 HIV-Associated Dementia***

In the CNS HIV Antiretroviral Therapy Effects Research project study, HAD was diagnosed in 2% of participants fulfilling this definition (Heaton et al., 2010). HAD represents the most severe form of HAND, with significant functional impairments, and is synonymous with HIV encephalopathy and AIDS dementia complex. HAD is characterised by a severe cognitive impairment ascertained by neuropsychological testing outcomes that are less than two standard deviations below demographically related means in at least two cognitive domains, and a decline in everyday functioning that is not attributable to a co-morbid condition such as delirium (Antinori et al., 2007).

According to this definition, two of the following functional impairments are required to satisfy a diagnosis of HAD: 1) unemployment due to cognitive impairment; 2) patient or an informant reporting dependence in two areas of daily living that are related to cognitive problems; 3) patient or informant report of declines in at least four cognitive areas of daily living (this criterion can only be satisfied if based exclusively of a self-report in the absence of depression); 4) performance at least two standard deviations below the mean on a performance based laboratory measure of everyday functioning (or one standard deviation below the mean of two functional tests) (Woods et al., 2009; Antinori et al., 2007). Like that

of MND, HAD diagnosis requires that everyday functioning is only attributable to HIV, in this instance determination that the neurocognitive impairment cannot be explained by a co-morbid condition is required in order to make a diagnosis of HAND.

In a recent study examining HAND in a sample of 536 HIV+ patients, between the ages 18-65; attending a primary health care facility in South Africa. HAND was found in 23.5% of the sample. Age exerted a significant effect on neurocognitive impairment, whereby older participants demonstrated significantly higher levels of HAND than younger participants. It may be that people who have been living with HIV for a longer period of time have been exposed to the neurotoxic effects for a longer period which make them more susceptible to cognitive impairment. For example, advanced age is a known risk factor for dementia (Hietanen & Teravainen, 1988). HAND is also present in other parts of the world. Studies conducted in other parts of the developing world reveal a similar trend. In Uganda 31% of individuals met the criteria for HAD (Wong et al., 2004), while in India it was found that 51% of individuals showed significant neuropsychological impairment in at least two cognitive domains of function (Yepthomi et al., 2006).

At a critical level, the above classification system of HAND, are based on neuropsychological test performance and everyday functioning abilities, which is a complicated area of investigation. Consequently, a diagnosis of HAND rests on the presence or the absence of declines in everyday functioning abilities. Assessing everyday functioning is plagued by many complications, as such there are currently no agreed upon measures of everyday functioning (Morgan & Heaton, 2009). Assessments of everyday functioning are usually based on questionnaires and the patient's level of insight through self-reports to make a judgement on their condition. Self-reports are likely influenced by a host of factors like co-morbid conditions, meta-cognition (i.e., degree of insight) and the degree of objectivity one can have in assessing the complexity of everyday activities.

Excluding co-morbidities is a challenge since most HIV+ individuals around the world have co-morbidities (Robertson, Liner, & Heaton, 2009). In developing regions like sub-Saharan Africa the prevalence of tuberculosis, malaria, malnutrition and Hepatitis C may preclude the direct affects of HIV on the nervous system (Robertson et al., 2009). More importantly, is that symptoms may also be under-reported due to direct disease variables on cognition. Memory loss may be a significant factor in HIV, in which case an individual may be unaware of a decline in functional day-to-day activities (Woods et al., 2009). This section focused on the adult literature on HIV-associated neurocognitive impairment, which supports a spectrum of HAND. The next section will focus on learning disabilities in children which can result from neurologic, environmental and behavioural disturbances. However, none are more devastating than the effects of HIV on children's learning abilities. HIV encephalopathy is one of the most serious and developmentally devastating disease indicators of paediatric HIV. This section will briefly discuss the definitions and classifications in HIV+ children.

### **1.8.2 Encephalopathy**

In adults HIV attacks the mature CNS and results in dementia. In children, HIV impacts on the immature and developing brain resulting in progressive encephalopathy, a severe form of HIV-associated disease (Smith, Colleen, & Eley, 2008). HIV encephalopathy is a term used to describe cognitive impairment that occurs in advanced disease stage, at a CD4 cell count less than 200 cubic millimetres and is an AIDS defining illness (Singh, 2012). Encephalopathy is defined as a failure to a) attain neurodevelopmental milestones (motor, mental and language), or b) a loss of intellectual ability, and c) severe motor defects such as hyperreflexia, paresis, ataxia and gait disturbance (Belman et al., 1988; Tindyebwa et al., 2004). Another characteristic of paediatric HIV, is that CNS dysfunction in children occurs before there is significant immunosuppression (Cooper et al., 1998; Lobato, Caldwell, Ng, & Oxtoby, 1995; Tardieu et al., 1995). This is the first AIDS-defining illness in 18% of the paediatric population (Gabuzda & Hirsch, 1987).

Medical science has further conceptualized HIV encephalopathy into different patterns of presentation and severity. Several patterns of encephalopathy have been suggested with regard to HIV encephalopathy and these are namely: (1) a sub-acute progressive course (most severe); (2) plateau progressive encephalopathy (followed by deterioration or improvement) and; (3) static encephalopathy (Armstrong et al., 1993; Belman et al., 1988).

Sub-acute progressive encephalopathy is characterized by a gradual loss of previously obtained developmental milestones. Within this stage, children can remain stable for an extended period of time before a new loss of developmental milestones is experienced (Armstrong et al., 1993). The plateau progressive encephalopathy stage involves children who do not progress in their cognitive development, but may not show deterioration for periods of time. However, these children eventually deteriorate in terms of cognitive functioning and lose previously acquired skills. The result of this is that such children experience deleterious cognitive and motor impairment. Cognitive dysfunction in these children has been associated with cortical and subcortical brain regions that may be affected as a result of HIV neural infection (Armstrong et al., 1993). Lastly, static encephalopathy has been identified in children vertically infected with HIV, and involves no deterioration of attained milestones. This stage is characterized by delayed developmental goals such as the acquisition of new skills at a slower rate than is expected for a specific age group. Furthermore, there is a subset of children that display mild neurocognitive deficits, and a group with average intellectual functioning who have specific learning problems, language and visual-motor problems (Armstrong et al., 1993).

The definitive diagnosis for HIV encephalopathy is determined by a number of tools such as brain computed tomography scans and cognitive tests (World Health Organisation, 2006). The neuroradiological signs of plateau progressive encephalopathy include cortical atrophy, basal ganglia calcifications on computer tomography scans, white matter lesions, and central atrophy on magnetic resonance imaging (DeCarli, Civitello, Brouwers, & Pizzo, 1993). These neuroradiological abnormalities are associated with an advanced disease stage and precede clinical manifestations (Czornyj, 2006).

The previous section discussed the nomenclature of HAND in the era of ARV therapies, the next section will now move on to discuss the neuropsychological profile of HAND that is evidenced in children.

## ***1.9 Neuropsychological profile of HIV-associated neurocognitive disorders in children***

In order to diagnose HAND it is necessary to understand the affected brain systems and cognitive profile of HAND seen in children. The regions of the brain most commonly damaged are the deep white matter, basal ganglia, hippocampus and cerebral cortex (Dawes et al., 2008; Ghafouri, Amini, Khalili, & Sawaya, 2006; Schiller, Foley, Burns, Sellers, & Golden, 2009; Woods et al., 2009). The above subcortical pattern is consistent with further neuroimaging evidence of fronto-striatal-thalamo-cortical damage as a result of HIV (Dawes et al., 2008; Thompson et al., 2005; Woods et al., 2009). In the HIV+ paediatric population, developmental deficits include a) information processing (Koekkoek et al., 2008; Tse et al., 2004), b) motor skills, learning, and memory (Ruel et al., 2012; Smith et al., 2008), c) executive functions, visuo-perception, language, visuo-spatial integration and attention (Hoare et al., 2012; Wolters, Brouwers, Civitello, & Moss, 1997). The subsequent sections will briefly review the neuropsychological profile of paediatric HIV in an effort to arrive at the key focus of the thesis: the rehabilitation of sustained attention in HIV.

### **1.9.1 General Cognitive Performance**

The most general measures of neurodevelopmental outcomes are measures of general cognition. These assessments provide a global score on the performance of cognitive domains. In Africa, the most commonly used cognitive assessments are The Kaufman Assessment Battery for Children (Kaufman, 1983), The Wechsler Abbreviated Scale of Intelligence (WASI) (Wechsler, 1999), and The Bayley Scales of Infant Development (BSID-II) (Bayley, 1999) which has been found to be an appropriate developmental test, made up of

cognitive, language and motor components and is appropriate for South African children (Potterton et al., 2009).

The BSID-II has been normed for younger children (aged 1- 42 months) and is inclusive of three scales: the Mental scale, the Motor scale, and the Behaviour Rating scale. The Mental scale assess memory, learning, abstract thinking, mathematical number concepts, early verbal communication, and sensory-perceptual abilities (Bayley, 1999). The Motor scale assesses fine and gross motor skills. The Behaviour Rating scale assesses attention, orientation/engagement, emotional regulation and motor quality (Bayley, 1999). The Kaufman Assessment Battery for Children is a measure of intelligence for children (K-ABC) aged 2 years and 6 months through 12 years and 5 months. The K-ABC includes 4 scales: 1) the sequential-processing scale, 2) the simultaneous-processing scale, 3) achievement scale, and a 4) nonverbal scale (Kaufman, 1983). The WASI measures general intellectual functioning and is inclusive of verbal and performance IQ (Wechsler, 1999).

Studies assessing children making use of the BSID-II have found that HIV+ children perform poorly on neurodevelopmental assessments compared to HIV negative (HIV-) controls. In a study conducted in Soweto, which included 122 HIV+ children under the age of 2.5 years, it was found that the baseline developmental scores of children with HIV were extremely low, with 78% having delayed cognitive development and 87% having delayed motor development (Potterton et al., 2009). Similar results were found in Kinshasa, the Democratic Republic of Congo, in a study where 35 HIV- , 35 HIV+ and 90 controls were assessed. Overall, the study found that the HIV+ children had significantly lower developmental mean scores compared with the HIV- and controls. The same study also found that 60% of HIV+ children experienced severe cognitive delay, 29% had severe delay in motor skills, with 91% demonstrating severe mental and 82% demonstrating severe motor delay. The high level of developmental delay in children is in keeping with findings from other studies (Lindsey, Malee, Brouwers, & Hughes, 2007; Lowick, Sawry, & Meyers, 2012; Martin et al., 2006; Moore et al., 2006; Nozyce et al., 2006; Smith et al., 2012; Woods et al., 2009).

In a study conducted in Uganda, inclusive of 93 HIV+ children and 106 HIV- children using the KABC-2 it was found that the HIV+ children performed significantly worse than controls on KABC-2 on developmental measures (Ruel et al., 2012). Moreover, a higher plasma HIV RNA level and low CD4 cell counts (below 350 cells) in the HIV+ group was associated with poorer cognitive functioning among these children (Ruel et al., 2012). Similarly, Hoare et al. (2012) found that HIV+ children in Cape Town performed significantly poorly than HIV- controls on the WAIS global verbal IQ score (87.8 versus 101.2) and performance IQ score (73.7 versus 85.7) (Hoare et al., 2012). However, it is important to note that in some studies there was no significant differences between HIV+ and HIV- groups on general cognitive performance (e.g., Bagenda et al., 2006; Shanbhag et al., 2005). The mixed effect of the role of ARVs is a theme that will be revisited as the thesis progresses.

In conclusion, HIV appears to affect global cognitive performance in HIV+ children. However, large neuropsychological batteries of general cognition often overlook subtle neurocognitive deficits in specific areas. In many cases children who perform within normal limits on measures of general cognition can still be impaired on specific cognitive domains. This is even more probable in children with cortical atrophy and CD4 counts below 500 cells (Hoare et al., 2012; Martin et al., 2006). The following section will focus on specific cognitive domains affected by HIV/AIDS.

## **1.9.2 Information Processing**

Information processing skills are defined as those skills that involve dealing with different types of information which involves for example: observing our surroundings, solving problems, reading and writing (Kolb & Whishaw, 2009). Therefore information processing skills enable one to decode and organize information, in order for one to make sense of it (Burton et al., 2001). Processing speed includes both mental (information processing) and motor speed (psychomotor speed) and these are often a good indicator of cognitive functioning (Burton et al., 2001). Moreover, the speed at which children process information and execute cognitive processes is a significant predictor for their performance on cognitive

tasks such as, working memory, inductive reasoning, and accuracy of arithmetic word problems (Kail & Ferrer, 2007). It has been noted that deficits in this area would significantly impact on a child's learning abilities.

Several studies that measure information processing combine a potpourri of related yet separable cognitive constructs which have been operationalized in different ways. At the crux of information processing is that speed of information as measured by reaction time where 'time' is often used as an indicator of the integrity of information processing. Most assessment instruments such as the Amsterdam Neuropsychological Tasks (De Sonneville, 2003), the Digit Symbol subtest of the Wechsler Adult Intelligence Scale (Wechsler, 2003) and the Kilifi Developmental Inventory (Abubakar, Holding, Van Baar, Newton, & Van de Vijver, 2008), are based on detection and discrimination of either auditory tasks, coloured lights or psychomotor speed. In summary, information processing is best summarised as the time taken between the presentation of a stimulus and the behavioural response (Posner, 1978). As noted above, deficits in this area are thought to be an indicator of a child's learning abilities and processing of information.

With regard to HIV, Koekkoek et al. (2008) found that HIV+ children assessed with a simple reaction time task performed significantly slower than the normative mean. Other studies which have used large neuropsychological batteries like the WISC-IV (Wechsler, 2003) have also found significant impairment in processing speed in children with HIV. Smith et al. (2012) found that processing speed scores for vertically infected children with an AIDS defining illness were six points lower than vertically infected children without an AIDS defining illness and uninfected youth. This is not an isolated finding, Hoare et al. (2012) found that processing speed was one of the worst domains affected by HIV. Results suggest that HIV+ children performed significantly more poorly with a mean score of 75.00 compared to HIV- controls who achieved a mean of 83.50 on the WISC-IV (Wechsler, 2003). This further supports the finding that processing speed is most vulnerable to the effects of HIV/AIDS (Hoare et al., 2012).

In terms of psychomotor speed, further research suggests that HIV+ children perform worse than uninfected children. A cross sectional study which involved 48 Kenyan children between 6 and 35 months who were either HIV+, HIV exposed and uninfected (Abubakar, Holding, Newton, Van Baar, & Van de Vijver, 2009). Abubakar et al. (2009) showed that the HIV+ group was characterized by severe impairment in all subtests of the Kilifi Development Inventory: psychomotor, locomotor, and eye-hand coordination skills (Abubakar et al., 2009). Another study by Shead, Potterton & Stewart (2010) using the Bayley Scales of Infant development compared the neurodevelopment of vertically infected HIV+ children not on antiretroviral treatment and HIV uninfected children in South Africa over a 6-8 month period. The authors found that scores for the HIV+ group were extremely low at both points in time, indicating a severe developmental delay (Shead et al., 2010).

### **1.9.3 Motor skills**

Motor disorders are a potential neuropsychological complication of HIV (Tse et al., 2004; Valcour, 2009). HIV's predilection to affect subcortical deep grey structures such as basal ganglia dopaminergic regions as well as cortical frontal regions has been implicated in psychomotor deficits and a myriad of motor abnormalities which have been observed in patients with HIV. Complications include bradykinesia (slowed movement), bradyphrenia (slowed information processing), hypomimia (reduced facial expression), postural tremor, and hand agility (Tse et al. 2004; Woods et al. 2009); gait velocity (Robertson et al., 2006); finger tapping (Heaton et al., 1995); and manual dexterity (Carey et al., 2004).

It is imperative to note that some research suggests that ARV therapy does not significantly reverse motor deficits evidenced in HIV+ children. Paediatric HIV research focussing on motor skills done by Walker, Pierre, Christie & Chang (2013) found that predominant motor abnormalities were present in 287 HIV+ children. HIV+ children in the above study showed signs of hyperreflexia (5%), spasticity (74.6%), and quadriparesis (31.3%) (Walker et al., 2013). Similarly, Van Arnhem et al. (2013) evaluated 59 perinatally infected children on ARVs and found that 14% had abnormal muscle tone (hypertonia), 10% had overactive

reflexes (hyperrflexia), and 8% suffered from muscle tightness (spasticity) (van Arnhem et al., 2013). Studies on motor integrity conducted in Cape Town by Ferguson & Jelsma, (2009) also found that motor delay was evidenced in 66.7% of the HIV infected sample compared with 51% of the age-matched sample without HIV. HIV+ children further displaying motor dysfunction such as abnormal muscle tone, less muscle bulk or less muscle strength are believed to be at risk for increased disease progression (Pearson et al., 2000). Research also suggests that the short term benefits of ARV therapy do not reverse motor deficits in HIV+ children. Smith et al. (2008) assessed the short term affect of ARVs on a group of 40 HIV+ children, enrolled on ARV treatment programme from the Red Cross Children's Hospital in Cape Town. A number of motor tests were run on HIV+ children and they showed no major change in motor skills after being on ARVs.

#### **1.9.4 Learning and memory**

Memory is a multifaceted construct that includes, amongst other constructs, working memory (Baddeley, 1992) and episodic memory (Tulving, 2002) and prospective memory (Kolb & Whishaw, 2009). A review of the literature shows that within the paediatric domain, a diverse number of tests such as the Digit Span forward (Wechsler, 2003), the Children's Memory Scale (Cohen, 1997), and the Rey-Osterrieth Complex Figure (Knight & Kaplan, 2004) have been used in neuropsychology literature to assess memory.

There appears to be a dearth of studies that have specifically studied memory functions in HIV+ children. In a recent study, Hoare et al. (2012) recruited 12 HIV+ and 12 HIV- children from the Red Cross Memorial Children's Hospital in Cape Town. Children were assessed on verbal memory with the Rey Complex figure. The HIV+ children performed significantly lower than controls on the visual memory test, with a mean of 29.88 compared to controls with a mean of 38.30. The HIV+ children also scored lower on delayed recall ( $M=29.88$ ) compared to controls ( $M=36.40$ ) (Hoare et al., 2012). In another study Martin et al. (2006) evaluated neurocognitive functioning of 41 HIV+ children who were treated with HAART for one year. The participants were divided into two groups based on brain scan

abnormalities and it was found that the group with more severe brain scan abnormalities scored significantly lower than the group with normal scans on the digits backward and arithmetic subtest of the WISC-IV. This is not an isolated finding, Smith et al. (2006) also found that memory functioning in HIV infected children with an AIDS defining illness was significantly lower than HIV+ infants without an AIDS defining illness and those without HIV (Smith et al., 2006).

### **1.9.5 Executive Functions**

The term executive functions acts as an umbrella term, for essential cognitive domains that lead to independent abstract thoughts such as: problem solving, self-directed independent behaviours, set shifting and reasoning (Kolb & Whishaw, 2009). Executive functions have rarely been examined in relation to HIV dysfunction (Woods et al., 2009). This is surprising since it is widely accepted that HIV is associated with executive dysfunction, especially in the later part of disease stages and their association with activities of daily living (Dawes et al., 2008; Reger, Welsh, Razani, Martin, & Boone, 2002).

Koekkoek et al. (2008) evaluated 22 children on ARV therapy compared with age-appropriate norms. The HIV+ children performed significantly slower on measures of executive function compared to age appropriate norms. Furthermore, these children were slower and less accurate on tasks that required executive functions such as manipulating and monitoring working memory and set-shifting (Koekkoek et al., 2008).

In Uganda, Ruel et al. (2012) evaluated 300 HIV+ children between the ages of 2-12 years with the Kaufman Assessment Battery for Children and found that HIV+ children performed significantly worse in planning/reasoning ( $M=11.5$ ) compared with the controls ( $M=13.8$ ). (Ruel et al., 2012). There still continues to be a paucity of research examining the cognitive

processes of executive dysfunction in HIV, compared with other cognitive domains. More research is needed to elucidate the neural mechanisms of executive dysfunction of HIV. As this cognitive domain holds important implications for frontal lobe functions as these are endemic to activities of daily living such as medication adherence and social planning (Benedict, Mezhir, Walsh, & Hewitt, 2000).

### **1.9.6 Visual spatial perception**

Visual spatial perception involves how we perceive objects in our environment and how we interpret these spatial relationships among the objects and ourselves (Kolb & Whishaw, 2009). Visuospatial skills are endemic to a child's academic success since the way a child perceives and orients in space will be important for their motor coordination and their handwriting skills.

Standard neuropsychological measures used to evaluate visuospatial perception mostly involve memorizing visual spatial patterns. The Kaufman Assessment Battery for Children (Triangles subtest) and the Wechsler Intelligence Scale for Children (Block design) have been widely reported in the HIV literature as assessment tools used in this cognitive domain. In a study by Tardieu et al. (1995) who assessed 33 HIV+ children with the Wechsler Intelligence Scale and the Rey-Osterrieth complex figure, it was found that more than half (54%) had abnormal results on visual-spatial tests. In another study by Smith et al. (2008) conducted at Red Cross Children's hospital which comprised of 39 HIV+ children who were evaluated before the start of ARV therapy and six months later. At baseline assessment, visual perception scores were below the normal range and these scores remained similar after ARV therapy (Smith et al., 2008). Similar findings on the impairment of visual spatial skills as a result of HIV have been reported elsewhere in the literature (Koekkoek et al., 2008; Woods et al., 2009) and research continues to suggest a strong correlation between fronto-

striatal pathways and spatial reasoning in HIV (Bogdanova, Nearing, & Cronin-Golomb, 2008).

An emerging analysis from the above is the effect that the HIV virus has on the integrity of a number of cognitive domains. The thesis will now progress into some detail to outline the key cognitive domain under consideration: attention.

### ***1.10 Attention***

In this section I will explain the concept of attention and its related properties of sustained, selective and divided attention. The rest of this section will outline how this attentional system is affected by HIV/AIDS.

Attention is a complex system and involves multiple anatomical structures and different neural networks (Mesulam, 1981; Parasuraman & Davies, 1984). Early research by William James (1890) began to suggest that attention was a unitary cognitive construct that enables the voluntary ability to perceive and focus stimuli. Cognitive Psychology has since suggested a number of distinct, yet related properties of attention and these include: a) sustained, b) selective, and c) divided attention (Parasuraman & Davies, 1984). I will now go on to describe these in more detail and how these form higher order cognitive functions using Posner and Peterson's theory of attention (Posner & Peterson, 1990).

According to Posner and Peterson (1990), attention provides the underlying foundations for all cognitive skills to function properly (e.g., memory, executive functions, and visual perception). Posner and Peterson (1990) divided attention into three subsystems that each performs different but interrelated cognitive operations and these are namely: (a) orienting to

sensory events; (b) detecting signals for conscious processing; (c) maintaining a vigilant or alert state (Posner & Peterson, 1990). These three major systems have been prominent in cognitive accounts of attention (Kahneman, 1973; Posner & Boies, 1971). Brain injuries to these three areas will result in an inefficiency to shift one's attention (Posner, 1988), albeit each anatomical area produces different deficits (Posner & Peterson, 1990).

An important caveat is required before the three subsystems of attention are discussed: (1) the first is that it is conceived that the attention system is anatomically separate from other cognitive systems such as information processing, which handles incoming information. Hence, Peterson and Posner (2012), rather emphasize the sources of attentional systems, not the processing systems (i.e., speed of information processing) that could be affected by attention. (2) It is also thought that the three subsystems of attention subserved anatomically distinct networks in the brain and, (3) each attentional subsystem carries out separate functions which can be defined in cognitive terms (Posner & Peterson, 1990).

#### **1.10.1.1      *Alerting Network***

The alerting system mediates sustained attention or vigilance which is the focus of this research project. Sustained attention represents a basic attentional function in which the efficacy of selective and divided attention is premised on (Sarter, Givens, & Bruno, 2001). Therefore, impairments in attention would not necessarily be restricted to one cognitive modality of dysfunction; in this case, impairments seen in sustained attention may translate to and affect other cognitive modalities (Sarter & Bruno, 1997). Sustained attention involves the ability to keep one's attention on a task; for a sufficient amount of time, to enable one to get enough information in order to understand the task and to remember it (Malia et al., 2004). Alerting can be broken down further into the cognitive control of tonic alertness and phasic alertness. Tonic alertness is defined as wakefulness and arousal, this function is assessed with simple reaction time tasks (Strum & Willmes, 2001). While phasic alertness is the ability to increase response readiness to a target following an external warning. This function is

typically assessed with reaction time tasks in which a warning signal precedes the target (Sturm & Willmes, 2001).

The concept of alerting goes back to Moruzzi & Magoun (1949) seminal work on the role of the brain stem in maintaining alertness. In terms of the cognitive psychology approach, alertness has been operationalized in terms of maintaining optimum vigilance during tasks. For example, alertness is measured by using a warning signal prior to a target stimulus to produce a change in attention (Posner & Peterson, 1990). The target event prepares the individual to detect and respond to the expected target signal. Therefore, the alerting networks main function is to increase vigilance to an impending stimulus (Fan et al., 2009). After an impending stimulus is perceived there is a change in internal state in order to prepare for the stimulus. For example, after the presentation of a warning signal, changes in heart rate and brain activity are witnessed in individuals. These changes in internal state serve to inhibit competing activities (Kahneman, 1973).

The alerting system is controlled by the reticular activating system in the brainstem, some parts of the thalamus, the right parietal lobe and the right prefrontal areas which allow for processing of a target stimulus (Sarter et al., 2001). Research supports this theory and has shown that demands on monitoring stimuli such as listening out for a target stimulus activates the fronto-parietal-temporal regions of the brain (Fink et al., 1997). It is believed that sustained attention is premised on the brain stem arousal systems, and is lateralized in the right hemisphere (Peterson & Posner, 2012). Further research supports this idea, Posner, Inhoff, Friedrich and Cohen (1987), found that patients who had right parietal lesions were impaired when a warning signal was omitted before a target, while patients with left parietal damage were not. Right-hemispheric lesions also produce deficits in alerting to galvanic skin responses in humans (Heilman, Watson, & Valenstein, 1985), and with heart responses to warning signals (Yokoyama et al., 1987). In terms of the related the properties of the alerting system, tonic and phasic alertness have been found to also be lateralized in the right hemisphere and thalamic areas (Sturm & Willmes, 2001).

Recent research and imaging studies have deepened our understanding of the pharmacology of the alerting system. Evidence points to the norepinephrine system which arises in the locus coeruleus which may have an important role in maintaining an alert state (Sarter & Bruno, 1997). In accordance with this idea, Aston-Jones and Cohen (2005) found that in animals, norepinephrine cells mediated changes in arousal and vigilance. In conclusion, sustained attention is mediated by the posterior attention system which has a strong right hemispheric lateralization and is influenced by the norepinephrine system. The previous section discussed the neural underpinnings of sustained attention, the subsequent section will show that sustained attention is affected by HIV.

### **1.10.2 HIV/AIDS and Sustained Attention**

A review of the literature shows that deficits in sustained attention are a hallmark of paediatric HIV. There have been no meta-analysis studies performed on the relationship between HIV and sustained attention due to the diverse number of neuropsychological batteries that have been used to assess sustained attention which include the TEA-Ch (Manly, Robertson, Anderson, & Nimmo-smith, 1999), Conner's Continuous Performance Test (Conners, 2004), Digit Span Forward and Digit Span Backward (Wechsler, 2003). The assessment of sustained attention is most commonly evaluated with continuous performance tests, also known as vigilance, this is tested when a subject has to keep watch of certain stimuli (such as letters or digits) over a prolonged period of time. The subject has to make a response by pressing a key when a specified target appears among distracters. The ability of the observer to respond to unpredictable occurring signals is characterized by the observer's ability to detect signals known as vigilance level (Sarter et al., 2001).

In a recent continuous performance task, Foster et al. (2012) evaluated 38 HIV+ and 35 HIV- children with an average age of 13 years old. The HIV+ children were slower to respond to

every letter that appeared on the screen ( $M=54.8$ ) compared to the HIV- participants ( $M=52.9$ ). However, both of these scores did not reach statistical significance  $p=.63$  and  $p=.78$ , respectively (Foster et al., 2012).

In another study, Martin et al. (2006) assessed sustained attention in 41 HIV+ children with minimal to moderate brain abnormalities as shown on the computer tomography brain scans. The HIV+ children with brain scan abnormalities scored significantly lower on sustained attention on the WISC-IV ( $M=7.8$ ) compared with children within normal brain scans on the digit span forward ( $M=8.4$ ). Although the digit span forward did not reach statistical significance, the digit span backward reached statistical significance with the HIV+ children with brain abnormalities performing poorly ( $M=6.6$ ) compared with HIV+ children with normal brain scans ( $M=9.6$ ). This study suggests that children commenced on ARV therapy with brain abnormalities are at increased risk for poorer cognitive functioning.

In another study, Hoare et al. (2012) administered the WISC-IV to 12 asymptomatic HIV+ children between 8 to 12 years old as well as aged matched controls. Results showed that HIV+ children performed worse on the WISC Digit Span Forward ( $M=6.78$ ) compared to the healthy controls ( $M=8.10$ ), however, these results did not reach statistical significance ( $p=.14$ ). This is most likely attributable to the small sample size. The results revealed that there was a correlation between lower fractional anisotropy levels which is indicative of demyelination in the corpus callosum and poorer performance on the neuropsychological tests (Hoare et al., 2012). These findings suggest that demyelination of the white matter fibres accounts for cognitive decline in sustained attention in asymptomatic HIV+ children.

There is a paucity of research evaluating sustained attention functions in HIV+ children. This is surprising since sustained attention is crucial for day-to-day functioning as the ability to detect, and select relevant stimuli directly impacts on instrumental activities of daily living. Research suggests that attention, working memory and executive functioning impairments are the strongest predictors of dependence of instrumental activities of daily living (Heaton et al.,

2004). Sustained attention deficits have also been predictive of medication adherence (Levine et al., 2008); adherence to ARV medication (Hinkin et al., 2002); being able to respond to appropriate social cues in order to communicate (Posner & Dehaene, 1994); visual attention abilities associated with tasks such as driving ability (Sarter et al., 2001), and reading (Stern & Shalev, 2013). It was the key aim of this research study to assess the effects of cognitive rehabilitation in this domain of HIV in a paediatric population as sustained attention is a foundational cognitive skill in which other cognitive functions need to function properly.

### **1.10.2.1      *Sensory orienting system***

The sensory orienting system mediates selective attention. Selective attention is conceived as the ability to select and attend to certain stimuli in the face of competing stimuli (Dayan, Kakade, & Montague, 2000). The literature divides selective attention into exogenous and endogenous orientation. Exogenous orienting is considered reflexive and automatic attention; whereas endogenous orienting is considered voluntary, whereby a person allocates their attention to a predetermined location in space (Fan et al., 2009).

Research shows that two brain systems are involved in orienting to external stimuli (Corbetta & Shulman, 2002). For example, when subjects are cued toward the presentation of an arrow a more dorsal system is involved such as the frontal eye fields and the intraparietal sulcus (Corbetta & Shulman, 2002). However, when the target arrow was miscued, participants had to break their focus of attention on the cue and switch to the new target location. This switch involved the temporoparietal junction and the ventral frontal cortex (Corbetta & Shulman, 2002). It is believed that selective attention shifts are invariably performed by saccadic eye movements (Rizzolatti, Riggio, & Sheliga, 1983). In line with this, functional magnetic imaging resonance studies have shown that covert and overt shifts of attention are performed by saccadic eye movements (Corbetta & Shulman, 2002).

Research suggests that the posterior parietal lobe mediates selective attention. In support of this, Posner and Cohen (1984) found that damage to the posterior parietal lobe resulted in an

inability to disengage one's attention to a target contralateral to the side of the lesion. Moreover, parietal lobe lesions result in a difficulty returning to an already examined location (Posner & Cohen, 1984; Posner, 1988). Research shows that monkeys with chemical injections into the lateral pulvinar show difficulty in covert orienting as do patients with lesions in the thalamus (Posner et al., 1987; Posner, 1988). Also, injections of scopolamine made into the lateral intraparietal area of monkeys' affects their ability to shift attention to a target (Marrocco & Davidson, 1988). This area corresponds to the superior parietal lobe in humans, containing cells influenced by cues about spatial locations (Marrocco & Davidson, 1988). These findings show that the computation that is ostensibly involved in selective attention is impaired as a result of parietal lobe lesions (Posner & Peterson, 1990). The subsequent section will now discuss research on the effects of HIV on selective attention.

### **1.10.3 HIV and Selective Attention**

Research on selective attention has used reaction time tasks to measure this modality of attention. Tests such as The Test Variables of Attention (Greenberg, Kindschi, & Corman, 1996) is a computer based task as well as The Test of Everyday Attention (Map Mission) (Manly, Robertson, Anderson, & Nimmo-smith, 1999) are just some of the tests often reported in the literature on HIV and selective attention. In a nutshell, selective attention tasks require the preferential selection of certain information over others. For example, The Test Variables of Attention involves an activity of a flashing square which is presented for 1/10th of a second in two second intervals. The square will either flash on the top of a larger square or it will flash in the bottom portion of the square. The participant is required to press a button when they see the square on top (target) and every time they see the square at the bottom (non-target) they must refrain from pressing the switch (Greenberg et al., 1996).

In a research study conducted in Uganda, 93 HIV+ children and 106 HIV- controls were administered The Test Variables of Attention. The HIV+ children had significantly poorer scores on the visual reaction time attention modules (Ruel et al., 2012). Children with HIV RNA levels above the median ( $Mdn= 4.7 \log_{10}$  copies/mL) performed worse in overall

reaction time compared to HIV+ children with HIV RNA levels below the median ( $p < .001$ ) (Ruel et al., 2012). This suggests that higher plasma HIV RNA levels are associated with poorer cognitive functioning in the children. In another study Walker et al. (2013) administered The Test of Everyday Attention (Map Mission) to 15 randomly selected encephalopathic HIV+ children aged between 7-10 years and 15 matched controls (non-encephalopathic HIV+). Selective attention was measured with the Map Mission search, a subset from The Test of Everyday Attention<sup>1</sup>. HIV+ encephalopathic children achieved significantly lower scores with a median of 15 compared to the non-encephalopathic children with a median of 23 (Walker et al., 2013). Koekkoek et al. (2008) reveals a similar trend in the poor performance of HIV+ children by showing that HIV+ children performed significantly slower and less accurate on attentional control measures than the comparison to the age appropriate norm (Koekkoek et al., 2008). In conclusion, HIV interrupts the functioning of the parietal lobe, and disturbs the processing of selective attention. I will now move on to discuss the executive attention system. The executive attention system mediates divided attention (Posner & Peterson, 1990).

### **1.10.3.1      *Executive attention system***

The third major subsystem of attention is called divided attention. Divided attention is the ability to attend to two or more stimuli at the same time (Malia et al., 2004). It is possible to process multiple target stimuli at the same time; however, when a target is detected this causes the slowing of processing demands for another target (Posner & Peterson, 1990). The slowing of certain processing demands and the concomitant awareness of another target has thus been called divided attention (Petersen & Posner, 2012). Divided attention is needed in

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<sup>1</sup>In the Map Mission, children are given one minute to quickly locate small target symbols in an array of distracters on a city map. For example, children are given an A3 city map with 80 targets of small restaurants knife and fork symbols randomly placed on the map. Distracting symbols of supermarket trolleys, cups and cars are also present. Children are instructed to find and circle with a pen, as many target symbols as possible within one minute. The number of targets correctly marked results in the selective attention score (Manly et al., 1999).

everyday situations that involve situations involving: planning, decision making, and conditions judged as difficult or dangerous to mention but a few (Fan et al., 2009).

The awareness of a target and executive control of attention is mediated by the medial frontal cortex and the anterior cingulate cortex (Botvinick, Braver, Barch, Carter, & Cohen, 2001; Dehaene & Changeux, 2011), as these areas are activated when there is a conflict of stimuli. This process is said to happen when a subdominant response has to be chosen over a dominant response (Botvinick et al., 2001). Research suggests that activity in the anterior cingulate cortex and medial frontal cortex are activated during conflict situations such as: the perception of pain (Rainville, Duncan, Price, Carrier, & Bushnell, 1997); situations involving social exclusion (Eisenberger, Lieberman, & Williams, 2003); and rewards (Hampton & Doherty, 2007). The subsequent section will now discuss how this attentional function is affected by HIV.

#### **1.10.4 HIV and Divided Attention**

To the researchers knowledge there have been no studies assessing divided attention in HIV+ children. This is surprising since HIV+ individuals frequently complain about difficulties managing multiple responsibilities and as such find it difficult to divide their attention between different tasks (Hinkin, Castellon, & Hardy, 2000). For example, occupational and social functioning is dependent on an intact attentional system as multi-tasking abilities are needed for everyday functioning such as adherence to complex medicine regimes (Hinkin et al., 2000).

With regards to HIV research a number of authors have found that HIV+ adults perform poorly on divided attention tasks in comparison to HIV- controls. Martin et al. (1995) found that HIV+ individuals were selectively impaired on tasks of controlled attentional processing, particularly under conditions of divided attention Hinkin, Castellon & Hardy (2000) extend this finding by showing that HIV+ participants performed poorly ( $M=684$ ) under dual task

conditions compared to healthy matched controls ( $M=784$ ). During the dual task, participants in the study were required to respond to an auditory tone with a button push while completing a visual discrimination task with a speeded vocal response (Hinkin et al., 2000).

In conclusion, the advances in the treatment of HIV have dramatically improved the survival of HIV+ children into adolescence. However, HIV-associated neurocognitive decline continues to accrue regardless of successful ARV treatment and poses significant challenges to child and adolescent psychology. Substantial progress has been made in revealing the neuropsychological profile of HAND. The central mechanisms of HAND revolve around a subcortical pattern of neuropsychological dysfunction involving: information processing; motor skills; learning; memory; executive functions; visual spatial perception; and attention. This pattern of neuropsychological dysfunction is consistent with damage of frontostriatal circuits which mediate motor, cognitive and behavioural functions within the brain (Marsh, Theusner, & Pelchen-Matthews, 2009). I have outlined the extent of neurocognitive decline in the paediatric population, in the subsequent section I will introduce some literature that suggests that cognitive functioning is well preserved in HIV+ children on ARV therapy.

### ***1.11 Neurocognitive gains in response to ARV Therapy***

In the 1990s the treatment for HIV changed with the introduction of combination antiretroviral therapy (cART). The introduction of cART regimes resulted in the decline of HIV-associated morbidities (e.g., opportunistic infections) and mortalities, due to cARTs effectiveness in suppressing HIV RNA in plasma and restoring immune functioning (CDC, 2010). Some research suggests that cognitive functioning is generally preserved in HIV+ individuals who have well controlled CD4 cell counts and HIV replication.

In a prospective study in the Democratic of Congo, HIV+ children demonstrated improved motor development scores similar to those of HIV uninfected, affected children after being on ARVs for 6-12 months (Van Rie, Dow, Mupuala, & Stewart, 2009). However, the children

were unable to reach motor scores similar to those of healthy controls which may suggest that ARV therapy may be restricted due to other variables such as poor living environments and parental illness (Van Rie et al., 2009). Shanbhag et al. (2005) assessed 146 HIV+ children in a retrospective cohort study. Progressive and static encephalopathy was assessed before and after combination antiretroviral therapy. Progressive encephalopathy was diagnosed in 29.6% of the children before ARV therapy and in 12.1% after 24 months. Similarly, static encephalopathy was diagnosed in 14.2% of HIV+ children and after ARV treatment this dropped to 3% (Shanbhag et al., 2005). These are not isolated findings, Patel et al. (2009), in a cohort study of 2 398 HIV+ children, found that there was a 50% reduction in HIV encephalopathy in children taking ARVs after six months. These studies support the idea that ARVs are associated with improved yet subtle neurocognitive benefits in HIV+ children.

The literature on neurocognitive functioning in the era of ARV therapy is highly variable, the true incidence and range of cognitive problems associated with HIV is still unclear. Some research shows highly divergent findings in terms of the benefits of ARVs on neurocognitive functioning. These incongruent findings may be dependent on many factors such as a) the context where the studies are conducted, b) including children without HAND, c) significant differences in the age range of the participants in different studies, d) the nature of neuropsychological measurement tools used, and lastly, e) the wide range of design methodological differences associated with different research (e.g., cross-sectional versus longitudinal investigations) in different settings (Weber et al., 2013). For instance, longitudinal studies would be important in understanding the developmental differences in study populations, as well as understanding the contribution of disease markers such as CD4 count and viral load on the impact of neurocognitive functions, whereas cross sectional designs might not be able to provide this depth of information (Kammerer, Isquith & Lundy, 2013). In addition to the above, investigations into HIV-associated neurocognitive functioning may also be hindered by a lack of age appropriate control group which also reduces the external validity of findings as researchers are unable to separate out virus exposure effects and environmental effects (Zondo & Mulder, 2014).

In conclusion, although only a few studies have seen improvements in response to ARV therapies, this is against a large body of evidence that suggests that HIV-associated neurocognitive impairment continues to accrue regardless of ARVs (Section 1.8). In the absence of pharmacological interventions to improve neurocognitive decline a number of researchers have suggested that ARV therapy is beneficial and is best when accompanied by enhanced cognitive modifiability programs to help stem the effects of HIV on the brain (Smith et al., 2008). There is an abundance of research which suggests that a combination of approaches which include ARV regimes and cognitive rehabilitation are needed to address neurocognitive dysfunction (Koekkoek et al., 2008; Weber et al., 2013). I will now go on to discuss techniques that have been emerging in the HIV literature as an alternative to supplement ARV medication to improve neurocognitive decline.

### ***1.12 Cognitive Rehabilitation Therapy of HAND***

Since the effectiveness of ARV therapy on neurocognitive functioning remains variable, a number of researchers have stressed that ARVs are best when accompanied with cognitive behavioural approaches. However, few studies have sought to address the effects of cognitive decline as a direct result of HIV in children and adults. A review of the literature shows that only three studies have been published on the cognitive rehabilitation of HAND. All three studies have used a compensatory approach of neural plasticity which focuses on the ability of the brain to modify its neural connections and networks as a result cognitive training exercises. In this section, I will review the studies on cognitive rehabilitation in the HIV literature.

A review of the literature indicates that the first study in Sub-Saharan Africa to investigate the potential benefits of cognitive rehabilitation on neuropsychological functioning of children on ARV therapy, demonstrated the neurocognitive benefits of cognitive rehabilitation therapy in aspects of attention functioning and executive functioning (Boivin et al., 2010). Boivin et al. (2010) evaluated the feasibility of using computerized cognitive rehabilitation therapy in a sample of HIV+ children in Uganda. The sample consisted of 60

children, with a mean age of ten. The sample had a history of immunosuppression and high current HIV RNA levels in plasma. Children were randomly assigned in a non-blinded fashion, into non-contact control ( $n=32$ ) and intervention group ( $n=28$ ). The intervention group underwent ten, 45 minute training sessions over a period of five weeks using the Captain's Log battery which targeted: attention, memory, visual motor and logic. The Captain's Log Computerized Training System is a computerised instrument developed by Sandford (2007) which is inclusive of 35 computerized cognitive training exercises targeting different aspects of cognition and is inclusive of a reward system which fosters a game-like atmosphere. The present study included four exercises from the Captain's Log attention modules (e.g., clicking the mouse if the colour of several different images matches the colour of the screen's border); four from conceptual/memory (e.g., finding the missing part of a sequence from a number of choices), three from visual motor (e.g., watching a number of targets and clicking on any that change), and four from the logic module domain (e.g., figuring out the secret rule in a number of images) (Sandford, 2007).

Baseline assessments did not include a HAND diagnoses. However, HIV+ children had significantly lower neurocognitive performance at baseline than a seronegative comparison group in sequential processing, simultaneous processing and learning. Pre- and post-intervention neurocognitive assessments were performed using the Cogstate neuropsychological battery (Darby, Maruff, Collie, & McStephen, 2002). Results showed that the computerized cognitive rehabilitation group showed significant improvement in two cognitive domains, namely executive functioning (Cohen's  $d=0.77$ ) ( $p<.001$ ) and attention (Cohen's  $d=0.69$ ) ( $p<.001$ ) compared to the controls at post-intervention. Although this study showed improved performance of some aspects of cognition in children, the authors have stressed the need for more evidenced based experimental studies to investigate cognitive rehabilitation in HIV children over a prolonged intervention period.

Becker et al. (2012) conducted the second study on the cognitive rehabilitation of HAND using a computerized stimulation program (Smartbrain) (SmartBrain Technologies, 2013). The sample was inclusive of 30 HIV+ and 30 HIV- adults who were either assigned to the

cognitive intervention or a no-contact control group. In the HIV+ group, 60% had AIDS; 83.3% were on cART; mean CD4 cell count for the HIV+ group was 523.3 and with a mean viral load of 2.05 log which is indicative of a moderately healthy sample (Becker et al., 2012). Baseline neurocognitive scores for the HIV+ participants was measured with the Heaton Global Impairment Rating and included normal range a global neurocognitive scores. The intervention group were instructed on how to use SmartBrain from their home computers for a period of 24 weeks. The initial session length for using the SmartBrain program was 10 minutes, this was increased to a weekly maximum of 30 minutes a session. The SmartBrain program consists of computer game activities which targeted cognitive domains including: memory, attention, gnosis and executive functions. Results from the study revealed that there was no significant improvement for the intervention group after using Smartbrain. However post-hoc analyses revealed that participants who engaged in the most computer training sessions showed improvements in cognitive functioning over a 24-week period ( $p=0.03$ ) (Becker et al., 2012).

In the last known study, Vance, Fazeli, Ross, Wadley and Ball (2012) used a computerized self-administered training program known as the Posit Science InSight program (Posit Science, 2013) which is designed to improve speed of information processing. The study design was conducted in a non-blind, randomized way in which 46 HIV+ participants, with a mean age of fifty one were assigned to an intervention group ( $n=22$ ) and a no-control group ( $n=24$ ). The sample had an average CD4 count of 453 with 52% of the sample having nadir CD4 counts below 200 which is indicative of AIDS. Pre-and posttesting on a number of neuropsychological measures were conducted using the Useful Field of View test (visual speed of processing), the Finger Tapping Test (psychomotor test), the Wisconsin Card sorting Test (executive function), and the Times Instrumental Activities of Daily living (everyday functioning). The intervention group underwent ten computer training sessions which consisted of one hour of training per day with posit science InSight computer program. The intervention lasted for a period of 24 weeks and included training on the InSight computer program. InSight is inclusive of five games which vary in regard to stimuli presented aimed at improving participants' visual processing speed. The tasks on the InSight game are

programmed in a manner to provide positive and negative feedback to aid learning. Positive reinforcement included, earning points indicated by a pleasant sound. Similar to most cognitive rehabilitation tasks, training tasks were programmed in a hierarchical manner whereby material becomes increasingly harder if the participant responds correctly to the exercises. Participants in the intervention group experienced greater baseline-to-posttest improvements, compared to controls, on speed of processing measures of everyday functioning ( $d=0.42$ ) and visual speed of processing ( $d=0.34$ ) (Vance et al., 2012).

Cognitive gains must be weighed against the methodological limitations which may hamper the external validity of the results. None of the cognitive rehabilitation studies made use of an active control group which means that participants may have improved due to exposure to computers (Boivin et al., 2010). Another equally important limitation is that none of the studies made HAND diagnoses during baseline assessments or included this into the inclusion criterion. Therefore, the computer cognitive rehabilitation could have been performed on HIV+ individuals who did not really need rehabilitation (Weber et al., 2013). Despite these methodological limitations, the three studies provide evidence that there can be compensatory potential following cognitive rehabilitation through brain plasticity.

### ***1.13 Summary of the reviewed literature***

In conclusion, HIV has a profound impact on the brain insofar as the virus compromises cognitive functioning in children (Koekkoek et al., 2008). The treatment of HIV changed with the introduction of ARVs. These drugs are effective in suppressing plasma HIV RNA (viral load) and as a result reduce mortalities and opportunistic infections have declined (CDC, 2010). However, the effectiveness of ARVs on neurocognitive functioning remain variable (Weber et al., 2013). This may be due to the fact that the CNS may be able to contain a reservoir of the virus that can remain untouched by ARVs (Iglesias-Ussel & Romerio, 2011). The developmental deficits seen in paediatric populations include impaired motor functions, executive functions, visual-spatial integration, and attention (Baillieu & Potterton, 2008; Koekkoek et al., 2008; Smith et al., 2008). It has since been suggested that other

avenues (e.g., cognitive rehabilitation) be pursued to stem the effects of cognitive decline in children living with HIV.

### ***1.14 Purpose of Current Study***

The primary purpose of my study was to conduct a pre- and posttest to investigate the impact of cognitive rehabilitation program using the Brainwave-R to improve compromised sustained attention in children living with HIV. Attention is conceived as the primary modality of cognition and all secondary levels of cognition are dependent upon this modality (Posner & Peterson, 1990). Although extensive research has been conducted on the use of cognitive rehabilitation therapy, no experimental studies exist in the South African context on the cognitive rehabilitation of paediatric HIV. This is against the backdrop that South Africa has the highest number of people living with HIV (UNAIDS, 2012). It is therefore necessary to examine the effectiveness of cognitive rehabilitation in a sample of HIV+ children on ARV therapy in the Eastern Cape, South Africa. Insights gained from the present study will extend the existing body of knowledge around HIV+ children's psychological functioning in an African context. Furthermore, findings from this study would help develop comprehensive interventions incorporating Brainwave-R to help HIV+ children already on ARV therapy to function cognitively well.

## **RESEARCH METHODOLOGY AND RESEARCH DESIGN**

This section explores the methodology as well as the research design that was employed to achieve my research objectives. This section is written with an acknowledgment of the methodological complexities that exist in assessing children infected with HIV in the African context. The methodological complexities of assessing children with HIV have been well documented by Kvalsvig and colleagues and these include amongst others: a) disentangling the biological, disease and environmental factors which are associated with HIV, b) the fact that children living in sub-Saharan Africa are at risk for a myriad of developmental complexities such as: poor nutrition, a lack of health care and educational facilities as these risk factors may be compounded by the HIV disease, c) difficulties in identifying appropriate principles for the selection and adaptation of measures of test instruments for cognitive assessment, which are culturally sensitive and adequate to the South African context and lastly, d) and incorporating the appropriate linguistic tools and processes when translating from one language to another (Kvalsvig, Taylor, Kauchali, & Chhagan, 2013). To circumvent some of these methodological complexities that pertain to HIV, certain paradigm shifts were implemented into the research design and these will be briefly discussed in the subsequent section.

Due to the paucity of research on the cognitive rehabilitation of children with HIV/AIDS, a research design specific to the goals of this new project endeavour had to be pursued as early in the academic year of July to November 2013. A pilot study related to the cognitive rehabilitation of children with HIV was run and this was later to inform the current research design adopted for the study. The aims for conducting the pilot study were as follows:

- a) To establish whether the Attention Processing Training (APT) (Sohlberg, Johnson, Paule, Raskin, & Mateer, 2005) as an appropriate intervention tool to rehabilitate attention.
- b) To establish the reliability and validity of using the TEA-Ch as a measure of selective attention in a South African context.
- c) To identify trends that could inhibit the completion of the research such as timing of intervention and how many intervention sessions would be necessary to establish lasting effects of the rehabilitation program.
- d) To establish whether it would be possible to run an experimental research study in a community with a small population of children living with HIV/AIDS. The population of Grahamstown is roughly 50 217 according to the 2011 South African census (Statistics South Africa, 2011).

The pilot study was conducted over a two month period between August and mid-September 2013. The aim of this quasi-experimental pilot study sought to provide preliminary findings on adaption of the APT program to improve selective attention in children living with HIV/AIDS. Three HIV+ children ( $M=11$ ;  $SD=1$ ) were assigned to eight APT sessions. The rehabilitation sessions were conducted on an individual basis at a school in Grahamstown. Pre and post selective attention scores were assessed using the TEA-Ch. Pilot results showed slight improvement in pre-post selective scores after the intervention but these changes were nonsignificant ( $Z = 1.15$ ,  $p = 0.25$  and  $Z = 0.00$   $p = 1.00$ ) (Zondo & Mulder, 2014).

Overall, the most significant findings from the pilot study that were later adopted into my study were that:

a) The APT was not a convenient intervention tool for the rehabilitation of children in the South African context due to the intervention exercises being heavily embedded in Western linguistic paradigms and modes of cognitive processing.

b) The Brainwave-R was adapted as the cognitive rehabilitation intervention for the current study after being further piloted on a sample of children who would later participate in the research.

c) The TEA-Ch was deemed a culturally fair test for assessing attention in the sample of children under study. However, in the pilot it was deemed appropriate to use photograph illustrations for some of the tasks on the TEA-Ch subtest of selective attention for explanatory purposes, as some tasks were highly embedded within Western concepts of child development.

d) It was deemed appropriate to have a Xhosa speaking translator for the pilot study as early phases of the research to explain the nature and context of the research. However, a trial run of the experiment using the TEA-Ch and Brainwave-R revealed that the need for a Xhosa translator was unnecessary as a number of materials used in the TEA-Ch and the intervention were non-linguistic in nature.

Although the pilot study had a number of methodological limitations including a small sample, lack of control group and generated insignificant findings, it was necessary to conduct further research in South Africa to verify the viability of cognitive rehabilitation to improve neurocognitive decline in HIV+ children on ARV therapy. Learning from the methodological complexities arising from the pilot study, it was necessary to increase the sample size, include a control group and run the intervention over a longer period of time. However, the particularly vexatious issue of sample size could not be circumvented due to the small population of the town and the small number of children who were HIV+ and could

consent to take part in the research study. With this in mind, I will now venture into the research design of the project based on the lessons learned from the pilot study.

### ***1.15 Research Objectives and Aims***

The aim of this research was to conduct a pre- and posttest to investigate the impact of cognitive rehabilitation to improve compromised cognitive faculties, particularly compromised sustained attention in children living with HIV. As previously mentioned, attention is the primary modality of cognition and all secondary levels of cognition are dependent on this modality (Posner & Petersen, 1990). The aim of my research was to investigate the feasibility of extending the rehabilitative literature to rehabilitate sustained attention in children with HIV by using the Brainwave-R rehabilitation program. Thus far, no known studies encompassing longitudinal experimental designs have been conducted in South Africa to study cognitive rehabilitation in this population. This study, therefore, aimed to provide preliminary evidence based conclusions on the feasibility of cognitive rehabilitation in a sample of HIV+ children over a prolonged period of time. The impact of the research will mainly be in the form of providing a cognitive rehabilitation paradigm to enhance the quality of life of children who may experience cognitive decline as a result of HIV/AIDS. As far as the researcher is aware, such a contribution will contribute to the medical, bio- psychological and biosocial debate around medical HIV/AIDS.

### **1.15.1 Research Hypotheses**

Hypothesis 1: Brainwave-R rehabilitation improves sustained attention in the experimental group compared to the control group.

Hypothesis 2: Brainwave-R rehabilitation improves sustained attention in the HIV+ experimental group compared to the HIV+ control group.

Hypothesis 3: Brainwave-R rehabilitation improves sustained attention in HIV+ children on ARVs.

### **1.16 Research Design**

This study employed a longitudinal crossover design using a waiting list control group. A longitudinal crossover design is a repeated measurements design whereby experimental groups are observed over a period of time before and after an event (Figueiras, Carracedo-Martinez, Saez, & Taracido, 2005). Within clinical and psychological experiments the term crossover is used to describe the process whereby subjects pass through both treatment and placebo phases, as such subjects crossover between exposure and non-exposure (Figueiras et al., 2005; Maclure, 1991).

Two groups were utilised in this research and these included: (1) experimental group, which received the cognitive intervention: Brainwave-R; (2) a control group (non-therapeutic exposure) which did not receive the intervention. Inclusions of a control group allowed the researcher to expose participants to a sequence of treatments (e.g. Brainwave-R) in order examine the effects of the treatment on sustained attention scores.

Data collection was conducted from March 2014 to October 2014 and included four phases. In phase one a baseline assessment of sustained attention using the TEA-Ch was conducted on 20 prospective participants. Following the inclusion and exclusion criteria set out in section 2.4.1 participants were chosen if they met these criteria. From the pool of 20 participants, 11 participants met the inclusion criteria and they were divided into experimental and control groups and matched as far as possible on HIV status, age, gender, and grade at school. In phase two, the Brainwave-R intervention was conducted on the experimental group (3 HIV+ and 3 HIV-) which was followed by a follow up assessment of sustained attention using the TEA-Ch. In phase three, the control group (2 HIV+ and 3 HIV) participated in a placebo activity and a follow-up assessment of sustained attention was again conducted using the TEA-Ch. In phase four, the control group crossed over and received the Brainwave-R intervention, which was followed up by an assessment of sustained attention. The research design is tabulated in Table 2.1.

Table 2.1 *Research Design*

<b>Groups</b>	<b>Baseline Assessment (Pretest)</b>	<b>Intervention</b>	<b>Posttest Assessment</b>	<b>Intervention</b>	<b>Follow-Up Assessment</b>
<b>Experimental group</b>	$O_1$	$X_1$	$O_2$	–	–
<b>Waiting list control group</b>	$O_1$	–	$O_2$	$X_2$	$O_3$

The baseline assessments of sustained attention took place on an individual basis, in a quiet room, furnished with a table at a comfortable height for all participants. The cognitive interventions took place in a group setting. Group intervention was conducted whereby the HIV+ and HIV- participants were divided into the experimental group and the control group based HIV status, age, gender and grade at school. Therefore, the experimental group and the control group were not defined by their HIV status as HIV- participants were included into both groups. Group intervention is common within the cognitive rehabilitation literature and has been used to rehabilitate executive functions (Stablum, Umiltà, Mogentale, Carlan, & Guerrini, 2000), information processing (Fasotti, Kovacs, & Eling, 2000) and problem solving deficits (Rath, Simon, Langenbahn, Sherr, & Diller, 2003). My research made use of a group intervention in order to circumvent the inadvertent disclosure of HIV+ participants. The study used a purposive sample to access the prospective sample of 11 participants who were recruited from a local school in the Eastern Cape, Grahamstown.

### ***1.17 Procedure***

This longitudinal research study contained a four phase intervention: In Phase One, the researcher conducted a baseline assessment of sustained attention with individual participants using the Code transmission (sustained attention) of the TEA-Ch (Version A) in the staff room at the school. In Phase Two, the experimental group took part in the intervention which was conducted over two months. The children in the intervention took part in 12 exercises lasting 25-45 minutes each. Afterwards, a follow up assessment of sustained attention with the code transmission of the TEA-Ch (Version B) was conducted. In Phase Three, the control group participated in sessions of the same frequency, length, and format except they did not receive the intervention and participated in placebo activities. This was followed up by an assessment of the TEA-Ch (Version B) on the control group. In Phase Four the waiting list control group took part in the intervention for 12 exercises over two months, lasting 25-50 minutes each. Thereafter, a follow up assessment of sustained attention (Version A) was conducted. The research was conducted after school hours between 14:30 and 15:15 from Monday to Thursday. During school holidays and vacations no research was conducted.

After school the participants would meet the researcher in the staff room at the school and be briefed before the commencement of the intervention. Each participant would sit at a desk in the staff room for the duration of the intervention. The procedure of how the research was carried out is summarised in Table 2.2.

Table 2.2 *Procedure*

	<b>Procedure</b>	<b>Months</b>	<b>Instrument</b>
<b>Phase 1:</b>	Baseline assessment of sustained attention	1	TEA-Ch
<b>Phase 2:</b> <b>experimental group</b>	Intervention	2-3	Cognitive rehabilitation
	Follow up assessment of experimental group	3	TEA-Ch
<b>Phase 3:</b> <b>Waiting list control group</b>	Placebo	4-5	Placebo activities
	Follow up assessment of control group	5	TEA-Ch
<b>Phase 4: Waiting list control group</b>	Intervention	6-7	Cognitive rehabilitation
	Follow up assessment of waiting list control group	8	TEA-Ch

### **1.18 Participants**

Participants were selected from a school situated in the Eastern Cape, Grahamstown. This school was the site of the pilot study that launched my project. The study used purposive sampling to recruit eleven participants (7 male and 4 female) who were assigned to either the experimental or control group. Although purposive sampling as a category of non-probability sampling, with an inherent bias and lack of generalizability, the method of recruitment provided a greater degree of representivity in line with the study focus (Tongco, 2007). A number of methods were used for recruiting participants:

- 1) Letters were sent out to the grade 5, 6, and 7 pupils at the school, inclusive of the letters were consent forms and demographic questionnaires for both the parent and participant. All of the materials sent to participants and parents were translated into Xhosa.
- 2) Parents and pupils who responded by returning the consent forms participated in the study.
- 3) The school administrators also helped in recruiting participants by calling parents and informing them that a study was taking place at the school. Parents who showed interest came to the school and a small workshop was held with the parents informing them about the study. Those parents and pupils who were interested signed consent forms and participated in the study.

All participants in the experimental and control group were matched on HIV status, gender, and age. Participants were aged between 10 and 15 years of age ( $M=12$ ,  $SD=1.4$ ). This age range was proposed to circumvent language barriers as children in this age range are more

likely to converse in the English language. In order to circumvent the inadvertent disclosure of HIV+ participants both HIV+ and HIV- participants were recruited into the study.

### **1.18.1 Inclusion and Exclusion Criteria**

Participants were either included or excluded from the study based on the criteria developed by Boivin et al. (2010). In line with previous research on the topic, participants were included in the study if they met the following inclusion criteria: (1) were between the ages of 10-15 years of age, (2) were either HIV+ or HIV-; (3) HIV+ participants were included only if they were on a course of ARV therapy; (4) were adequately proficient in English<sup>2</sup>. The exclusion criteria excluded children with (1) auditory deficits; (2) visual impairments; (3) illness such as TB and (4) other CNS diseases (i.e. cerebral palsy, post meningitis neurological disease). This exclusion criterion was applied to all children to make sure that all children could understand instructions therefore eliminating confounding variables that may impede on the results. The above exclusion information was solicited after consultation with the school administration which keeps a medical health report of all attending students.

## **1.19 Measures**

### **1.19.1 Questionnaires**

A Demographic Questionnaire (*Appendix A*) was administered to obtain information about the participants' HIV status, gender, age, current education, grade at school, whether participants' had repeated a grade, class at school and home language. A similar Demographic Questionnaire (*Appendix B*) was administered to the parent/caregivers

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<sup>2</sup> Children at the school begin English education in Grade 3. Children were selected if they 1) could converse in English with the researcher; 2) understood instructions from the TEA-Ch and 3) the children's English proficiency was also confirmed by teachers at the school. These factors served as an indicator of proficiency in the language of testing.

enquiring about HIV status of the child, education level, language, child's eating and reading habits, and whether there were any cognitively stimulating instruments in the house such as books, toys and games.

### 1.19.2 TEA-Ch

The instrument used in assessing sustained attention (dependent variable) was the code transmission subtest from the TEA-Ch. The TEA-Ch is a standardized clinical battery inclusive of nine subsets for the assessment of Attention (Manly, Robertson, Anderson, & Nimmo-Smith, 1999). The TEA-Ch was standardized in United Kingdom for children between the ages of 6-16 (Manly et al., 1999). The instrument has not been normed in a South Africa population. The psychometric properties of the TEA-Ch such as the a) reliability and b) the internal and external validity of the instrument have been well documented in the psychometric literature (Robertson, Manly, Andrade, Baddeley, & Yiend, 1997). For instance, the reliability measures of the test-retest correlation coefficients for the 7 of the 9 subsets ranged from .57 to .87 (Manly et al., 1999). The reliability measures of the test-retest correlation coefficients for the Code Transmission subtest was 0.78. The validity measures of 6 of the 9 subtests ranged from 0.51 to 0.79 (Manly, 1999). The measure of validity for the Code Transmission was 0.49 (Manly, 1999).

The instrument is well cited in the attention literature in diverse contexts including Jamaica (e.g., Walker, Pierre, Christie, & Chang, 2013) and South Africa (e.g., Zondo & Mulder, 2014).

### **1.19.3 Sustained Attention Subtest**

The Code Transmission is an auditory vigilance-level measure that assesses sustained attention. Sustained attention tasks have been used in both normal and clinical populations under vigilance tasks, in which people are asked to monitor a stream of information for the occurrence of a target (Koelega, 1996; Mackworth, 1948; Mackworth, 1970). Children are asked to listen to a long, monotone series of numbers and listen for two 5s (Pretest) and for two 7s in a row (Posttest). When this pattern is noted, the child must state the number presented immediately before the target 5s or 7s. The target sequence was constant throughout the test. Following the practice sequence to ensure the child comprehends the test, 40 targets were presented which need to be identified (Manly et al., 1999). Please see *Appendix C* illustrating the code transmission.

### **1.20 Overview of intervention program**

The instrument used for my intervention (independent variable) was the Brainwave-R (Malia, Bewick, Raymond, & Bennett, 1997) which was developed in the United Kingdom. The Brainwave-R is widely used cognitive rehabilitation program designed to remediate attentional deficits. The Brainwave-R materials consist of a group of hierarchically organized tasks that exercise different components of attention commonly impaired after brain injury including sustained, selective, alternating, and divided attention (Malia et al., 1997).

The instrument is based on a number of tasks that include auditory attention tapes whereby the individual would have to listen to a sequence of descending number sequences, listening for specific numbers and letters, detecting specific targets within the presence of a distracter noise, tasks requiring switching sets and listening for numbers whilst trying to find them on a piece of paper (Dot-to-Dot pictures). A number of the Brainwave-R tasks combine both auditory and visual tasks. I will now describe the sequence of exercises used in my intervention protocol.

**Exercise One** of the Brainwave-R is a paced random number exercise (*Appendix D*). A random selection of distracter numbers were presented on a Compact Disc (CD) and a target number had to be identified. The participants were instructed to carefully listen to the CD and that each time the number 'two' was mentioned from the CD, they had to circle it on a worksheet provided.

**Exercise Two** was a paced random words exercise (*Appendix E*). A random selection of distracter words were presented on a CD and a target word had to be identified among distracters. The participants were instructed to carefully listen to a random selection of words which were read aloud to them, and that each time the word 'tree' was read out on the CD, they had to circle it on their worksheet. For contextual reasons exercise two was edited as the words for the Brainwave-R task were not commonly used in South African English. For example, words like hymn, lobster, snow, magnolia, sherry and gull are words that are not common to children in South Africa. Instead, lists of preschool Dolch words were used. The Dolch word list is a list of the most commonly used words in the English language (Johnson, 1971). These words were inserted into Microsoft Excel and were randomly assorted to match the Brainwave-R set, the only word retained was the target word 'tree'. The Dolch words were presented to the children and they would explain what the word meant in English, this was to make sure that they understood the commonly used words in the English Language. This task was allowed to be presented orally, and instructions indicated it was necessary to allow two seconds between speaking each word on the list.

**Exercise Three** was a paced random letters task. In this exercise participants had to listen to a random selection of letters on a CD. The participants were instructed to listen a CD and instructed that each time they heard the letter 'B' they had to circle it on their worksheet.

**Exercise Four** was a word targeting exercise. In this exercise, a target word had to be identified while listening to a story. The participants were instructed to listen to the administrator read a book and when they heard the word 'the' they had to circle it on their

worksheet. An English textbook from the participants' life orientation class was read by the researcher.

**Exercise Five** was a contingent of random letters exercise. A target letter had to be identified among a number of distracter letters on a CD. The participants were instructed to carefully listen to the CD and when they heard the letter 'S' they had to circle it on their worksheet, but only if this letter was preceded by the letter 'A'.

**Exercise Six** was a sound targeting exercise. A target sound had to be identified on a CD among a number of distracter sounds. The participants were instructed that every time they heard the sound 'SHHHH', they had to circle it on their worksheet.

**Exercise Seven** consisted of categorizing random word task (*Appendix F*). A number of words had to be categorized into conceptual categories. Participants were instructed to listen carefully to the researcher who presented a number of words each belonging to different conceptual categories such as: a) animal, b) shape, and c) tree. Each time a word was read, the participants had to look at their worksheet and place a check mark under the heading that best describes the category to which the word belongs. This task was edited as the words were not common to South African English, for example, words like oak, maple, redwood, beech, raccoon and gerbil. The words in the Brainwave-R task were replaced with pre-school Dolch words belonging to the aforementioned conceptual categories (Johnson, 1971). Instructions indicated that this task could also be presented orally by allowing ten seconds between speaking each word on the list.

**Exercise Eight** comprised a category targeting word task (*Appendix G*). This task required participants to find a number of target words among distracter words. The participants were instructed to listen to the researcher read a list of words, and that every time they heard the name of an animal, for example, *cat* or *dog*, they had to write it on their worksheet. Exercise eight was edited as the words were found to be uncommon such as moose, raccoon, deer,

groundhog and pelican are not common animals found in South Africa. This task was again contextualised to include pre-school Dolch words of animals familiar to the South African school context. Instructions indicated that this task could also be presented orally by allowing two seconds between speaking each word on the list.

**Exercise Nine** was an unpaced random numbers exercise. Once again the CD would play a long list of numbers and a target number had to be identified. The participants were instructed to listen carefully to the CD which presented random numbers, and were instructed that every time they heard the number '7' they had to circle this number on their worksheet. The numbers that were presented on the CD had some long gaps between them.

**Exercise Ten** was a category targeting (vowels) exercise. Again, the CD would play a list of letters and target letters had to be identified among distracters. The participants were instructed to listen to the CD and each time they heard the vowels: *A, E, I, O, U*, they had to write it on their worksheet.

**Exercise Eleven** was a counting exercise. In this exercise a number of sounds had to be tallied from a CD. The participants were instructed to listen to a CD which presented sounds, they were then instructed to count the number of sounds they heard within a specified time.

**Exercise Twelve** was a random dot-to-dot picture exercise (*Appendix H*). A number of dots had to be connected to make a picture which was guided by listening to numbers which connect the dots. The participants were instructed to listen to the CD which presented a list of numbers. They were instructed that when they heard the first number from the CD, they had to find it on the picture, and that when they heard the second number they had to join the first number to the second. This task carried on until all the dots had to be connected which made a picture.

All the tasks that were edited for contextual purposes (Exercise Two, Seven, and Eight) were discussed with the developer of Brainwave-R (Kit Malia, personal communication, March 16, 2014) and the original author of Brainwave-R suggested these changes. The Brainwave-R's sustained attention subsets are divided into 12 hierarchical exercises each stage was performed between 25 minutes and 45 minutes depending on the requirements of the task. All together, the participants participated in 12 rehabilitative exercises of Brainwave-R tasks over two months. The duration of parameters for the rehabilitation was balanced against the need for consistent practice and within the projects timeline and feasibility. The duration of the exercises is consistent with previous rehabilitation research (e.g., Boivin et al., 2010).

All the Brainwave-R materials are premised on experience dependent plasticity whereby the adaptability of the brain circuits is the result of changes in neural activity (Malia et al., 1997). The Brainwave-R program is designed as a treatment tool and not as a test; in this instance, issues around validity and reliability are different and not applicable to this instrument (Malia et al., 1997).

## **1.21 Placebo activities**

The control group did not receive the intervention but participated in three placebo activities: namely a) The Rey complex Figure, b) the Wechsler Adult Intelligence Test (Symbol Search), and c) the Wisconsin Card-Sorting Test. The Rey Complex Figure required participants to draw a complex figure which is more an assessment of memory and does not aid attention (Anderson, Anderson & Garth, 2001). The Rey Complex Figure requires the participants to first copy as accurately as possible the geometrical figure by free hand (recognition). After an interval, the participants had to draw what they could remember of the figure (recall) (Anderson et al., 2001).

The Symbol Search Test required participants to view two symbols on the left side of a page, they then had to search for these symbols on the right side of the same page. If they identify

any target symbols on the left side of the page which look like one of the targets on the right they responded yes on the sheet (Hallam, Olver, McGrath, & Norman, 2003). The last placebo activity was the Wisconsin Card-Sorting Test. This test presents a number of stimulus cards to the participant which are matched according to colour, shape or number. The participants' task was to place each card from the pile with the appropriate card in the top row, sorting by one of the three possible categories (colour, shape and number). Participants were not told the correct sorting category but only whether their responses were correct or incorrect. After a number of correct matches, the stimulus changed without notice and the participant had to shift to a new mode of classification (Stuss et al., 2000). All these activities were meant to keep the control group occupied, whilst the experimental group received the intervention. See figure 2.1 of the Summary of Research.

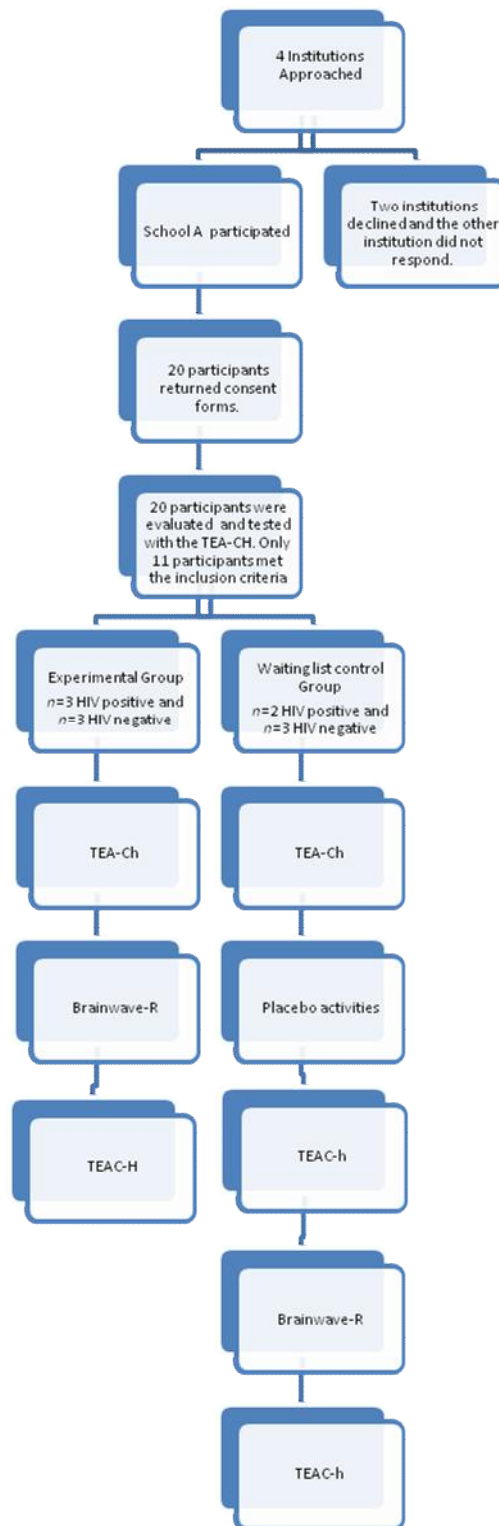


Figure 2.1 Summary of Research

## **1.22 Statistical Data Analysis**

Within health sciences research three major parametric assumptions: a) level of measurement, b) normal distribution of the dependent variable and c) data approximating the requirement of the central limit theorem which requires at least 30 participants aid data analysis. The latter is consistently violated in health sciences research due to small sample sizes, and for this reason non-parametric tests are used (Tomkins & Hall, 2006). My analysis employed independent and repeated measures analysis to find out if the experimental group improved after the intervention. Since the assumptions of the t-test were violated, the researcher used non-parametric tests. As such, a number of Mann Whitney U tests and Wilcoxon Signed Rank Tests were run on the data. Receiving a statistically significant result ( $p = 0.05$ ) on these tests would indicate that the intervention may have had an effect on the improvement on sustained attention functioning. All data was analysed using the statistical package IBM Statistics 22 (Pallant, 2010).

Data was collected from the TEA-Ch and was analysed in conjunction with the data from the demographic questionnaire to enhance data analysis. A number of analyses were carried out on the data. Descriptive statistics were used to analyse the demographic data. These statistics were used to facilitate a laconic presentation of the demographic data, as well as to make an easy comparison between the demographic items and the results (Shaughnessy & Zechmeister, 1994).

For hypothesis one, a Mann Whitney U Test was carried out to detect any differences on the posttest score of sustained attention between the experimental and control group. Hypothesis two used a Mann Whitney U Test to detect any differences on the posttest score of sustained attention between the HIV+ experimental group and the HIV+ control group. For hypothesis three, a Wilcoxon Signed Rank Test was run on the primary outcome measure of sustained attention, in order to detect any differences in the pretest and posttest scores of the HIV+

participants. Data was evaluated in terms of the results of statistical tests and working out the implications for the hypotheses.

Non-parametric statistics in academia are pervaded by stigma as it is perceived that these statistics are less powerful (i.e., power in this instance is premised on the ability to reject the null hypothesis) (Tomkins & Hall, 2006). However, research suggests that parametric tests are more powerful than non-parametric tests only if all parametric assumptions are met (Berg & Latin, 2007; Blair & Higgins, 1985; Gibbons & Subhabrata, 2010; Hunter & May, 1993; Pett, 1997). Empirical studies have found that when comparing parametric with non-parametric tests, the latter, are in fact more powerful with smaller sample sizes (Blair & Higgins, 1985; Conover & Iman, 1981). For example, Blair and Higgins (1985) compared a paired sample t-test to the Wilcoxon signed rank test using a simple pre- and posttest design with different sample sizes ( $N=10, 25, 50$ ). Blair and Higgins (1985) found that the t-test and Wilcoxon signed rank test are both highly adequate tests, however, the Wilcoxon signed rank test is particularly powerful with small sample sizes.

### **1.23 Ethical considerations**

This study received ethical approval from the a) Rhodes University Ethics Committee (*Appendix I*), b) The Humanities Higher Degrees Committee (*Appendix J*) both at Rhodes University as well as from c) The school where the research took place (*Appendix K*) and c) The Department of Education (*Appendix L*). Given the sensitive nature of the research, all the participants' information was kept strictly confidential and followed the Helsinki Protocol of Ethics (World Medical Association, 2001). In line with the protocol, parents and participants received a letter (*Appendix M*) which outlined the nature, purpose and objectives of the study. Informed consent was sought from the parents (*Appendix N*) as well as the participants (*Appendix O*) to provide consent for participation in the research. The consent forms were returned in an envelope in order to ensure anonymity. All participants were given the details of the primary researcher and were encouraged to communicate all questions or concerns. Participants were informed of the voluntary nature of the research and that they could

withdraw from the study at any point without any harm to themselves. Furthermore, participant confidentiality and the anonymous nature of the project were stressed at all times to the participants. No identifying information on participants was included in the dissertation. All the participants' information was kept confidential and any publication will not mention them. All data collected during the study was stored in a safe and secure location within the School of Psychology, at Rhodes University. The remaining data that was not utilized for the research and was destroyed

## RESULTS

In this chapter, the demographic data will be presented by descriptive statistics (means, standard deviations, and percentages). This will be followed by the sustained attention scores from the TEA-Ch of the pretest and posttest scores. Thereafter, normality and distribution of raw data from the TEA-Ch are examined through the inspection of skewness and kurtosis measures and standard errors, and a visual inspection of normal Q-Q plots. Levene's test was used to verify the equality of variances of the sample. Following this, statistical analyses were carried out to address the research questions. Subsequently, the dependent variable was used to structure the presentation of the main findings of the experiment. Since the data was found to violate the assumptions of normality, Mann-Whitney Tests was carried out on the dependent variable to evaluate differences between the experimental and control group on post sustained attention scores. This was followed by the Wilcoxon Signed-Rank Test to evaluate whether there was a change in the HIV+ participants' performance between the pre- and posttest sustained attention scores.

### **1.24 Demographic Characteristics of Participants and Parents**

The sample was comprised of 11 participants. The average age of participants was 12 years ( $SD=1.44$ ) and this population was in the early stages of adolescence. More than half of the sample was male (63.6%), with a smaller percentage comprising of females (36.4%). As depicted in Table 3.1, five participants were HIV positive (45.5%), and 6 were HIV negative (54.5%). Table 3.1 further indicates that 4 out of the 11 participants (33.3%) had repeated a school grade at the time of the research.

The school from which the sample was drawn services predominantly low-socio economic students. All participants were first language Xhosa speakers. Based on the medical health records obtained from the school, none of the participants had further neurological conditions such as epilepsy, meningitis, or traumatic brain injury.

In terms of the parent demographics, the majority of parents attended secondary school (54.4%), while a smaller percentage attended primary school (45.5%). The highest grade completed was grade 8.

Table 3.1 *Demographic Characteristics of the Sample*

Variables	Participants N=11	
	Mean	SD
Age	12.09	1.44
<b>Grade</b>	<b>Number of Participants (%)</b>	
4	2 (19%)	
5	3 (27%)	
6	1 (9%)	
7	5 (45%)	
<b>Repeated a grade</b>	4 (36.4%)	
<b>Gender</b>	<b>Number of Participants (%)</b>	
Male	7 (63.6%)	
Female	4 (36.4%)	
<b>HIV status</b>	<b>Number of Participants (%)</b>	
HIV positive	5 (45.5%)	
HIV negative	6 (54.5%)	
<b>Eating Habits</b>	<b>Number of Participants (%)</b>	
Breakfast every day	9 (81.8%)	
Lunch everyday	10 (90.9%)	
Dinner every night	10 (90.9%)	
<b>Reading</b>	<b>Number of Participants (%)</b>	
Daily	6 (54.4%)	
Weekly	4 (36.4%)	
Monthly	1 (9.1%)	
<b>Toys</b>	<b>Number of Participants (%)</b>	
Card games	9 (81.8%)	
Jigsaw puzzles	2 (18.2%)	

### 1.25 Matching Characteristics in the Experimental and Control Groups

The two research groups were matched on a number of demographic characteristics to ensure plausible conclusions, and these included a) HIV status, b) age, c) gender, and d) grade at school (Please see Table 3.2). The experimental group comprised of 3 HIV+ participants and 3 HIV- participants. While the control group comprised of 2 HIV+ participants and 3 HIV – participants. All HIV+ participants in the sample were on a course of ARVs. With respect to gender, the experimental group was made up of 4 males (66.7%) and 2 females (33.3%), respectively. In contrast to the experimental group there were 3 males (25.0%) and 2 females (40.0%) within the control group. The average grade in the control group was grade 6 ( $SD=1.32$ ) and the control group grade 5 ( $SD=1.14$ ). In terms of repeating a grade at school, responses showed that within the experimental group 3 children had repeated a grade at school. Interestingly, two of the participants who repeated a grade in the experimental group were HIV+. In the control group, one participant had repeated a grade and they were also HIV+.

Table 3.2 *Group Demographics*

Variables	Experimental Group $n=6$		Control Group $n=5$	
	Mean	SD	Mean	SD
Age	12.00	1.26	12.20	1.78
Average years of Education	6.17	1.32	5.40	1.14
	Number (%)		Number (%)	
Male	4 (66.7%)		3 (25.0%)	
Female	2 (33.3%)		2 (40.0%)	
Repeated a Grade	3 (50.0%)		1 (20.0%)	
HIV Positive	3 (50.0%)		2 (40.0%)	
HIV negative	3 (50.0%)		3 (60.0%)	

## 1.26 TEA-Ch: Characteristics of the sample

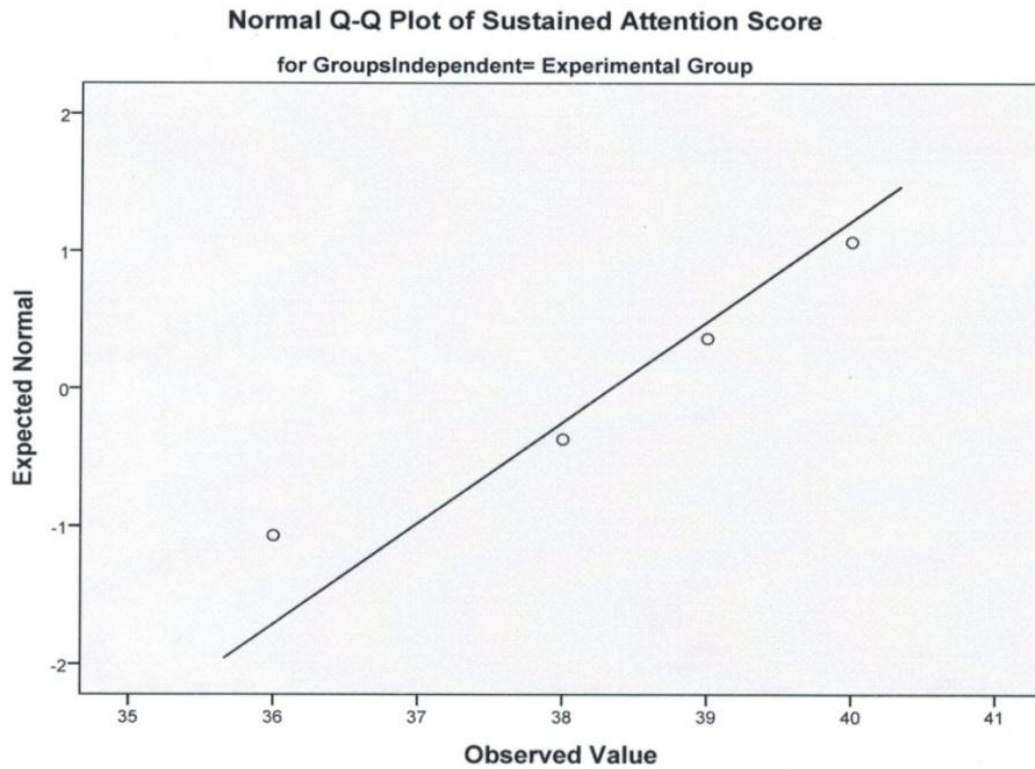
Sustained attention was measured with the TEA-Ch. According to Table 3.3 participants ranged between the bottom 3.3% to the top 93.3% of their age range. The HIV+ group scores ranged from 0.6% to performing better than 56.6% for their age and sex norms. The HIV- participants' scores varied between 0.2% all the way up to performing better than 93.3% of their age and sex norms.

Table 3.3 *Clinical characteristics of the Sample Before and After the Intervention*

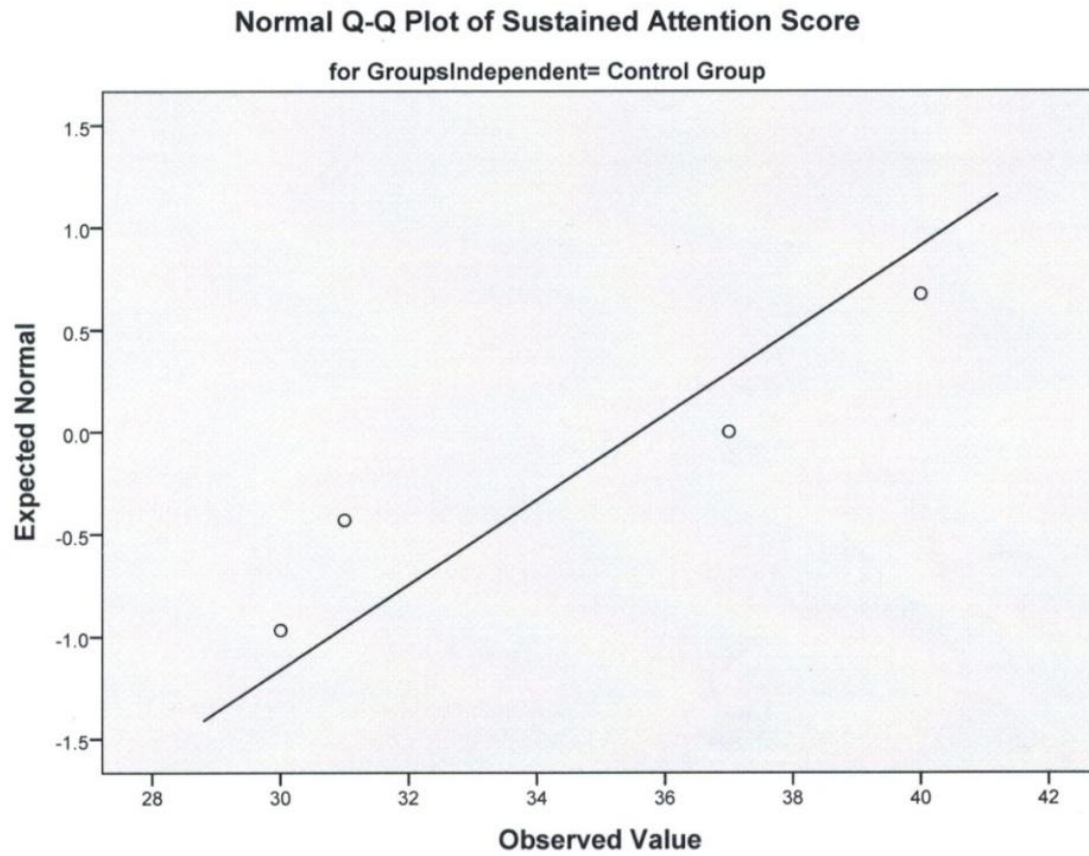
<b>Participants</b>	<b>Pretest Score</b>	<b>Posttest Score</b>	<b>Percentile Band</b>
HIV+	30	36	1.5-3.3
HIV+	31	38	3.3-6.7
HIV+	38	39	43.4-56.6
HIV+	35	38	12.2-20.2
HIV+	29	40	0.6-1.5
HIV-	38	39	43.4-56.6
HIV-	40	40	87.8-93.3
HIV-	28	38	0.6-1.5
HIV-	39	40	56.6-69.2
HIV-	26	40	0.2-0.6
HIV-	40	39	87.8-93.3

### **1.27 Normality Testing**

Due to the small sample size ( $N=11$ ) normality of data could not be assumed (Field, 2013). Firstly, parametric statistical methods require that the dependent variable is approximately normally distributed for each category of the independent variable (Field, 2013). In order to ascertain this, an inspection of the skewness and kurtosis measures, and a visual inspection of Q-Q plots (Figure 3.1 and 3.2) revealed that the sustained attention scores were not normally distributed for both samples. The experimental group had data scores with a skewness of -1.052 ( $SE=0.845$ ) and a kurtosis of 0.769 ( $SE=1.741$ ). The control group had data scores with a skewness of -0.405 ( $SE=0.913$ ) and kurtosis of -1.485 ( $SE=2.00$ ) signifying non-parametric distribution of scores (Cramer & Howitt, 2004; Cramer, 1998; Doane & Seward, 2011). An inspection of the normality Q-Q plots further highlights this non-parametric distribution as the majority of scores do not fall within the Q-Q plot line (Field, 2013). A non-parametric Levene's test was used to verify the equality of variances in the samples (homogeneity of variance). The result of the test was less than ( $p<.05$ ), therefore, variances are significantly different and parametric tests cannot be used (Nordstokke, Zumbo, Cairns, & Saklofse, 2011; Nordstokke & Zumbo, 2010).



*Figure 3.1* Normal Q-Q Plot Experimental Group's posttest test scores on the TEA-Ch Code Transmission subtest. The dots slightly deviate from the line which suggests that the data are not normally distributed.



*Figure 3.2* Normal Q-Q plot Control Group's posttest scores on the TEA-Ch Code Transmission subtest. The dots deviate from the line which suggests that the data are not normally distributed.

## 1.28 Statistical Analysis

For analytical purposes, effect sizes were calculated using the formula:  $r = Z/\sqrt{N}$  (Field, 2013). The following descriptors in Table 3.4 have been used to define the size of the effect (Cohen, 1992).

Table 3.4 *Definition of Effect Sizes*

Effect Size ( $r$ )	Definition
0.10	Small effect: The effect explains 1% of the variance
0.30	Medium effect: The effect accounts for 9% of the variance
0.50	Large effect: The effect accounts for 25% of the variance

### 1.28.1 Testing Hypothesis 1

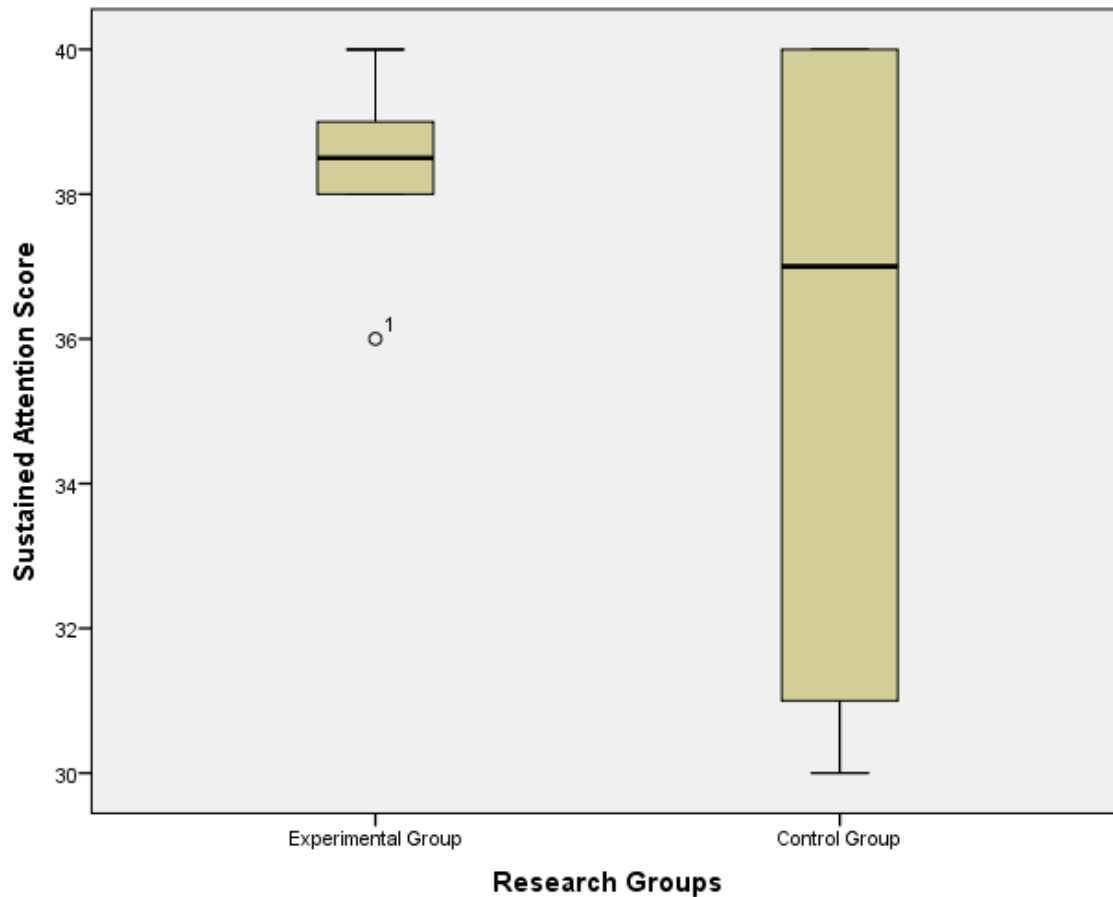
Hypothesis 1: This hypothesis states that following the Brainwave-R intervention, the experimental group will show improved posttest sustained attention scores on the TEA-Ch compared to the control group.

A *Mann Whitney U test* was performed to examine the effect of the cognitive intervention on the sustained attention scores. Post sustained attention cores on the TEA-Ch were used to derive conclusions on this hypothesis. The *Mann Whitney U Test* revealed that the experimental group ( $Mdn=38.50$ ) did not differ significantly from the control group ( $Mdn=37.00$ ) after the cognitive rehabilitation intervention,  $U=12.00$ ,  $z= -.55$ ,  $p= .66$ ,  $r= -.17$ . Table 3.5 and Figure 3.4 shows the results from this analysis.

Table 3.5 *Mann Whitney U Test between Experimental and Control Groups*

Groups	N	Mean Rank	Sum of ranks	Median	<i>U</i>	<i>Z</i>	<i>p</i>	<i>R</i>
Experimental	6	6.50	39.00	38.50	12.00	-.55	.66	-.17
Control	5	5.40	27.00	37.00	12.00	-.55	.66	-.17

Note. *U*= The Mann-Whitney Test Statistic; *Z*= A standardized score (i.e., the value of a statistic divided by its standard error); *p*= significance level; *r*= effect size.



*Figure 3.3* Performance of Experimental Group after the intervention versus Control Group after the placebo activities. The Box Plot of the experimental group is comparatively short to the control group suggesting that there is not more variability in the control group's posttest score. By looking at the Box Plot the score distribution reveals that most of the participants' scored on the high end of the spectrum compared to the control group (Field, 2013). The box plot of the experimental group suggests that one participant scored on the low end of the spectrum and therefore did not improve like the other participants. In terms of the control group, the Box Plot is long which reveals that there is a lot of variability on the posttest scores whereby some participants' scored low and some scored high. When comparing the median of the two Box Plots one can see that the experimental group's median is 38 whereas the control group's median is 37, therefore the experimental group performed slightly better overall despite the insignificant result.

### 1.28.2 Testing Hypothesis 2

In order to isolate the effects of the cognitive rehabilitation therapy a *Mann Whitney U Test* was run to determine whether there was a significant difference between the HIV+ participants from the experimental and the control group. The logic of running the analysis solely on the HIV+ group, was to control for the effect of the HIV- group who may not have challenges with sustained attention, and thus influence pre- and posttest results. This test was run as it was established from the TEA-Ch, that all of the HIV+ participants had scores ranging from 0.6% to performing better than 56.6% for their age and sex norms. In comparison, the HIV- participants' scores ranged from the bottom 0.2% to 93.3%. Overall, the HIV- participants scored higher than the HIV+ participants on the sustained attention measure. In order to control for the effects of those HIV- participants with normal attention functioning, which may in fact result in no improvement after the intervention, a *Mann Whitney U Test* was performed on all the HIV+ participants from the experimental ( $n=3$ ) and waiting list control group ( $n=2$ ), to establish whether there was an improvement after the intervention.

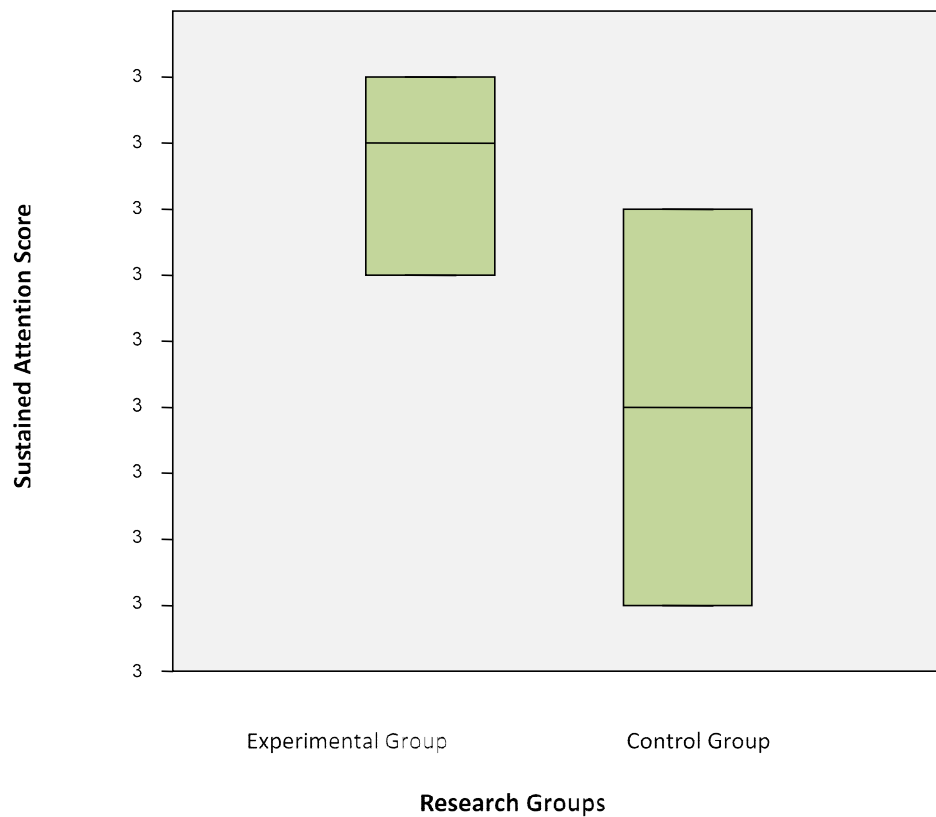
Hypothesis 2: This hypothesis states that HIV+ participants in the experimental group will show improved posttest scores on sustained attention compared to the HIV+ participants in control group after receiving the Brainwave-R cognitive rehabilitation.

The test statistic revealed that the HIV+ experimental group ( $Mdn=38.00$ ) did not differ significantly from the HIV+ control group ( $Mdn=34.00$ ) after the cognitive rehabilitation,  $U=1.00$ ,  $z=-1.15$ ,  $p=.40$ ,  $r=-0.52$ . The results are presented in more detail in Table 3.6 and Figure 3.5.

Table 3.6 Mann Whitney *U* test between experimental and control (HIV+)

<b>Groups</b>	<b>N</b>	<b>Mean Rank</b>	<b>Sum of ranks</b>	<b>Median</b>	<b><i>U</i></b>	<b><i>Z</i></b>	<b><i>p</i></b>	<b><i>R</i></b>
<b>Experimental</b>	3	3.67	11.00	38.00	1.00	-1.15	.40	-0.52
<b>Control</b>	2	2.00	4.00	34.00	1.00	-1.15	.40	-0.52

Note. *U*= The Mann-Whitney Test Statistic; *Z*= A standardized score (i.e., the value of a statistic divided by its standard error); *p*=significance level *r*= effect size.



*Figure 3.4* Performance of Experimental Group (HIV+) after the intervention versus Control Group (HIV+) after the placebo activities. The experimental group's scores do not show much variability in their distribution which suggests that the experimental group performed towards the high end of the spectrum with the lowest score being 36 and falling in the lower quartile, while the highest score was 39 falling into the upper quartile. Since there are no whiskers in the box plots the lower and upper quartile are equal to the minimum and maximum scores, respectively (Field, 2013). The box plot representing the control group's scores is more variable, which means that the scores were more widely distributed. The control group's lowest score was 31 which represent the lower quartile and the upper quartile was 37. In terms of the median scores, the experimental group reached a median of 38, while the control group scored a median of 34. Overall, it is clear from analysing the box plots that the experimental group performed slightly better overall.

### 1.28.3 Testing Hypothesis 3

It was established from the TEA-Ch that all of the HIV+ participants (in both the experimental group and control group) had below normative scores compared to their age and sex norms and the HIV- participants. Therefore, it was necessary to establish whether the HIV+ participants improved on the sustained attention measure after the intervention. Following the Declaration of Helsinki (2013) that states the extension of positive research findings on the experimental group must be applied to the control group; as such, the HIV+ participants in the control group later received the Brainwave-R intervention. To measure for pre-post sustained attention scores on this combined group (including both the HIV+ experimental and HIV+ control participants) a *Wilcoxon Signed Rank Test* was performed on all the HIV+ participants from the experimental ( $n=3$ ) and waiting list control group ( $n=2$ ), to establish whether there was an improvement after the intervention

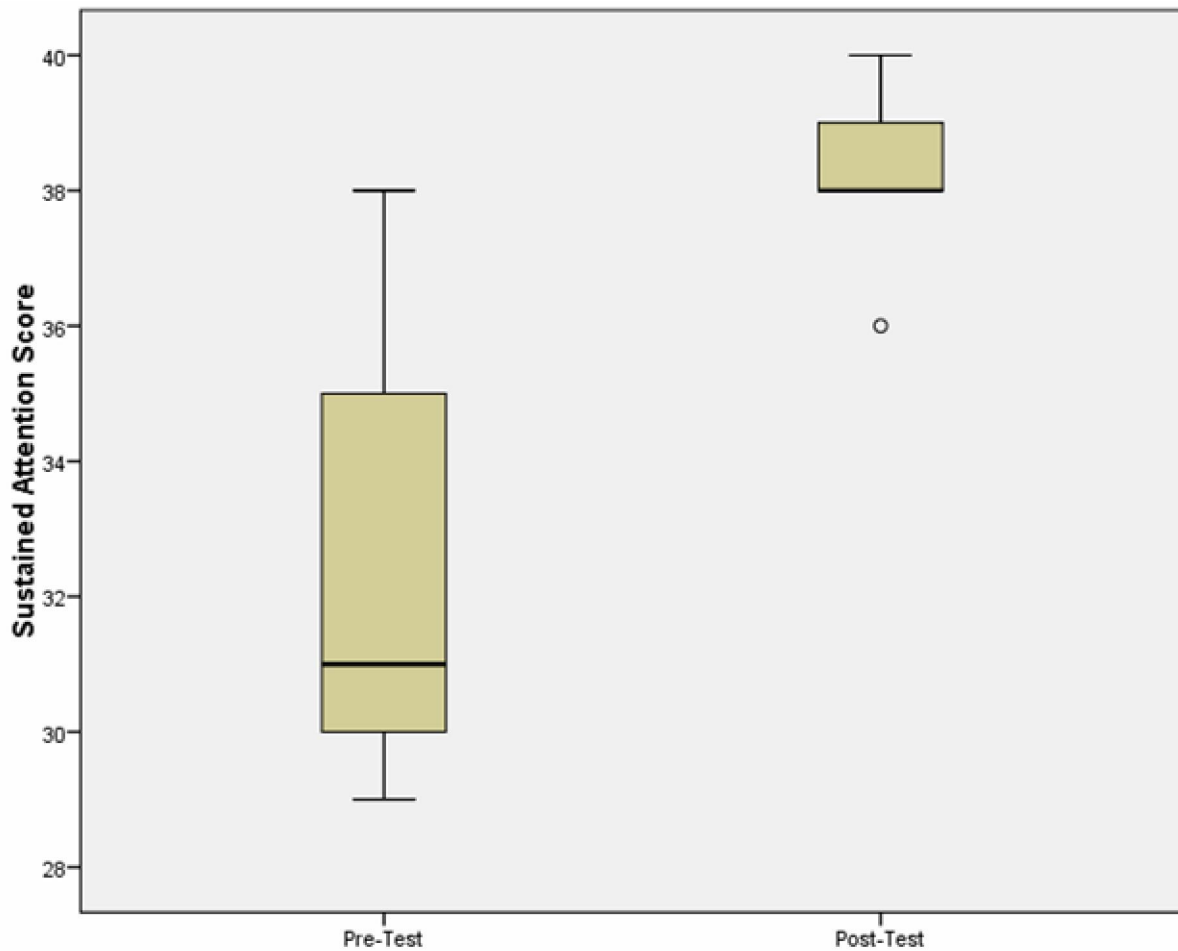
Hypothesis 3: This hypothesis states that there will be a significant effect with regard to pre and post attention scores following the Brainwave-R intervention scores with regard to the HIV+ participants.

The *Wilcoxon Signed Rank Test* revealed that there was a statistically significant effect between pretest scores ( $Mdn = 31.00$ ) and posttest scores ( $Mdn = 38.00$ ), after the intervention for the HIV+ participants from the combined sample,  $T=15.00$ ,  $z = -2.02$ ,  $p = .04$ ,  $r = -.90$ . The median pre- and posttest scores for the HIV+ group are tabulated in Table 3.9 and Figure 3.8.

Table 3.7 *Wilcoxon Signed Rank Test between Pretest and Posttest scores*

<b>Groups</b>	<b>N</b>	<b>Mean Rank</b>	<b>Sum of Ranks</b>	<b>Median</b>	<b>T</b>	<b>Z</b>	<b>p</b>	<b>R</b>
Pretest control	5	Negative:.00	Negative:.00	31.00	15.00	-2.02	.04	-.90
		Positive:3.00	Positive:15.00					
Posttest	5	Negative:.00	Negative:.00	38.00	15.00	-2.02	.04	-.90
		Positive:3.00	Positive:15.00					

Note.  $T$ = Wilcoxon Signed Rank test statistic;  $Z$ = A standardized score (i.e., the value of a statistic divided by its standard error);  $p$ =significance level ;  $r$ = effect size.



*Figure 3.5* Pretest and Posttest scores of all HIV+ participants after intervention. The pretest scores show a degree of variability in the cluster of scores. The minimum score is 29 while the maximum is 38. This shows that the HIV+ participants' scored very high and some very low on the pretest of sustained attention. In comparison, the posttest scores show much less variability with a minimum score of 38, and a maximum score of 40. Therefore, most participants improved on the posttest measure of sustained attention. The median score of the posttest measure of sustained attention is 38, which is a seven point improvement on the pretest median score of 31. The one outlier shows that someone did not reach the same high scores as the rest of the HIV+ participants.

## DISCUSSION

For HIV+ children living in Africa, access to ARV therapy and successful virologic management has dramatically improved survival rates of HIV+ children (Van Rie et al., 2007). However, even in clinically stable children with successful virologic management, ARV therapy does not reverse neurocognitive decline due to HIV infection (Koekkoek et al., 2008). In trying to meet the needs of this public health crisis, authors have stressed the need for experimental-based research examining the efficacy of cognitive rehabilitation for remediating HIV-associated neurocognitive impairment. The current research set out to examine the efficacy of utilising Brainwave-R rehabilitation program to redress sustained attention in a sample of HIV+ children. It is important to state that a number of variables are crucial in such a study investigating HIV, and these include, amongst others, nutrition (Walker et al., 2011), sociocultural context (Bradley & Corwyn, 2002), environmental context (Smith et al., 2006) and how these interact with experimental and methodological manipulations.

To the knowledge of the researcher, this is the first study to examine, the interface between cognitive rehabilitation and HIV cognition in an experimental manner. The study's specific hypotheses were drawn from the theoretical foundations of neuroscience and neuroplasticity. Both domains are within the broad field of neuropsychology. The convergent theoretical fields of neuroscience and neuropsychology have, over the years, begun to study the mechanism of brain plasticity as it relates to traumatic brain injuries. The domain of brain plasticity has recently been extended to the study of HIV and cognition.

The specific hypotheses tested in the current study drew very much from the theoretical work of Luria (1962) in his seminal work on *Higher Cortical Functions in Man*. Two key concepts arising from this work are the key theories that underpin brain plasticity and these are: brain *compensation* and brain *restoration*. These theories that form the crux of brain plasticity were extended to study HIV cognition and HIV cognitive rehabilitation, a critical field of medical

science and psychology that has not been well researched (Weber et al., 2013). To recap, ARVs have been found to not completely reverse the effects of HIV penetration into the brain and have been shown to cause cognitive decline in effected individuals (Koekkoek et al., 2008). New techniques to supplement ARVs have thus been suggested to stem the progression of HIV cognitive decline. In the subsequent sections, I will a) summarize the results of my findings, b) discuss ways in which these findings fit and extend the literature in this field, c) note the limitations of the research, d) discuss the interplay of disease and environment on cognition, e) propose directions for future research, and f) highlight the contributions that this research might make towards providing policy recommendation that will help towards a better understanding of HIV as it is related to cognition.

### ***1.29 Summary of Results: The state of the hypotheses***

Embedded in brain plasticity theory, the current thesis sought to test three specific hypotheses that were related to HIV and cognitive rehabilitation and these were: (1) Participants exposed to a cognitive rehabilitation program to aid sustained attention would show improved posttest sustained attention scores compared to a control group, (2), Controlling for the effects of HIV- participants, HIV+ participants in the experimental group would show improved posttest sustained attention scores compared to HIV+ participants in the control group, and (3) There would be a significant effect with regard to pre- and posttest sustained attention scores following the Brainwave-R intervention scores with regard to the HIV+ participants.

### 1.29.1 Hypothesis 1

Cognitive rehabilitation literature suggests that sustained cognitive rehabilitation over a period of time can have positive cognitive effects on the human brain following injury (Luria, 1963). Moreover, the research methodology literature suggests that should an intervention of any kind be possible, positive results would be evident on the experimental group receiving the intervention as opposed to the control group (Field, 2013). The hypothesis here, then, was that both HIV+ and HIV- participants in the experimental group will show improved post sustained attention scores (on the TEA-Ch) following the Brainwave-R intervention compared to the control group.

In hypothesis 1 a *Mann Whitney U Test* was run between the experimental group versus the control group to establish if the intervention worked on the experimental group. This hypothesis was inclusive of HIV+ and HIV- participants. This hypothesis was disconfirmed. Although posttest scores ( $Mdn=38.50$ ) of the experimental group following the intervention were larger than posttest scores ( $Mdn=34.50$ ) for the control group, participants in the experimental groups did not differ significantly on posttest attention scores compared to the control group's posttest scores.

When interpreting the results it is important to consider that neuropsychological tests on attention have found that attention functioning is worse in HIV+ adolescents compared to HIV- adolescents (Watkins et al., 2000). Our findings corroborated this by showing that the majority of HIV- participants' performed better than 0.2% up to 96.2 % of adolescents comparable in terms of their age and gender norms. In comparison, the HIV+ participants' performance on the sustained attention subtest of the TEA-Ch ranged from 0.6% to 56.6% for their age and sex norms. These scores on sustained attention are comparable to other

international and local studies on attentional functioning in HIV+ adolescents (Foster et al., 2012; Hoare et al., 2012; Martin et al., 2006).

Therefore, the majority of HIV- participants' sustained attention scores could have resulted in no improvement after the intervention as someone who is functioning with normal attention and does not have neurological damage would not need rehabilitation and as such would not improve. It is reasonable to conclude that the HIV- participants' scores may have diluted the results as someone performing better than 96.6% of adolescents who are comparable in terms of age and gender would not benefit from cognitive rehabilitation given the fact they are functioning cognitively well.

### **1.29.2 Hypothesis 2**

The hypothesis here, based on the same literature as cited above, was that HIV+ participants in the experimental group ( $n=3$ ) would show improved post sustained attention scores following the intervention as opposed to HIV+ participants in the control group ( $n=2$ ). Cognitive psychology research suggests that sustained attention deficits are the cornerstone of HIV-associated neurocognitive decline in paediatric HIV (Foster et al., 2012; Martin et al., 2006; Hoare et al., 2012). Additionally, neuropsychological tests on attention have found that attention functioning is worse in HIV+ children compared to HIV- adolescents (Watkins et al., 2000). It is important to note that this analysis excluded the HIV- participants from both the experimental and control group as it was thought that these participants may distort results.

The above hypothesis was disconfirmed. HIV+ participants in the experimental group ( $Mdn=38.00$ ) did not show improved post attention scores (on the TEA-Ch) following the intervention compared to the HIV+ participants in the control group ( $Mdn=34.00$ ). Although these results did not reach statistical significance, it is clear that in the experimental group there is an improvement in sustained attention scores following the rehabilitation compared to

the control group. In particular, when the HIV- participants were removed from the second statistical analysis this improvement is much bigger which suggests that some of the HIV- participants may have not needed the rehabilitation and therefore did not improve on the posttest measure. Although these results are not significant they are very suggestive of an improvement in the experimental group after the intervention. It is therefore important to consider the statistical constraints that could have influenced the results.

For both the above hypotheses, it is probable that these findings are reflective of a Type II error due to a small sample and small effect size (Field, 2013). Therefore, the small sample size made it difficult to detect a real relationship between the independent and dependent variables. In larger samples, improvements have been seen, for example, in Boivin et al (2010) study which included 60 HIV+ children in the cognitive rehabilitation group, significant improvements were seen on executive functioning and attention ( $p < 0.001$ ).

### 1.29.3 Hypothesis 3

Although Hypothesis 2 generated nonsignificant findings, the experimental group's posttest score ( $Mdn=38.00$ ) was bigger than the control group's posttest score ( $Mdn=34.00$ ). It was necessary to examine the pretest and posttest scores of the HIV+ participants after the intervention to establish how much they improved. If the interpretation of Hypothesis 2 is correct, that the findings of this hypothesis reflected a Type II error due to the small sample size, then increasing the sample would negate this constraint. In order to (a) increase the sample size and (b) for ethical reasons, the HIV+ participants in the control group underwent the cognitive rehabilitation. The result of the HIV+ control group receiving the intervention was that a relatively 'larger' composite HIV+ group consisting of 5 participants could be analysed.

Similar to the experimental group, participants in the control group were guided through a drill and practice of re-training sustained attention to try and re-acquire sustained attention

functions that may have been affected as a result of HIV-associated brain injury (Weber et al., 2013). Based on rehabilitation theory (e.g., Luria, 1963) it was predicted that cognitive rehabilitation and functional improvements would be noted as a result of rehabilitation of sustained attention. As such, the hypothesis here was that once examined as ‘one composite group’ that has received cognitive rehabilitation, all HIV+ participants would show improved attention scores following the rehabilitation. A *Wilcoxon Signed Rank Test* confirmed Hypothesis 3 ( $p=.04$ ).

Some results from the study crystallize the associations which have already been drawn between constructs under investigation in the literature review (section: 1.4), repeated training of sustained attention tasks increases the synaptic efficacy between neurons that fire together supporting functional reorganization of sustained attention (Luria, 1963). In support of this was the significant finding found after the rehabilitation for all the HIV+ participants ( $p=.04$ ). In particular, the HIV+ participants from the experimental and waiting list control group significantly improved after the intervention from a pretest score ( $Mdn=31.00$ ) to the posttest score ( $Mdn=38.00$ ). The magnitude of this effect between pretest and posttest scores is reflected in the large effect size ( $r=.90$ ). More importantly, the posttest measures of sustained attention after the intervention ranged between 30.9%-87.8% in comparison to the pretest measures of 0.6%-56.6% for their age and sex norms.

Explaining these improvements in terms of plasticity is not a straightforward task. One of the pervading enigmas of the human brain is how neurons and their synapses alter their structure to support plasticity in the human neocortex. This question relates to an unresolved issue in the literature on how neuroplastic gains should be measured and then linking those neural changes to behaviour. For a start it is impossible to track neuroplastic gains in response to rehabilitation. This is because the cellular responses as a result of plasticity are happening among 100 billion neurons, which are connected by 100 trillion synapses sending signals among the brain's neural networks (Zimmer, 2011). For this reason, it becomes difficult to link behavioural changes as a response to rehabilitation with what is happening at a neural level. This is because changes in behaviour alone are not direct measures of plasticity, since neuropsychological tests measuring behaviour do not explain how the brain is changing its

structure in response to learning and coding new experiences (Warraich & Kleim, 2010). But neuroscientists have found that a number of structural changes are possible which may support compensatory brain strategies, these involve changes in individual neurons such as: synapse size and number; spine density; dendritic and axon arbour; and receptor density. At a more theoretical level, there still remains unresolved issues in the literature as to whether functional reorganization in humans is the result of physical changes in brain anatomy (i.e., such axon growth or dendritic sprouting (Jain, Florence, Qi, & Kaas, 2000)), or if this is the result of an unmasking of already existing dormant synapses (Henderson, Gustin, Macey, Wrigley, & Siddall, 2011). One view of structural plasticity believes that it is the result of neural restructuring (Darian-Smith & Gilbert, 1994). Another hypothesis suggests changes in cortical connectivity which is mediated by individual synapses, without rearrangements of neuronal processes (Knott, Holtmaat, Wilbrecht, Welker, & Svoboda, 2006; Stepanyants, Hof, & Chklovskii, 2002; Ziv & Smith, 1996). It is likely that both models regarding structural plasticity take affect at different time-scales (Bailey & Kandel, 1993) and could explain the significant changes that account for the significant results accompanying this hypothesis.

Therefore, due to the lack of histological analyses, the present study cannot confirm that the improvements as a result of cognitive rehabilitation are necessarily due to the rehabilitation at a neural or dendritic level. But in principle, the literature claims that synaptic connections among neurons are highly malleable and plastic (Sjostrom, Rancz, Roth, & Hausser, 2008). Therefore, compensatory brain strategies, as practised in this research, could rely on brain plasticity by modifying existing synapses or through creating novel circuitry so that the lost cognitive function is supported in the brain. This characteristic may help explain the improvements seen after the intervention.

To the extent this is true, reorganization of sustained attention occurred through targeting the cognitive deficit through repeated training exercises. This translated into strengthening of neuronal connections in the brain. In order to support these new connections healthy residual brain tissue compensated for the deficit (Luria, 1963). A number of cellular changes are

possible as neural circuits are comprised of neurons, axons, dendrites and the synapses that connect neural circuitry together. Therefore, compensatory brain strategies could have occurred through new connections of axonal sprouting, dendritic growth or a change in the strength of synaptic connections. These cellular changes may underlie the remodelling of neural circuits in order to support the data.

### ***1.30 The Current Research Placed in the Context of Related Work***

The current research is an expansion of a very small group of research endeavours that have investigated cognitive rehabilitation and HIV. To date only three published studies have assessed the efficacy of cognitive rehabilitation in improving HIV-related cognitive decline and have provided evidence for the cognitive rehabilitation of HIV and these are the studies by Boivin et al. (2010), Becker et al. (2012), and Vance et al. (2012)<sup>3</sup>. The current study extends the literature on the cognitive rehabilitation of HIV-related cognitive decline and has provided further evidence for the potential of compensatory cognitive approaches. All together the studies demonstrate some positive findings of the benefits of cognitive rehabilitation from adolescence to adulthood. The magnitude of these results following cognitive rehabilitation range from medium to large effect sizes for attention  $r=0.77$  (Boivin et al., 2010), executive functions  $r=0.69$  (Boivin et al., 2010), and information processing speed  $r=0.42$  (Vance et al., 2012). The current study extends these findings by demonstrating the efficacy of improving sustained attention in HIV+ adolescents,  $r=0.90$  through cognitive rehabilitation.

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<sup>3</sup>The three published studies investigating the efficacy of cognitive rehabilitation in improving HIV-associated neurocognitive impairment were discussed in section 1.11 in the literature review

Looking beyond the success of the interventions it is worthy to consider the different methodologies used by these different studies and how these may have influenced findings. Noteworthy, is that out of the three studies which assessed cognitive rehabilitation, Becker et al. (2012) did not find significant effects of the intervention on cognitive performance. The nonsignificant result may, in fact, reflect a statistical artefact as only 30 HIV+ participants were included in their study, thus limiting the probability of detecting meaningful results. The same logic can be applied to the current study which was inclusive of 11 participants. On the contrary, larger samples by Boivin et al., 2010 ( $N=60$ ) and Vance et al., 2012 ( $N=46$ ) found meaningful results.

One of the limitations of the above three published studies was that they did not use an active control group; instead, they used a no-contact control group (Boivin et al., 2010; Becker et al., 2012; Vance et al., 2012). For example, all three studies used computerized rehabilitation programs. It is possible that the improvements seen here are due to more experience with the computer games. Furthermore, in the case of Boivin et al. (2010) study the significant gains as a result of the intervention may be the result of normal neural development as a result of maturation. Therefore, without an active control condition it is not possible to link compensatory brain strategies to cognitive rehabilitation therapy. The current study has contributed to the literature by including an active control group in the study design which isolates the effects of the cognitive intervention from a placebo condition. An additional conceptual limitation of the three published studies (Boivin et al., 2010; Becker et al., 2012; Vance et al., 2012) and the present study is that none included a diagnosis of HAND as a baseline assessment. This means that the cognitive interventions may have been performed on participants who did not need rehabilitation, thereby reducing the significance of these results. It is therefore necessary for future studies to include a HAND diagnosis in order to inform the intervention protocol used to include those who are cognitively impaired (Weber et al., 2013).

Another consideration of the three published studies was that they used global neuropsychological tests for assessments (Boivin et al., 2010; Becker et al., 2012; Vance et

al., 2012). For example, Boivin et al. (2010) used the Cogstate Neuropsychological Battery to measure attention. Traditional neuropsychological measurements are non-specific in that they measure attention among other areas of cognition as a whole construct, and do not take into account its discrete components (i.e., sustained attention as opposed to selective attention). Furthermore, most large batteries of neuropsychological measurement have considerable overlap with other cognitive functions; attention in this case, is ostensibly tied up with speed of information processing (Levine et al., 2008). Therefore, with large neuropsychological test batteries evaluating neuropsychological profiles is tricky as it becomes hard to delineate what is damaged from what is functioning within normal limits. The limitations of neuropsychological assessments tools reduce the validity of the assessment in that different neuropsychological instruments may not be comparable in that they vary significantly from study to study. Moreover, large neuropsychological instruments are designed to measure different aspects of cognitive functioning, and they often use different scoring systems and stress different aspects of cognition. Therefore, comparing the Kaufman Assessment Battery and the Cogstate Neuropsychological Battery or the TEA-Ch may result in different scoring systems which will not make for an accurate comparison between study findings. To the researcher's knowledge, this is the first study which has not used a global neuropsychological instrument. Rather it evaluated sustained attention impairments in HIV+ children using the cognitive psychology approach of attention based on Posner and Peterson's (1990) theory of attention. It is strongly suggested that future research use specific attention tests instead of global neuropsychological measures to define HIV-related neurocognitive decline as this would inform cognitive rehabilitation interventions.

Finally, it is important to acknowledge that HIV often occurs in the context of other stressors which influence cognitive development such as socioeconomic factors and other opportunistic infections that could account for neurocognitive scores. The current study tried

to account for socioeconomic<sup>4</sup> variables by measuring indicators such as a) frequency of eating habits b) number of toys in the household; c) parent and child reading frequency; and parental education as variables that could account for results (socioeconomic variables will be briefly explored later in the discussion). Other studies such as that by Boivin et al. (2010) accounted for socioeconomic status levels through number of items in a household and parental literacy. When interpreting neuropsychological results of HIV+ individuals it is important to account for comorbidities and environmental variables that could impact results and how these could impact analysis. A key variable that could further influence analysis and results is the methodology used in a research study. The subsequent section will now briefly discuss the methodological issues that could have influenced my results, namely: a) limitation of pre-post testing, b) the small sample size and c) instrumentation and d) the use of the Brainwave-R in HIV research.

### **1.31 Methodological Issues Affecting Interpretation**

In cognitive rehabilitation research, change is measured by improvements on the posttest measure as it relates to the pretest score. However, it may be premature to link improvements on the posttest measure with the intervention without taking into account other possible confounding explanations such as: history effects, maturation effects, test effects and regression towards the mean.

History effects refer to any confounding variable that intervened during the cognitive intervention (Marsden & Torgerson, 2012). This could refer to improving on a test measure as a result of a normal education. In a similar but different vein, maturation effects refer to any changes as a result of the maturation process (Marsden & Torgerson, 2012). For

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<sup>4</sup> Gladwell (2011) in his acclaimed *Outliers: The Story of Success*, explains how variables such as parental education, frequency of reading, the number of books and stimulating mental material in a household all contribute to cognition. Some of these variables were included very briefly in my research to try to make sense of attention scores collected in the study.

example, in the study conducted by Boivin et al. (2010), the researchers could attribute the positive results in this study as due to normal development. Although the brain does not increase in volume during adolescence, a number of changes in maturation such as increases in white matter, myelination, synaptogenesis and pruning of the frontal lobes may account for changes commonly accounted in the cognitive rehabilitation literature (Luna, 2009). Finally test effects, refer to improvements on a posttest measure as a result of being exposed to the instrument and the same task instructions (Marsden & Torgerson, 2012). However, history effects, maturation effects and test effects were controlled in this study by including an active control group (Shadish, Cook, & Campbell, 2002; Torgerson & Torgerson, 2008).

In addition, regression towards the mean is a phenomenon that occurs when natural variation in repeated data looks like real change in the posttest measure (Barnett, van der Pols, & Dobson, 2005). Regression towards the mean transpires when unusually large or small measurements are followed by measurements that are closer to the mean (Barnett et al., 2005; Marsden & Torgerson, 2012). This phenomenon is likely to occur with repeated measurements made on the same group of participants over a period of time. The phenomenon occurs because values are observed with random error (e.g., random measurement error or random fluctuations) which results in non-systematic variation in the values around the true mean (Barnett et al., 2005). In terms of repeated measurement designs, due to random fluctuations that occur one cannot expect that participants will have the same score if measured at different times (Marsden & Torgerson, 2012). This phenomenon is likely to occur as a result of non-random sampling which results in participants being chosen based on the fact that they will score low on a baseline assessment. The current study did not use random sampling but used purposive sampling which resulted in a small sample size consisting of only five HIV+ participants. Withstanding possible selection bias, although this study included a control group and an experimental group it is possible that pre-post testing could have resulted in biased significant results seen in Hypothesis 3, that could have been due to regression towards the mean.

Sample Size: One of the shortcomings of this study was the small sample size ( $N=11$ ) which meant the study had low statistical power. Statistical power in this sense is the ability of a study to be able to detect a true effect. According to the central limits theorem, small studies are more subject to random variation than larger samples and are only able to detect large effects (as is the case in my study) (Field, 2013). Moreover, studies with low statistical power are less able to detect a true effect if there is one (Type II error). On the other hand, it needs to be acknowledged that even low statistical power reduces the chances that a significant result actually reflects a true effect (Type I error) (Button et al., 2013). It follows that, small studies with low statistical power can find a large effect but this may be due to chance. This is a limitation in my study, as such there is a need for evidenced based experimental studies with larger sample sizes in order to investigate the efficacy of cognitive rehabilitation in HIV+ children on ARVs

Instrumentation: Finally, it needs to be acknowledged that by using the TEA-Ch UK norms, these norms could overestimate the level of actual impairment in a South African sample. However, this is not a shortcoming of the study and does not undermine my results as the study only needed a baseline assessment of attention to establish whether the groups improved after the intervention. It was not the aim of the study to compare norms from the TEA-Ch scores with UK norms. For example, by comparing the HIV+ and HIV- participants' attention scores these were not compared to another sample, it was just used to assess differences between the groups. However, this is an issue worthy of discussion for future research defining neuropsychological impairment in HIV + adolescents in South Africa.

In line with the above, although neuropsychological functions are considered pan-human (Van Rie et al., 2007), there still remains a dearth of appropriate normative neuropsychological tests, specifically standardized for South African populations (Moerdyk, 2009). Research has shown that performance on neuropsychological tests differs across cultures on a number of measures including, perception (Nisbett & Miyamoto, 2005); information processing (Llorente et al., 2010); verbal memory (Razani, Burciaga, Madore, &

Wong, 2007); and attention (Anger et al., 1993). Although these are pan-human attributes, they are also culturally influenced. The HIV cognition literature often relies on Western normed tests to derive cognition levels in African contexts. This lack of standardized instruments in South African contexts masks true findings between subjects and group differences in any study conducting research on cognition and HIV. Notwithstanding the challenges faced, neuropsychological assessments still remain the most important tools for diagnosing HIV-related cognitive decline. And this is especially true in South Africa, where there is a lack of neuroimaging technology to diagnose HIV encephalopathy (Robertson, Liner & Heaton., 2009).

Lastly, the Brainwave-R program is not a psychological assessment therefore the standards of reliability and validity do not apply to this rehabilitative instrument. The Brainwave-R program was developed in the United Kingdom and was therefore developed for cognitive rehabilitation within that context. As such, a number of examples used in the rehabilitation manual such as snow and reindeers were unfamiliar to the South African context. For contextual reasons, a number of tasks on the manual were redesigned to contextualise the instrument for the purposes of the current research. The above manipulation is not an uncommon practice in research; for example, a study undertaken at the University of Miami altered word lists and phrases of instruments measuring verbal learning memory and fluency in an effort to make the instrument more context specific (Wilkie et al., 2010). Studies which have translated instruments have found problems in translating from English to Xhosa. For example, translation problems were evident in the pilot study conducted by Zondo and Mulder (2014) who found that translating from English to Xhosa was problematic as certain words like “doughnut” were not understood and as such the instrument had to be modified. It is still not clear as to what are the effects of contextualising of cognitive rehabilitation instruments has on research results and findings. Further research on this topic is being carried out by the cognitive rehabilitation team at Rhodes University; as such it is not clear whether the Brainwave-R is the soundest instrument for cognitive rehabilitation therapy with HIV patients as it was initially designed for patients with traumatic brain injuries (Raymond, Bennett, Malia, & Bewick, 1996; Raymond, Malia, Bewick, & Bennett, 1996).

In summary, to overcome some of the above mentioned methodological shortcomings it is incumbent that future research in this field pursue a) longitudinal research to measure the efficacy of longer intervention exercises on HIV and cognition, b) use randomization of participants to experimental groups, 3) make use of double blinded enrolments and 4) control groups. Additionally, future research on this topic would benefit from including larger sample sizes and an ecologically valid assessment and rehabilitation instrument.

### ***1.32 Discussion of Results in Light of Environmental variables on Cognition***

Studying the factors that influence HIV-related CNS damage is complex as environmental and nutritional factors influence cognitive development. These complex socio-economic problems and HIV morbidity pose a challenge to determining the real effects of CNS disease on cognitive functioning and highlight the multiple layers influencing disease. The determination of whether a child's poor neuropsychological performance is the result of socio-economic status like poverty, poor nutrition or medical variables should be on the agenda of HIV research and is critical in diagnosis and informing treatment (Smith et al., 2006). Poverty is associated with poor health and nutrition, low maternal education, and reduced stimulation in early development (i.e., reading books and playing with toys) which often compound pathology (Baker-Henningham, Powell, Walker, & Grantham-McGregor, 2003; Bradley & Corwyn, 2002; Paxson, & Schady, 2007; Smith et al., 2006; Walker et al., 2011). In order to control for environmental variables that may pose a risk to cognitive functioning, a number of variables were included in the study in order to isolate the effects of HIV on cognition: eating habits; toys in the household; parent and child reading frequency; and parental education. These variables were included as children from low socio-economic circumstances have increased exposure to biological and psychosocial variables that pose a challenge to their development and learning.

Nutrition Levels and stimulation at home: In terms of controlling for environmental variables, it was found that the participants had normal eating habits. A substantial portion of the

sample ate breakfast (81.8%) and lunch (90.9%) every day and had dinner every night (90.9%). And played with toys at home, the majority of the children played card games 9 (81.8%) and 2 played with jigsaw puzzles (18.2%). More than half of the children in the sample (54.4%) read books daily, while a smaller percentage read books weekly (36.4%), and only 9.1% read books monthly. According to parental reading frequency, a substantial portion of the parents read weekly (45.5%), followed by daily (36.4%) and only two parents (18.2%) never read books.

**Socio-Economic Status:** In children the progression of HIV, measured by immune functioning, is correlated to the child's cognitive development, it is tenable that greater deficits are expected for children from poor socio-economic backgrounds that place these children at further risk for developmental delays (Kullgren, Morris, Bachanas, & Jones, 2004). In terms of the current study, three HIV+ participants in the sample had repeated a grade at school (see section 3.2). Research suggests that vertically infected children with prior encephalopathy have significantly lower academic achievement compared with HIV-, exposed and uninfected infants (Garvie et al., 2014). Neurodevelopmental assessments have consistently demonstrated that HIV+ children have delayed cognitive and motor development (Lindsey et al. 2007; Lowick et al. 2012; Potterton et al. 2009; Van Rie et al. 2009). This is indicative of poor developmental outcomes as a result of HIV which leads to poor school achievement, this can be exacerbated by inadequate schools and poor family support.

**Education of Parents:** The majority of parents (54.4%) attended secondary school, while 45.5% attended primary school. The highest grade completed was grade 8. It is suggested in the literature that low maternal education may in fact result in poor stimulation in the household and poor advice on nutrition which could lead the child to inadequate learning opportunities (Walker et al., 2011). It is not quite clear how one can generalise these above cited research findings to my study, but it is possible that low attention pre-scores could be confounded by social factors out of the control of the researcher.

## **Conclusions and Recommendations**

### ***1.33 Summary***

In conclusion, the treatment of HIV changed with the introduction of ARV therapies. These drugs have been shown to be effective in suppressing plasma HIV-1 RNA (viral load) and as a result have dramatically improved the survival of HIV+ children into adulthood. Despite significant advances in virologic management and pharmacological interventions of HIV infection, children on ARV medications still experience cognitive decline and neurodevelopmental delays (Koekkoek et al., 2008; Smith et al., 2008). As a result, HIV-associated neurocognitive impairments continue to persist in the era of ARVs and affect children's learning abilities. In order to improve neurocognitive decline as a result of HIV, this study assessed the feasibility of Brainwave-R rehabilitation as a complement to ARVs. The study made use of an experimental research design with pretest and posttest measures to assess the efficacy of Brainwave-R in improving sustained attention. The study made use of three hypotheses to investigate the research problem.

- 1) Brainwave-R improves sustained attention in the experimental group compared to the control group.
- 2) Brainwave-R improves sustained attention in the HIV+ experimental group on antiretrovirals compared to the HIV positive control group.
- 3) Brainwave-R improves sustained attention in HIV+ children on antiretrovirals.

Results from the study revealed that hypothesis 1 ( $p=.66$ ) and hypothesis 2 ( $p=.40$ ) were disconfirmed, however hypothesis 3 was confirmed ( $p=.04$ ) and lends credence to the efficacy of cognitive rehabilitation in improving sustained attention functions in HIV+ children on ARV therapy.

### **1.33.1 Contributions of the research**

Two significant contributions of this thesis include 1) the introduction of a cognitive psychology approach to define attentional deficits affected by HIV and 2) the introduction of an experimental approach to the cognitive rehabilitation of HIV.

Firstly, although considerable progress has been made in clarifying cognitive functions affected by HIV, clarifying specific attentional deficits as a result of HIV has been slower. A clearer understanding of attention deficits in paediatric HIV is needed, one that uses the cognitive psychology approach which takes into account the discrete component processes of attention (Woods et al., 2009). Models developed by Posner and Peterson (1990; 2012) which suggest three component processes of attention (sustained, selective and divided/alternating attention) are necessary to evaluate individual components of attention in relation to HIV-associated neurocognitive impairment. Using the cognitive psychology approach to understand attention will inform experimental based research that is grounded in cognitive theory, thereby improving neurocognitive assessments in HIV infection (Weber et al., 2013; Woods et al., 2009). With the introduction of this approach, it will further inform future research on the rehabilitation of attention to develop cognitive training centred within a cognitive psychology paradigm catered at specific domain of attention.

Secondly, one of the major limitations of the research on the cognitive rehabilitation of HAND is that all of the previous reviewed studies did not include an active control group. This study made use of an active control group which meant that an equal comparison could be made between the Brainwave-R and the placebo activities. By including an active control

group the researcher was able to make conclusions on the improvement seen in the intervention group as a result of Brainwave-R intervention. With the introduction of this approach, the current study has provided plausible experimental and evidence based findings on the benefits of rehabilitating sustained attention functions. Despite the methodological limitations, the findings of this study offer some initial insights on the positive effects of cognitive rehabilitation therapy, in HIV+ children on ARV therapy in South Africa. The positive effect was evidenced in the large effect size seen for the HIV+ children after the cognitive training intervention ( $r=-.90$ ).

### **1.33.2 Policy Recommendation Derived from the Current Study**

This is a South African study, featuring participants whose concerns cannot be divorced from discourses around HIV/AIDS in South Africa. It is therefore important that the findings of the study be made relevant to the South African public health fraternity. As noted earlier, although government and non-governmental agencies in South Africa have introduced successful ARV programs, the effect of HIV on cognition continues to be a concern. HIV and the effect it has on cognition is a complex field of study that is intricately related to ARVs, and different macro-systems such as socioeconomics and schooling. The fact that HIV has an adverse effect on cognition and that ARVs cannot reverse this decline is an issue of concern. What this project has sought to do, is introduce experimental based research to the complex topic of HIV and cognition. Embedded in neuroscience theory focused on brain plasticity, the research unearthed interesting findings that can further be enhanced on in the future. This study shows that a relatively short intervention that does not require a lot of resources can have tangible results. The addition of cognitive rehabilitation therapy provides a plausible supplement to ARVs in resource-poor contexts. This could be used by government to inform future policy recommendations and to provide qualitative improvements in the educational experiences of HIV+ children. Surely, in looking toward the future, it will be necessary to integrate evidence-based cognitive interventions into clinics, schools and HIV based organisations that help care for HIV+ children to improve their quality of life.

## **APPENDICES**

*Appendix A***Learner Demographic Questionnaire**



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### DEPARTMENT OF PSYCHOLOGY

Tel: +27(0)46 603 8500 Fax: +27(0)46 622 4032 Website:  
<http://www.rhodes.ac.za/academic/departmt/psychology>

Please complete the following questionnaire relating to demographic information. Please tick relevant responses, or clearly write where indicated.

#### Learner Demographic Questionnaire

1. Gender? (please tick one response)

Male	<input type="checkbox"/>
Female	<input type="checkbox"/>

2. How old are you?

\_\_\_\_\_

3. Current education? (please tick one response)

Primary School	<input type="checkbox"/>
Secondary School	<input type="checkbox"/>
Not Attending School	<input type="checkbox"/>

4. What Grade are you in at school? \_\_\_\_\_

5. Have you repeated a Grade at school? \_\_\_\_\_

6. What class are you in at school? \_\_\_\_\_

7. What is your home language? (please tick one response)

Xhosa	<input type="checkbox"/>
Zulu	<input type="checkbox"/>
Afrikaans	<input type="checkbox"/>
Tswana	<input type="checkbox"/>
English	<input type="checkbox"/>

Please be advised that all information provided in this document will be kept confidential and will only be available to the researcher of the study. None of the above information will be distributed to any other individual.

THANKS FOR TAKING TIME TO COMPLETE THE QUESTIONNAIRE

To be completed by the researcher:

Research Study Code \_\_\_\_\_

*Appendix B*

**Parent Demographic Questionnaire**



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<http://www.rhodes.ac.za/academic/department/psychology>

Please complete the following questionnaire relating to demographic information. Please tick relevant responses, or clearly write where indicated.

### Parent Demographic Questionnaire

1. Highest education completed? (please tick one response)

Primary School	<input type="checkbox"/>
Secondary School	<input type="checkbox"/>
Tertiary education	<input type="checkbox"/>
None of the above	<input type="checkbox"/>

2. Highest Grade Completed \_\_\_\_\_

3. What is your home language? (please tick one response)

Xhosa	<input type="checkbox"/>
Zulu	<input type="checkbox"/>
Afrikaans	<input type="checkbox"/>
Tswana	<input type="checkbox"/>
English	<input type="checkbox"/>
Other	<input type="checkbox"/>

4. How often does your child eat breakfast? (please tick one response)

Everyday	<input type="checkbox"/>
Sometimes	<input type="checkbox"/>
Never	<input type="checkbox"/>
I don't know	<input type="checkbox"/>

5. How often does your child eat lunch? (please tick one response)

Everyday	<input type="checkbox"/>
Sometimes	<input type="checkbox"/>
Never	<input type="checkbox"/>
I don't know	<input type="checkbox"/>

6. How often does your child eat dinner?(please tick one response)

Everyday	<input type="checkbox"/>
Sometimes	<input type="checkbox"/>
Never	<input type="checkbox"/>
I don't know	<input type="checkbox"/>

7. How often do you read books? (please tick one response)

Daily	<input type="checkbox"/>
Weekly	<input type="checkbox"/>
Monthly	<input type="checkbox"/>
Never	<input type="checkbox"/>

8. How often does your child read books? (please tick one response)

Daily	<input type="checkbox"/>
Weekly	<input type="checkbox"/>
Monthly	<input type="checkbox"/>
Never	<input type="checkbox"/>

9. Does your child play with toys/games at home? (Please tick one response)

Board games (e.g: chess, checkers)	
Lego	
Jigsaw puzzle	
None	

**PLEASE BE ADVISED THAT THIS INFORMATION WILL BE KEPT STRICTLY  
CONFIDENTIAL**

10. Is your child HIV positive?

Yes	
No	

11. Is your child on antiretroviral (ARV) drugs?

Yes	
No	

**Please be advised that all information provided in this document will be kept confidential and will only be available to the researcher of the study. None of the above information will be distributed to any other individual.**

THANKS FOR TAKING TIME TO COMPLETE THE QUESTIONNAIRE

To be completed by the researcher:

Research Study Code \_\_\_\_\_

*Appendix C*

**Code Transmission Subtest from the TEA-Ch**

### 9 Code Transmission

#### Administration

- On the tape there is going to be a very long list of numbers between 1 and 9. We have to find certain numbers in the list, like a code. The code is that we have to listen out for two 5's in a row (Version B: two 7's in a row). A '5' (B: '7') on its own is no good. It has to be two 5's (B: 7's) in a row. When we hear two 5's (B: 7's) in a row you have to tell me the number that came just before. Listen to these numbers and see if you can spot the number that comes before the two 5's (B: 7's) in a row.
- Say: 2 7 4 3 5 5 (version B: 2 5 4 3 7 7)
- Did you hear that the number 3 came just before the two 5's (7's)


- in a row? OK, let's practice now with the tape.
- Ensure that the child has at least detected one of the target numbers in the practice.
- This test goes on for quite a while, which means that you will really have to concentrate. If you hear two 5s (7's) in a row and can't remember the number that came before them, just wait until the next time they come up and try again. Are you ready to go?

#### Scoring

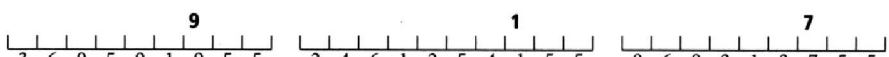
- Number of targets detected (maximum = 40)

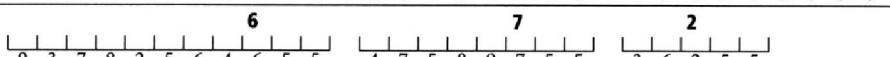
#### Version A (Version B overleaf)

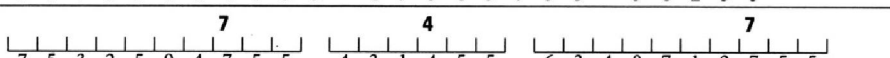
##### Practice

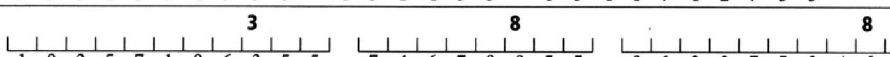
Targets ✓/✗    
 Sequence 1 3 6 9 2 5 5 9 8 7 5 9 1 5 5 3

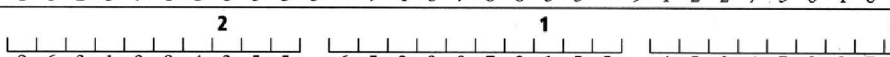
##### Test

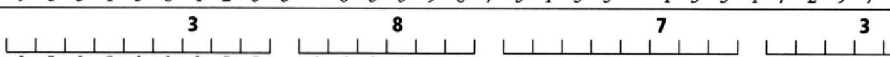
Targets ✓/✗    
 Sequence 3 6 9 5 9 1 9 5 5 2 4 6 1 2 5 4 1 5 5 9 6 8 2 1 3 7 5 5

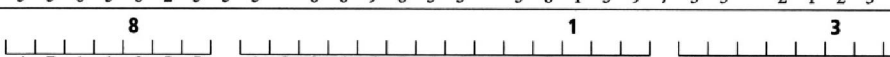
Targets ✓/✗    
 Sequence 9 3 7 8 2 5 6 4 6 5 5 4 7 5 8 9 7 5 5 3 6 2 5 5

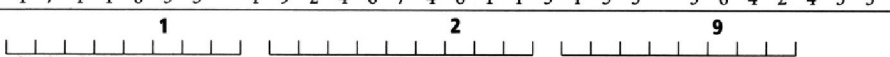
Targets ✓/✗    
 Sequence 7 5 3 2 5 9 4 7 5 5 4 3 1 4 5 5 6 3 4 8 7 1 2 7 5 5

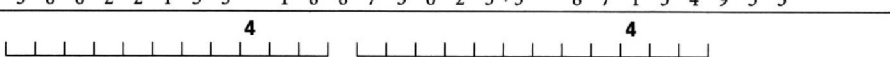
Targets ✓/✗    
 Sequence 1 8 2 5 7 1 8 6 3 5 5 7 4 6 7 8 8 5 5 9 1 2 2 7 5 8 4 8 5 5

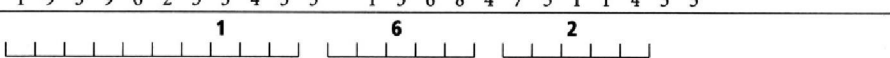
Targets ✓/✗    
 Sequence 9 6 3 1 3 8 4 2 5 5 6 5 3 9 8 7 3 1 5 5 4 5 3 4 7 2 9 7 6 5 5

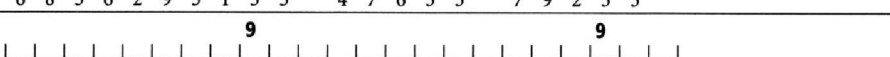
Targets ✓/✗    
 Sequence 3 5 8 5 8 2 3 5 5 6 6 9 8 5 5 3 6 1 5 9 7 5 5 2 1 2 3 5 5

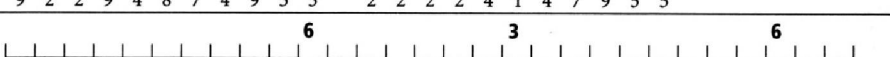
Targets ✓/✗    
 Sequence 4 7 1 1 8 5 5 1 9 2 4 6 7 4 6 1 1 5 1 5 5 3 6 4 2 4 3 5 5

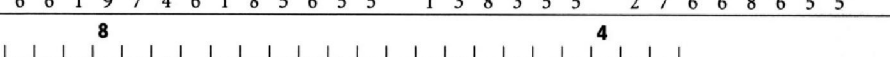
Targets ✓/✗    
 Sequence 3 8 6 2 2 1 5 5 1 8 8 7 5 6 2 5 5 8 7 1 3 4 9 5 5

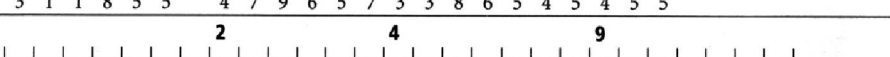
Targets ✓/✗    
 Sequence 1 9 3 9 6 2 3 3 4 5 5 1 3 6 8 4 7 5 1 1 4 5 5

Targets ✓/✗    
 Sequence 6 8 5 6 2 9 3 1 5 5 4 7 6 5 5 7 9 2 5 5

Targets ✓/✗    
 Sequence 9 2 2 9 4 8 7 4 9 5 5 2 2 2 2 4 1 4 7 9 5 5

Targets ✓/✗    
 Sequence 6 6 1 9 7 4 6 1 8 5 6 5 5 1 3 8 3 5 5 2 7 6 6 8 6 5 5

Targets ✓/✗    
 Sequence 3 1 1 8 5 5 4 7 9 6 5 7 3 3 8 6 5 4 5 4 5 5

Targets ✓/✗    
 Sequence 9 6 9 3 2 2 9 2 5 5 3 1 4 5 5 9 4 5 9 5 5 3 8 5

Total correct

**BB**

*Appendix D*

**Brainwave-R Exercise One**

3 1 9 7 2 1 5 3 3 1 4 0 9 7 2 9 2 2 5 5 8 4 9 3 2 6  
6 1 9 6 8 1 4 0 2 4 2 0 8 7 2 4 9 3 8 2 4 4 9 2 0 6  
5 3 7 2 1 4 2 8 5 9 8 6 2 3 1 2 3 9 8 5 2 1 7 6 2 4  
9 2 7 1 2 6 5 4 2 7 3 2 2 9 8 7 1 5 6 2 3 9 2 4 1 7  
2 6 7 3 2 4 1 5 2 6 3 7 4 8 5 9 0 5 2 4 3 2 6 8 2 7  
5 2 11 6 2 3 8 9 2 7 8 5 2 1 9 2 3 2 7 1 0 3 2 4 6  
5 2 9 3 1 2 1 8 5 3 8 4 1 6 0 2 2 8 3 1 2 4 2 6 0 0  
0 3 8 2 4 5 2 1 4 6 0 9 5 2 8 4 6 2 5 4 3 2 1 5 7 2  
4 8 1 3 2 5 2 3 3 9 4 7 6 2 1 8 2 1 0 9 3 7 4 2 1 2  
6 9 1 5 4 3 1 2 4 5 2 2 8 7 6 2 3 9 2 7 3 1 2 6 5 1  
7 3 2 4 6 8 2 1 9 2 2 7 3 9 2 4 6 2 2 3 5 7 1 2

## **Appendix E**

### **Brainwave-R Exercise Two (Edited task)**

him	six	fall	sing	full	walk	buy	cold	you
<b>tree</b>	think	draw	down	ride	be	is	every	away
keep	do	<b>tree</b>	by	together	big	seven	yellow	one
some	because	made	make	<b>tree</b>	we	never	upon	for
come	help	<b>tree</b>	first	will	who	write	can	ten
very	<b>tree</b>	thank	good	run	read	he	does	they
<b>tree</b>	<b>tree</b>	on	over	small	get	any	funny	best
to	<b>tree</b>	after	yes	like	round	went	two	give
don't	shall	old	find	<b>tree</b>	its	five	jump	little
not	did	all	from	let	only	sit	stop	<b>tree</b>
far	always	six	put	call	why	grow	<b>tree</b>	ask
sleep	ate	light	gave	got	red	<b>tree</b>	wish	better
start	what	pull	them	please	both	and	or	play
again	white	which	soon	been	pretty	in	<b>tree</b>	three
help	show	black	open	<b>tree</b>	came	carry	hold	hot
blue	fast	myself	live	it	four	many	see	done
must	hurt	tree	look	under	were	our	with	these
<b>tree</b>	just	tell	clean	wash	kind	well	how	bring
take	<b>tree</b>	clean	had	as	an	would	new	long
drink	eight	has	warm	their	going	there	green	brown
your	but	this	fall	laugh	no	know	me	him
she	then	may	today	around	pick	have	go	are
<b>tree</b>	try	could	<b>tree</b>	so	the	that	<b>tree</b>	<b>tree</b>
those	<b>tree</b>	here	about	eat	before	of	laugh	some

*Appendix F***Brainwave-R Exercise Seven (Edited task)**

Lion	Snake	Strawberry	Pear	Zebra	Apricot	Grapes
Circle	Apple	Dog	Circle	Cat	Elephant	Apricot
Triangle	Bird	Peach	Square	Banana	Apricot	Cheetah
Mango	Plum	Triangle	Cat	Apricot	Naartjie	Donkey
Pig	Lion	Lemon	Triangle	Goat	Cow	orange
Apricot	Bird	Zebra	Horse	Plum	Circle	Pear
Spider	Triangle	Circle	Banana	Strawberry	Mango	Lemon

## **Appendix G**

### **Brainwave-R Exercise Eight (Edited task)**

away	cat	hurt	as	Will	try	only	dog	Zebra	once	right	come
those	I	them	shall	snake	before	play	open	to	lion	ten	don't
white	bring	horse	eight	would	blue	this	away	gave	bird	fish	will
made	yellow	for	he	Full	dolphin	here	those	I	them	shall	never
hold	eat	brown	fish	Out	ate	lion	donkey	bring	your	eight	would
not	over	buy	its	Fox	they	ask	moose	yellow	for	he	full
ride	all	me	think	rabbit	snake	good	hold	eat	brown	chicken	out
after	were	first	went	Very	could	get	dolphin	over	buy	its	mouse
had	just	live	from	horse	go	many	ride	all	me	think	giraffe
she	walk	say	wish	upon	their	fast	after	ant	first	went	very
and	show	drink	fall	Sing	any	both	had	just	live	from	bird
see	together	give	sheep	Long	must	did	monkey	walk	say	wish	upon
red	do	why	but	Help	so	some	and	show	dog	fall	sing
stop	funny	take	clean	Is	keep	better	see	together	give	sleep	long
know	cow	let	three	Soon	which	pig	red	do	why	but	help
four	be	goes	horse	In	or	we	stop	funny	take	clean	is
well	are	with	does	giraffe	light	may	know	there	let	three	soon
crocodile	done	what	own	Far	black	pick	four	be	goes	look	in
then	pull	you	our	Start	tiger	six	well	are	lion	does	two
thank	grow	how	by	giraffe	draw	kind	please	done	what	own	far
like	one	cold	today	Him	make	horse	then	pull	you	our	start
big	small	the	again	Run	snake	into	thank	grow	how	by	because
some	jump	dog	around	Find	five	warm	cat	one	cold	today	him
got	been	am	write	round	mouse	always	big	rhino	the	again	run
best	bird	yes	down	cheeta	that	green	some	Hippo	wash	around	find
going	put	seven	hot	every	on	tell	got	been	am	write	round
can	donkey	right	come	carry	pig	laugh	best	it	lion	down	pretty
cow	too	ten	bird	myself	who	zebra	going	put	horse	hot	every
laugh	rat	spider	open								

*Appendix H*

**Brainwave-R Exercise 12**



*Appendix I*

**Rhodes University Ethics Committee**

*Appendix J*

**The Humanities Higher Degrees Committee**

*Appendix K*

**Ethical Clearance Letter from the School**

*Appendix L*

**Department of Education**

*Appendix M*

**Parent and Participant Letter**



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<http://www.rhodes.ac.za/academic/departments/psychology>

**PARTICIPATION INFORMATION LETTER**

Dear Parent/Guardian,

I am a Psychology Master's student at Rhodes University. My research pertains to cognitive functioning amongst a range of learners. I am interested to know whether particular interventions that promote attention can help learners with their learning. The purpose of my research is to study whether a form of cognitive rehabilitation known as Brainwave-R improves attention in children. Attention is defined as the ability to attend to information.

The type of training is useful for children and helps in attention and learning. If your child is between 10 and 15 years old then they are eligible to take part in this important study. Research shows that the Brainwave-R may improve attention in a diverse spectrum of children, including children with or without HIV; children with attention difficulties such as attention deficit hyperactivity disorder (ADHD) and other children in general.

Any results gained from the study could help better understand whether cognitive rehabilitation improves attention in children. To achieve the aims of the study, I intend to recruit participants who are: (1) between the ages of 10-15 who are (2) HIV positive (and receiving ARVs); and (3) HIV negative; (4); are adequately proficient in English; and (5) who are willing to participate in the research for a period of four to seven months.

The research will run over a period of four to seven months. You as a parent have been approached for consent for your child to take part in the study to investigate the effects of attention training before and after the use of Brainwave-R. The Brainwave-R program is a widely used cognitive rehabilitation program designed to remedy attention.

With your permission, taking part in the study will require the researcher to have access to your child's medical records; you as a parent are not obliged to consent to this. Participation in the study is totally voluntary and your child can be withdrawn from the study at any point in time. Your child's name and other personal information will not be disclosed by the researcher to the school or any other organization. If you have any queries regarding the study about anything mentioned above please do not hesitate to contact me or my research supervisors.

Yours sincerely,

Student Researcher: Ms Candice Basterfield email: [candice101101@gmail.com](mailto:candice101101@gmail.com) Cell: 083 624 3959

Student Supervisor: Mr Sizwe Zondo email: [s.zondo@ru.ac.za](mailto:s.zondo@ru.ac.za) (046-603-8503)

Student Supervisor: Professor Charles Young email: [c.young@ru.ac.za](mailto:c.young@ru.ac.za) (046 603-8541)

*Appendix N*

**Parent Consent Form**

RHODES UNIVERSITY  
DEPARTMENT OF PSYCHOLOGY  
AGREEMENT BETWEEN STUDENTRESEARCHER  
AND PARENT/CAREGIVER OF RESEARCHPARTICIPANT

I (parent/caregiver's name) \_\_\_\_\_ agree for my child, (child's name) \_\_\_\_\_ to participate in the research project of Candice Basterfield on: The Cognitive Rehabilitation of a sample of HIV/AIDS children: A specific focus on the Cognitive Rehabilitation of Sustained Attention

**I understand that:**

1. The researcher is a student conducting the research as part of the requirements for a Master's degree at Rhodes University. The researcher may be contacted on 083 624 3959(cell phone) or candice101101@gmail.com(email). The research project has been approved by the relevant ethics committee(s), and is under the supervision of Mr Sizwe Zondo Psychology Department at Rhodes University, who may be contacted on 046 603 8503 (office) or s.zondo@ru.ac.za (email) and Professor Charles Young Psychology Department at Rhodes University, who may be contacted on 046 603-8541 (office) or c.young@ru.ac.za.
2. The researcher is interested in understanding if thinking abilities can be improved in children after sustained cognitive intervention or cognitive training. I as the researcher aim to investigate whether I can train children to attend to information after cognitive intervention (Please see the accompanying letter for further information).
3. My child's participation will involve either (a) doing some mind games, or (b) being part of a cognitive intervention rehabilitation to evaluate thinking before and after the cognitive intervention program. The cognitive remediation program is called Brainwave-R and has been shown to foster improvement in training attention in children. A number of the Brainwave-R tasks combine both auditory and visual tasks. Examples of the Brainwave-R materials include auditory attention tapes whereby the child would have to listen to a sequence of descending numbers, alphabetizing words in an orally presented sentence, detecting specific targets within the presence of a distracter noise.

4. If I agree that my child can participate, in the study, my child will be expected to participate in the study for approximately 30 minutes a session, four times a week, over a period of four to seven months. The reason for this period is that the remediation training has to be sustained over a period of time to show changes in brain training.
5. The research will be carried out after school.
6. I may be asked to answer questions of a personal nature about my child, but I can choose not to answer any questions about aspects of my life or my child's life which I am not willing to disclose.
7. I am invited to voice to the researcher any concerns I have about my child's participation in the study, or consequences that may be experienced as a result of my child's participation, and to have these addressed to my satisfaction.
8. I am free to withdraw my child from the study at any time.
9. My child's name and other personal information will not be disclosed by the researcher to the school or any other organisation. All personal information gathered during research will be kept in locked file cabinets kept at Rhodes University only accessible to the researcher. Furthermore, any reports or publications about the study will not identify you or any other study participant.
10. There are no risks to your child participating in the current research. However, should you wish to, please do not hesitate to contact my research supervisor (076 478 1463) or Rhodes University Department of Psychology (046-603-7212).

11. I can contact the Rhodes University Psychology Clinic (046 603 8502) or the Rhodes University Department of Psychology (046-603-7212) for any Psychological harm incurred during the study.

Signed on (Date): \_\_\_\_\_

Parent/Caregiver: \_\_\_\_\_ Researcher: \_\_\_\_\_

*Appendix O*

**Participant Consent Form**

RHODES UNIVERSITY  
DEPARTMENT OF PSYCHOLOGY  
AGREEMENT BETWEEN STUDENT RESEARCHER  
AND RESEARCH PARTICIPANT

I (participant's name) \_\_\_\_\_ agree to participate in the research project of Candice Basterfield Master's on The Cognitive Rehabilitation of a sample of HIV/AIDS children: A specific focus on the Cognitive Rehabilitation of Sustained Attention

**I understand that:**

1. The researcher is a student conducting the research as part of the requirements for a Master's degree at Rhodes University. The researcher may be contacted on 0836243959 (cell phone) or candice101101@gmail.com (email). The research project has been approved by the relevant ethics committee(s), at Rhodes University. The research is under the supervision of Mr Sizwe Zondo Psychology Department at Rhodes University, who may be contacted on 046 603 8503 (office) or s.zondo@ru.ac.za (email) and Professor Charles Young Psychology Department at Rhodes University, who may be contacted on 046 603-8541 (office) or c.young@ru.ac.za.
2. The researcher is interested in understanding how children perform on some thinking games after being trained to think differently over a long period of time (four to seven months).
3. My participation will involve either (a) doing some mind games and (b) being trained to think differently over a period of time. The researcher wants to see if there is a change in my thinking before and after the thinking training.
4. The researcher will use a thinking program known as Brainwave-R that trains children to think differently over a period of time. The program looks at how well children can pay attention to something.

5. I might be asked to do the thinking games after my school time.
  
6. I am free to stop with the thinking training at any time that I want to. I am allowed to voice to the researcher any concerns that I may have during the study.
  
8. My personal name will not be used to identify me as having taken part in the study.
  
9. My parent/guardian can call either the Rhodes University Psychology Clinic (046 603 8502) or the Rhodes Department of Psychology (046- 603-7212) should I experience any harm or experience problems during the study.

Signed on (Date): \_\_\_\_\_

Participant: \_\_\_\_\_ Researcher \_\_\_\_\_

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