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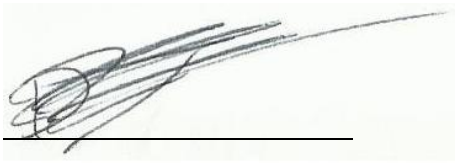
The Visuospatial Abilities of HIV Positive Adolescents on Antiretroviral Treatment in South Africa

Daniel John Greenslade

Declaration

"A research project submitted in partial fulfilment of the requirements for the degree of Master of Arts in Neuropsychology, for the Faculty of Humanities, University of the Witwatersrand, Johannesburg, March 2013".

"I declare that this research entitled "The Visuospatial Abilities of HIV Positive Adolescents on Antiretroviral Treatment in South Africa" is my own, unaided work. It has not been submitted before for any other degree or examination at this or any other university".

Signed: 21 November 2013

Daniel John Greenslade

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Abstract

This researched aimed to explore the effects of the Human Immunodeficiency Virus (HIV) upon the visuospatial abilities of HIV-positive adolescents on antiretroviral treatment in South Africa. The literature suggests that the neurology responsible for visuospatial abilities (specifically various white-matter tracts in the brain) is very susceptible to the damaging effect that HIV has on the brain. The research sample consisted of vertically transmitted HIV-positive adolescents, on first line antiretroviral treatment, with a HIV-negative control group comparable on age and SES. The results indicated that there is a significant difference in the visuospatial abilities between adolescents with and without HIV. The expressions of these deficits were displayed differently between males and females, highlighting a differing developmental neurology, and the effect of HIV upon it. The viral strength and health of the immune system were also examined as variables and illuminated interesting results. Overall, the research illustrates the negative effect that HIV has upon developing neurology and the subsequent effects on visuospatial abilities.

Keywords: Human Immunodeficiency Virus (HIV), Antiretrovirals (ARV), Visuospatial Abilities

Acknowledgements and Dedication

Firstly my thanks must go to God. My faith and your strength and light have always kept me going in the hardest and darkest of times. Without you, I am nothing

My thanks must go to Professor Ashraf Coovadia, for all his assistance with regards to gathering the data for the research, and for all of the resources and personal he made available to this research.

Next thanks must go to the rest of the MA Neuropsychology class. Thanks for all the support and participation with regards to the research. And congratulations on surviving what was an extremely trying year.

To Liesl Zachar. Your support throughout the year kept me strong. For making dinner more often than not, and being a supportive presence when things went badly.

Huge thanks must go to Tammi Mayson (again). You provided invaluable support during the year, which kept me going. And specific thanks for all you did at the last minute in helping me with this report. You are a true friend!

To my parents, Mark and Roswitha, for supporting (and paying) me through my second Master's degree. Your constant support and belief in me, though often not acknowledged by me, provides the foundation to my strength.

And finally to Enid Schutte. You have now supervised me for three successive degrees, and I am still constantly astounded by your intelligence, compassion, passion and dedication. Without your support over the last year I would not have made it to the end. A simple thank you cannot convey the depth of my gratitude to you nor my respect of you. You have become a true friend to me over the past 8 years.

This research is jointly dedicated to Enid and my parents, Mark and Rose. You are all my inspiration!

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Research Aims

The aim of this research was to explore the effects of HIV on the Visuospatial Abilities of HIV-positive adolescents on antiretroviral treatment in South Africa. The literature suggests that the neurology responsible for visuospatial abilities (specifically various white-matter tracts in the brain) is very susceptible to the damaging effect that HIV has on the brain (Klingberg, Forssberg & Westerberg, 2002; Stebbins et al, 2007; Pomara, Crandall, Choi, Johnson, & Lim, 2001). This research focused on a very specific population, who acquired HIV through mother-to-child transmission at birth, and who also did not begin antiretroviral treatment until late in their life due to government legislation at the time (Coovadia, 2009). As this population are generally multilingual, and educated in other than their mother-tongue, there is a higher level of importance on visuospatial abilities.

Chapter 1: Literature Review

Rationale

This research project is embedded within a larger project entitled "The Neuropsychological Profile of HIV Positive Adolescents on Anti-Retroviral Treatment in Johannesburg, South Africa" (See Appendix 1 for overarching research proposal submitted to Medical Ethics).

HIV is a serious threat to the world's population and has become a pandemic with approximately 34 million people living with this disease (World Health Organisation, 2012). In 2010 approximately 250,000 children had died from AIDS-related causes (World Health Organisation, 2011) and approximately 87% of children living with HIV live in sub-Saharan Africa (Wachsler-Felder & Golden, 2002). From a practical perspective, empirical (Fundaro, et al., 1998) and anecdotal evidence from medical practitioners and educators alike suggest that learning difficulties are observed in HIV positive children. Moreover, given the historical South African scenario, ARV-naïve children also have the added disadvantage of only being placed onto an anti-retroviral regimen on presentation of clinical symptoms, by which time, some CNS functionalities may have already been compromised (Laughton, et al., 2010; Puthanakit, et al., 2010). Historically, peri-natally acquired HIV positive children in South Africa had limited access to ARV treatment at birth until changes in legislation in 2006 (Department of Health, 2008). Consequently, treatment may only have been initiated after clinical presentation of immune deficiency.

HIV has been shown to affect the body and the brain, producing similar symptoms to other infections, as well as damage to certain brain regions producing neurocognitive deficits (Civitello, 2003; Ellis, Calero & Stockin, 2009; Spach & Hooton, 1996). The damage to the brain during HIV infection is thought to be more detrimental during brain development, as occurs in infancy and adolescence (Gay et al., 1995). This damage has been researched, especially with regards to language development and motor skills (Wachsler-Felder & Golden, 2002). However, other abilities such as visuospatial abilities have not been researched as extensively, even though visuospatial abilities form part of most other neurocognitive abilities, such as eye-hand co-ordination and certain types of memory (Mazzocco, Bhatia, & Lesniak-Karpiak, 2006). These abilities are thought to have a basis in the areas seen to be damaged by HIV.

Given the lag in treatment, as well as the damage to the CNS during development, the aim of this study is to examine whether, and how visuospatial abilities of young seropositive adolescents, who are currently on a managed anti-retroviral programme, are affected by HIV. These results will be compared to a control group (with similar age, demographics and educational systems) (Puthankit et al, 2010). The results will also include analysis between the genders as research has shown there is a difference in the development between male and female visuospatial abilities (Downing, Chan, Downing, Kwong & Lam, 2008).

Literature Review

HIV and associated Neuropathology

The human immunodeficiency virus (HIV) has become a pandemic. In 2010, approximately 34 million people worldwide were estimated to be living with HIV (World Health Organisation, 2012). Sub-Saharan Africa still remains the region most affected by HIV with this region accounting for almost three quarters (70%) of all people worldwide living with HIV (World Health Organisation, 2012) and accounting for 72% of AIDS-related deaths in 2008 (Shisana et al., 2009). Despite exhaustive efforts to reduce the prevalence of HIV, the rate of new infection is still extensive, with approximately 2.7 million new infections in 2008 in the world and 1.9 million of those in sub-Saharan Africa alone (UNAIDS, 2009). According to the World Health Organisation (2011) South Africa is home to the largest population of HIV-infected people in the world with approximately 5.6 million people living with HIV. Furthermore, 87% of HIV-infected children under the age of 15 are found in sub-Saharan Africa (Wachsler-Felder & Golden, 2002) and approximately 250,000 children worldwide died from AIDS-related causes in 2010 (World Health Organisation, 2011).

HIV can be spread by the exchange of some bodily fluids, namely blood, semen, vaginal secretions and breast milk (Libman & Makadon, 2007). Modes of transmission and infection include unprotected sex, breast feeding and sharing injection needles during drug use, among others. If a person is exposed to HIV positive bodily fluid, they can be put on a treatment plan involving antiretroviral (ARV) post-exposure prophylaxis and counselling. This involves putting the person on an ARV or combination of ARVs within 72 hours of exposure and continuing treatment for at least 28 days, after which they are tested for HIV. Once infected, if untreated, the person goes through four stages (Ellis et al., 2009). These stages are not always noticeable and so the infected person may not realise that they have been infected with HIV. The first stage lasts approximately two to four weeks and the person experiences no symptoms. This is followed by the second stage, another roughly four week period of acute infection symptoms and the person still may not realise that HIV is the cause. These acute infection symptoms are similar to other viral infection symptoms and often include a fever, sore throat, lack of energy, headaches and possible weight loss (Spach & Hooton, 1996). Other symptom sets may include meningitis and ulcerations or rashes on the body, along with neurocognitive symptoms once the virus enters the CNS, which is fairly early in

the disorder's progress. According to Ellis et al. (2009) the third stage is similar to the first in that there are largely no physical symptoms, however the virus is silently busy destroying the host immune system. This stage can last from weeks to decades and is followed by the fourth and last stage which is acquired immune deficiency syndrome (AIDS). It is diagnosed when the immune system is severely compromised and the CD4+ lymphocyte (T-cell) quantity falls below a certain level. The patient's immune system is then too weak to fight off opportunistic infections and they often succumb to these infections.

In South Africa, the primary mode of infection in children is from mother to child which is referred to as vertical transmission (Shisana et al., 2005). It was estimated that 96 228 babies born in 2003 were infected with HIV through vertical transmission (Department of Health, 2003) and more than half were predicted to die within two years (Newell, Coovadia, Cortina-Borja & Rollins, 2004). However, Shisana et al. (2005) found fairly even distributions across different age groups of seropositive children. This therefore suggests a better survival rate than the 50% that was postulated by Newell et al. (2004) within their research. It has been estimated that there is a 25% risk that a newborn will contract HIV from their HIV-infected mother if there are no ARV medications used during the pregnancy (Libman & Makadon, 2007). This transmission is mostly due to the exposure of the newborn to the mother's blood and vaginal fluids. The baby can also contract the virus through infected breast milk. It is thus recommended that a caesarean pregnancy be performed and the newborn be fed with formula milk rather than breast milk. Doctors recommend that ARV medications be administered throughout the pregnancy as well as to mother and child after birth. The use of ARV medication during early infancy has been shown to reduce infant mortality rates and HIV progression by approximately 75% (Violari et al., 2008). As such, in more affluent countries, ARV administration during pregnancy and early infancy was initiated and controlled from birth for seropositive neonates (Coovadia, 2009). In South Africa, however, the scenario was different in that many children were only placed on ARV treatment based on the severity of clinical symptomology and/or viral loads. The very limited access to ARVs in South Africa during the late 1990's, and at least within the first five years of the new millennium, was due largely to the high cost of ARV treatments as well as the limitations imposed by the health policies of the time (for both preventative mother to child transmission prophylaxis and post-partum treatment). As a result of the high cost of ARV treatments and the policies of the South African government, HIV patients were only allowed access to ARV treatments after a change of legislation in 2006 (Department of Health, 2008). Studies from the US show that

ARV-naïve children (seropositive children not on ARVs) placed on ARVs after presenting symptomatically show greater neurocognitive deficits as compared to children who are placed on ARVs from birth (Laughton, 2009; Lindsey, Malee, Brouwers, & Hughes, 2007; Lowick, Sawry & Meyers, 2011). Consequently, it can be expected that South African children who were born HIV positive would be inclined to greater amounts of neurocognitive deficits (Smith, Adnams, & Eley, 2008) despite being placed on ARVs several years after vertical acquisition.

The HI-virus is a retrovirus, belonging to the family of lentiviruses, which leads to Acquired Immune Deficiency Syndrome (AIDS). Immune deficiency in HIV manifests once the virus has entered the body through fluids, infecting the T-cells and macrophages of the immune system (Ellis et al., 2009). In the central nervous system (CNS), HIV collects in the cerebrospinal fluid (CSF). It therefore does not affect neurons directly but rather indirectly through viral factors, host factors and co-factors, thereby making its effects on the nervous system diffuse and far reaching (Civitello, 2003; Ellis et al., 2009). Viral factors are neurotoxic proteins produced by the HIV genome. There are many viral factors in the HIV genome, one of which, gp120, impairs some of the neuronal pathways, specifically the glutamate pathways, and also harms the neurons by influencing the cytokine production. In addition it alters the "activation state of microglia and astrocytes" (Ellis et al., 2009, p.147). Complex synaptodendritic networks are the underlying basis for higher cognitive functions thus injury to neurons in these networks would result in cognitive dysfunction. Another viral factor involved in neuronal injury is transactivator of transcription (Tat) which is associated with injury and death to neurons and damage to the dendritic network. Neurotoxic host factors are the secondary effects of HIV infection on the immune system. These produce inflammation as well as chemokines and cytokines. The abnormal production and activation of chemokines and cytokines causes neuronal cell changes, both structurally and functionally. These changes are suggested to be somewhat reversible by Lipton (1998), and this is supported by Ellis et al. (2009). Cofactors in HIV-induced injury to the brain are factors such as co-morbid diseases and disorders, such as substance abuse disorders and types of infections made possible through the suppression of the immune system, for example Hepatitis C.

According to Civitello (2003), the brains of children with AIDS show structural deformities that are different to those shown in adults. The deformities include calcification in the basal

ganglia that includes vascular/perivascular mineralisation that occasionally extends in the white matter areas. Myelin loss is also characteristic in children with AIDS as well as reactive astrocytes. Studies have shown that HIV positive children do not show overt changes in everyday functioning, however, with disease progression neurological deficits emerge as cognitive, motor and behavioural impairments (Wachsler-Felder & Golden, 2002). These are generally seen by teachers in observing normal (or in the case of HIV, failure to obtain) developmental milestones (Lowick et al., 2012; Wachslet-Felder & Golden, 2002), such as motor functioning and language abilities (Coplan et al., 1998).

The lack of specific neuropathologies in HIV infection is not unexpected given that CSF is distributed within the ventricles and around the meninges of the brain, resulting in diffuse rather than focal effects (Koekkoek, de Sonneville, Wolfs, Licht & Geelan, 2008). In their review, Wachsler-Felder and Golden (2002) conclude that the lack of a standardised neuropsychological battery for HIV testing, the small sample sizes as well as the large age differentials within studies (ranging from newborns to 16 years), transmission history, environmental issues and immunological states in the various studies has added to the lack of clarity of the precise neuropathology and hence contributes to the 'mixed' neuropsychological profiles. In this respect, it was suggested that tests be conducted on larger groups with a narrower age band so as to adjust for age differentials.

Neurocognitive Development and HIV

It is well-known that the brain is vulnerable to disease and injury in vitro, for example through environmental toxins, malnutrition and maternal acquired infections that pass into the uterus, as well as developmental abnormalities like spina bifida and diseases such as rubella that affect the foetus' development. (Zillmer, Spiers & Culbertson, 2008). Thus, once the child has been born, one can assume HIV may affect this early stage of neurodevelopment (Gay et al., 1995). Two major events of brain development during this developmental period include the myelination of neurons, corresponding to cognitive and behavioural changes, and the "proliferation and organisation of synapses" (Lenroot & Giedd, 2006, p.719). These stages of brain development begin in vitro and undergo a burst of development in the first two years after birth, reaching a level that is roughly 50% more than in adults. By the age of two, the human brain should be approximately 80% of its adult weight (De Luca & Leventer, 2008; Lenroot & Giedd, 2006), which suggest that these first two years are rich with vital growth and development. A longitudinal MRI study by the Child Psychiatry Branch at the

NIMH revealed peaks in cortical grey matter volume at different ages in childhood, according to specific regions, and then a decline (Lenroot & Giedd, 2006). Cortical grey matter follows a predictable development course with specific areas developing in patterns. Specifically the primary functions, such as motor skills and sensory functions develop first, followed by the higher order functions, such as language and reasoning. As the higher order functions develop, they integrate and make use of the primary order functions. The volume of white matter, however, increases through childhood and adolescence, specifically in the frontal areas, with a decrease in grey matter. The increase in white matter seen on MRI scans is myelination taking place, while the decrease in the grey matter is the pruning of unnecessary synapses and neurons (Gazzaniga, Ivry and Mangun, 2009). This suggests the strengthening and consolidation of the white matter networks necessary for higher cortical functioning (De Luca & Leventer, 2008).

Functional Magnetic Resonance Imaging (fMRI) studies have been conducted comparing healthy children's brains with those children displaying developmental disorders, such as Attention Deficit Hyperactivity Disorder (ADHD) and Foetal Alcohol Syndrome (FAS) (Toga, Thompson & Sowell, 2006). Differences were found in terms of structural changes and cognitive changes. One would therefore expect to find differences in the HIV-positive child's brain. Radiological studies with seropositive children have revealed some CNS abnormalities, as briefly mentioned above, such as cortical atrophy and calcification, especially in the basal ganglia, frontal cortex, and general white matter (Belman et al., 1985; Belman et al., 1986; Epstein, Berman, Sharer, Khademi & Desposito, 1987; Civitello, 2003), and myelinopathy (Gay et al., 1995). The progression of HIV is logically faster and more diffuse in children than in adults, due to its effect on the developing immune and nervous systems (Belman, 1997; Brouwers et al., 1996; Kovacs, 2009). This can be explained through HIV attacking a fully developed and myelinated nervous system in adults, whereas in infants these are still in the process of development and are therefore vulnerable. Features of HIV-associated progressive encephalopathy in children include increasing loss of motor skills and delayed gains in motor skills expected for the age (Wachsler-Felder & Golden, 2002). There is no set progression of HIV in children – it may be progressive (follow a steady process) or rapid. However, the declines in the neurological development are shown in the poor brain growth, which can be assessed by measuring the serial head circumference. There is also progressive and measureable atrophy and white matter abnormalities such as "progressive basal ganglia calcification with or without mineralisation of frontal white matter" (Washler-

Felder & Golden, 2002, p. 444). Considering this research and the brain and development abnormalities, one would expect cognitive and behavioural deficits to be present and measureable in HIV positive children.

Earlier studies have explored the neuropsychological sequelae of HIV positive children (Koekkoek et al., 2008; Martin et al., 2006; Patel et al., 2009; Smith et al, 2008; Wachsler-Felder & Golden, 2002). Deficits that may be displayed include a broad range of disorders arising from pervasive CNS dysfunctions and neurodevelopmental delays, to CNS opportunistic infections. In older school-going children, the first signs were usually declining academic performances, behavioural changes, psychomotor impairment with eventual progressive cognitive impairment and the emergence of new pyramidal tract signs (Civitello, 2003). Research has found that the use of ARV treatments (either single or combination therapy) has produced some reduction in neurocognitive deficits caused by the HIV infection (Govender, Eley, Walker, Petersen, & Wilmshurst, 2011; Robertson et al., 2004; Shanbhag et al., 2005). Smith et al. (2008) found slightly different results in that their sample showed neither improvement nor decline in their cognitive functioning. They suggest that the age of starting antiretroviral treatment is an important predictor for neuropsychological outcome (Smith et al., 2008). Additionally, Sherr, Mueller and Varrall (2009) describe several methodological issues with the HIV paediatric literature that could account for the difference in research findings. They suggest that the population sample, risk factors (such as maternal drug use and illness), age range of the children and neurocognitive tests used can all influence the results of studies. They also state that some of the research studies do not include adequate demographic information, such as gender, on their samples. They conclude that this field of research on childhood HIV infection and its effects on cognitive functioning needs to be more closely monitored so that better studies are produced and a better understanding can be reached.

The Neurocognitive Effects of Antiretroviral Treatment

A number of antiretroviral treatments are able to penetrate the blood-brain barrier and attack the HI-virus from inside the brain. This is an important factor in the mode of action of the antiretrovirals and their efficacy in reducing the HIV viral load. The antiretrovirals attack the virus reservoir that is normally protected inside the brain, specifically within the cerebrospinal fluid (Marra et al., 2009). This manner of action in which the antiretroviral treatment works, should be considered as part of a good treatment plan with regards to

lowering the HIV viral load in the different organs of the body. However some research has proposed that certain HIV treatments, especially the antiretrovirals which are able to penetrate the blood brain barrier, may have adverse effects on the central nervous system, and therefore on the cognitive functioning underlying the neurological areas affected by the antiretroviral treatment (Gounden, van Niekerk, Snyman & George, 2010; Liner, Reeker & Robinson, 2010; Marra et al., 2009). For example, Liner et al. (2010) tested a variety of single antiretroviral treatments as well as combination antiretroviral treatments on rats to measure the effects on each of the therapies on neurons in the brain. They found that when the concentration of the antiretrovirals in the brain reached the levels required to inhibit viral growth, there was a physical neurological risk to the neurons. Specifically Liner and colleagues found that some antiretrovirals resulted in dendritic beading, excess pruning of dendrites and actual loss of neuron density (2010). Specifically Efavirenz, part of the first-line HAART program, resulted in the severe effect of loss of neuronal density. In their study, they found that one antiretroviral medication caused a maximum of a 53.3% cell loss at levels required to be therapeutic. Marra et al. (2009) also tested a variety of antiretroviral treatments, however this research was performed on human subjects infected with HIV. They found that although the antiretrovirals that had better penetrative abilities with regards to the blood brain barrier, and were therefore negatively correlated to viral growth in the cerebrospinal fluid, were also found to be related to poorer cognitive functioning as measured by neuropsychological testing. They do state, however, that bigger trials and experiments are needed in order for the results to be conclusive. Research from South Africa has also found that certain antiretroviral treatments are associated with detrimental side effects. These side effects are located in the domains of both the physical and the neurological/neuropsychological (Gounden et al., 2010). These researchers deduced that this relationship may depend on certain genes which affect the metabolism of the antiretrovirals. This metabolism of the antiretrovirals influences the concentrations found within the cerebrospinal fluid. The research concluded that the higher the concentration of antiretrovirals within the cerebrospinal fluid, and therefore in the central nervous system, the more neurological related symptoms were found in the patient.

As is the case with most issues subject to vast amounts of research, such as with HIV due to its pandemic status has research whose results are contrary to the above studies have also been found. Smurzynski et al. (2011) and Tozzi et al. (2007) found in their respective studies that the use of high penetration antiretroviral treatments were associated with better cognitive

scores, after the antiretroviral treatment was initiated. Tozzi and colleagues (2007) stated that those participants who had persistent cognitive deficits, despite receiving antiretroviral treatment, began the study with lower initial cognitive scores. They thereby suggest that the persistent cognitive deficits are due to a naturally premorbid lower functioning cognition, and therefore is not a result of the antiretroviral treatment, which their research states has a positive effect on cognition.

This contradictory evidence may, at first glance, present a conundrum with regards to understanding the effect that antiretroviral treatment may have on neurology and cognition. However one cannot forget the effect that the actual HI-virus has on neurology, as has been explored above. This evidence may therefore suggest a dichotomous effect with regards to HIV and antiretrovirals. HIV has a negative effect on neurology and cognition. Treatment with antiretrovirals lowers the viral load of HIV in the central nervous system. However antiretrovirals also may have a negative effect on neurology and subsequent cognition, specifically with regards to other contributing factors, such as certain genes influencing the concentrations of antiretrovirals in the central nervous system (Gounden et al., 2010). One must therefore question whether HIV, or antiretrovirals, would have a worse effect on neurology and cognition. As HIV is a progressive illness, with the HI-virus constantly multiplying and evolving (Wachsler-Felder & Golden, 2002), one could say with certainty that HIV infection would cause the worse effects on neurology and cognition. Antiretroviral treatment would therefore be a requirement to slow that progression. Yet, as the very treatment that slows the progression of the destructive HI-virus creates its own neurocognitive deficits, one could postulate that there would be some deficit to neurocognitive function either way. This is an important factor to take into consideration with regards to this research, as all of the participants within the HIV-positive Research group were on antiretroviral treatment at the time of testing.

Visuospatial Ability

Visuospatial abilities are those related to understanding and conceptualising visual representations and spatial relationships in learning and performing tasks. These abilities cannot be examined in isolation, as they form an integral part of many other neurological functions and general cognition. Visuospatial ability is not a singular concept in and of itself, but rather a concept to describe a collection of visual, spatial, temporal, motor and general cognitive functions that work together to form one's visuospatial abilities (Mazzocco et al.,

2006). One of the earlier, and simplest, ways to subcategorise visuospatial processing is to differentiate the ability to identify visual objects, from the ability to discern the spatial location of objects, otherwise known as the 'what' and 'where' pathways of the visual system (Ungerleider, & Mishkin, 1982). This system, although seemly simplistic at first, can be split further to examine the many other facets that make up visuospatial ability.

One of the important functions underlying general visuospatial ability is visuospatial construction. Visuospatial Construction is the ability to

> …see an object or picture as a set of parts and then to construct a replica of the original from these parts...Examples of visuospatial construction include drawing, buttoning shirts, constructing models, making a bed, and putting together furniture that arrives unassembled. Visuospatial construction is a central cognitive ability. At the same time, there are enormous individual differences among people in their ability to perform visuospatial constructive tasks. Some individuals draw extremely well; others cannot draw at all. Some people can copy complex patterns accurately and rapidly; others can copy accurately but slowly; still others can copy only simple patterns or none at all. The importance of visuospatial construction for everyday life, coupled with the wide range of ability shown by individuals of the same age, has led to the inclusion of measures of visuospatial construction on virtually every full-scale assessment of intelligence (Mervis, Robinson, & Pani, 1999, p 1222)

Another visuospatial function is found within working memory. Working memory contains a visuospatial sketchpad (Baddeley, 2000). This sketchpad is used in the temporary storage and manipulation of spatial and visual information, such as remembering shapes and colours, or the location or speed of objects in space. It is also involved in planning of spatial movements, such as planning one's way through a complex building. The visuospatial sketchpad can be divided into separate visual, spatial and possibly kinaesthetic (movement) components. These components have different neurological correlates within the lateral prefrontal cortex. Neurons in the dorsolateral prefrontal cortex are specialised to spatial working memory, whereas neurons in the ventrolateral prefrontal cortex specialise in non-spatial (object) working memory (Meyer, Qi, Stanford, & Constantinidis, 2011). The visuospatial sketchpad is an important part of working memory. This therefore highlights the importance of visuospatial abilities on one's executive functioning.

Spatial-temporal reasoning is also a visuospatial construct. This is the ability to visualize spatial patterns and mentally manipulate them over a time-ordered sequence of spatial transformations. This ability is important in the generation and conceptualisation of solutions to multi-step problems that arise in areas such as architecture, engineering, science,

mathematics, art, games, and everyday life. Visuospatial ability is also important in the aspect that it can simultaneously tap into multiple other cognitive modalities. An example is research by Masedu, Sabatino, Benzi, Tarnorri and Valentl (2010) which showed the different aspects of visuospatial abilities by displaying that expert chess player's employed working memory, short-term memory and long-term memory simultaneously whilst playing chess.

Eye-hand coordination is the visuospatial ability that coordinates the control of eye movements along with the movement of one's hands, together with the processing using visual input and proprioception (unconscious perception of movement and spatial orientation) of the upper limbs and hands to guide reaching and grasping as well as guide the eyes (Johansson, Westling, Bäckström & Flanagan, 2001). Essentially eye-hand coordination involves coordinating vision and motor (hand) movement to execute a specific task. Crawford, Medendorp and Marotta (2004) state that eye-hand co-ordination is a "defining characteristic of typical human life" (p. 10) in that it is used, and is fundamental, in many everyday activities, such as eating, writing and using tools. Considering this, they state that any failure in eye-hand co-ordination and visuospatial abilities in general, because of disease, developmental disorder or injury, can lead to a disruption in productivity and quality of life.

There are recognised differences in visuospatial abilities between males and females. These differences are observed colloquially and scientifically with research spanning decades in support of these differences. In the examination of more than 25 studies spanning over 30 years that were examined by Downing and colleagues, the irrefutable conclusion was

> All of these studies suggest some gender differences in scores on various intelligence test items and sub-tests and, whilst not all results are consistent, a gender stereotype emerges which suggests that males generally outperform females on sub-tests of numerical and visuo-spatial ability whereas females outperform males on sub-tests of verbal ability (Downing et al., 2008, p. 6).

Visuospatial ability in humans impacts broadly. It is present in many simple processes such as the ability to walk or pick up objects, to more complex and advanced mechanisms such as engineering, most sports, science, and art. It also affects the basics of everyday life such as judging the distance and speed of an approaching car when crossing the street. These abilities have specific neurological correlates with regards to the specific cognitive functions. Visuospatial abilities are governed by the white-matter tracts in the parieto-preoccipital subareas of the cerebral cortex (Mishkin, Lewis, & Ungerleider, 1982). These abilities rely

very heavily on the fronto-striato-parietal networks (Woods et al, 2009), especially during the development of these areas (specifically the frontal lobe) that occurs at the onset of adolescence (Klingberg, Forssberg & Westerberg, 2002). More specifically the frontal areas correlate to the working memory and temporal aspects of visuospatial ability. The striato-parietal networks (including the parieto-preoccipital areas) localise the visuospatial functions underlying the visual pathway and the fronto-striatal pathways and links them together.

HIV and Visuospatial Functioning

HIV has been shown to negatively affect the white-matter of the brain, specifically causing a direct loss of axonal integrity, as well as a loss of complexity to the underlying axonal matrix of the white matter (Stebbins et al, 2007). This disruption to the white matter has been shown to be specifically prevalent within the frontal lobe (Pomara et al., 2001). Should there be disruption of this white matter, one could assume that visuospatial ability would be negatively affected as a consequence, as visuospatial abilities rely very heavily on the various white matter tracts, as well as on frontal lobe functioning. The potential effect that HIV has on visuospatial ability is therefore important. Specifically in adolescence, where white matter network development is strengthened and frontal lobe maturation is starting to occur (Klingberg et al, 2002). Therefore the effects that HIV has on this development, and on the functions that result from this development, are of interest. Motor and language skill development in seropositive children have been thoroughly researched. Visuospatial abilities, however, have not been as extensively researched.

Another important area of concern would be the differences of the effects of HIV on visuospatial development between males and females (Bellis et al, 2001). As mentioned above, research has found differences between healthy HIV-negative males and females with regards to visuospatial functioning, with males displaying advanced visuospatial abilities in comparison to females during adolescence. This can be attributed to the differences in neurological development between males and females during the adolescent period of neurological development. Neuroimaging studies have found that during adolescence “males had more prominent age-related gray matter decreases and white matter volume and corpus callosal area increases compared with females” (Bellis et al, 2001, p. 552). As visuospatial abilities’ development is reliant upon the white matter tracts within the brain, it is therefore logical that males, who during adolescence have a larger white matter volume, would have a neurological advantage with regards to visuospatial abilities.

As HIV has a specifically strong negative effect on the white matter tracts within the brain (Stebbins et al, 2007), and the amount of white matter differs significantly between males and females due to age-related neurological development (Bellis et al, 2001), the effect that HIV has on the visuospatial abilities of male and female adolescents should be notably different. This is an area of study that has significant implications for HIV-positive adolescents, as one must therefore consider the possibility that as HIV may neurologically (and thereby cognitively) affect males and females differently, the compensatory, remedial or rehabilitatory work that could be implemented, would need to be designed differently for males and females.

Instruments

To examine the effect of HIV upon the various visuospatial abilities described above, a battery of assessments was used that tap into the various visuospatial abilities. This battery includes subtests from the WISC-R, which although not specifically designed to produce neuropsychological information, neuropsychological information can be gathered from the subtests. The battery also includes tests and subtests from other specifically neuropsychological assessments which were designed to generate neuropsychological information. The subtests being examined in this research ostensibly are widely considered to tap into various aspects of visuospatial functioning, consist of the following: The Rey Osterrieth Complex Figure Test (ROCFT) – Copy and Recognition Trials; Trail Making Test (Parts A and B); Delis-Kaplin Executive Function System – Colour Naming Test (Stroop); Grooved Pegboard (Dominant and Non-Dominant Hand); and the performance subtests of the WISC-R (Picture Completion, Picture Arrangement, Block Design, Object Assembly, Coding and Mazes).

The Rey Osterrieth Complex Figure Test (ROCFT) evaluates the participant's visuospatial constructional ability, visual memory and executive function mediated by the prefrontal lobe (Shin, Park, Park, Seol & Kwon, 2009). The ROCFT is made up of three conditions. In the initial phase, the participant is given the Complex Figure to copy, which is essentially reliant upon the individual's ability for Visuospatial Construction. Five minutes later, the second phase requires the participant to draw from memory the Complex Figure. Thus providing, given that the testee is not specifically cued that information should be transferred to long term memory, an indication of incidental memory for visually perceived data. Finally, following a delay of thirty minutes, the participant is asked to again draw the Complex Figure

from memory. The way in which the administrator scores the tests is related to the location, accuracy, and organisation of the individual features of the figure at each of the three stages (Strauss et al, 2006). Finally a Recognition trial is administered, which consists of pieces of the original figure mixed with pieces of an alternate complex figure, in which the participant has to correctly identify which pieces belonged in the original figure.

A study conducted by Skuy, Schutte, Fridjhon and O'Carroll (2001) compared a group of Soweto middle school student's (152 learners, split equally between males and females, with an average age of 14 years 3.5 months) results in the ROCFT to the age-related norms as found in the test manual. Their results found that the mean standard of the copies on a South African Soweto sample yielded lower scores (31.27; Sd: 3.14) than the American norms (35.1; Sd:1.5), while the reproduction scores after a lapse of thirty to forty-five minutes resulted in a mean score of 19.9 for the Sowetan sample and 23.2 for the American norm. Thus the administrator should expect the scores by South African children to be lower than the norm before accounting for the effects of HIV. The scoring system that was developed with the test by Rey in 1941 and later elaborated on by Osterrieth in 1944, evaluates fragmentation, planning, organisation, presence and accuracy of various features, placement, size distortions, perseveration, confabulation, rotation, neatness, symmetry and immediate and delayed retention and results in a score for each category (Strauss et al, 2006). This scoring system therefore allows for examination of not only visuospatial functioning, but also of visual memory as well as executive functioning (specifically planning). This provides a reliable method for scoring the ROCFT, nevertheless good inter-rater reliability is essential in order to produce reliable scores (Stern et al, 2007).

The Wechsler Intelligence Scale for Children Revised (WISC-R) comprises of ten subtests, and two additional supplementary scales which have been combined in such a way that the WISC-R is a measure of Verbal IQ (VIQ), Performance IQ (PIQ), and Full Scale IQ (FSIQ) (Franzen, 2000). The composite VIQ is comprised of the Information, Similarities, Arithmetic, Vocabulary and Comprehension subtests whereas the composite PIQ score is comprised of the Picture Completion, Coding, Picture Arrangement, Block Design and Object Assembly subtests. The WISC-R is an individual test that does not require the participant to engage in any reading or writing. The test administrator sits with the participant and facilitates the completion of each of the subtests. The PIQ subtests as listed above will be examined by this research given their loading on visual ability, are nonverbal problems that

the participant solves while being timed (in most subtests) by the test administrator (Slate & Jones, 1992).

Overall internal consistency reliability coefficients have been generated where PIQ has a reliability coefficient of 0.90, VIQ of 0.94, and FSIQ of 0.96 respectively. Correlation coefficients for Performance subtests (where the subtests for this research are being extracted from) range from 0.59 for Picture Completion to 0.80 for Object Assembly (Franzen, 2000). The validity of the use of the WISC-R in a sample with neural impairment is high as the results of the WISC-R delineate profiles of skills and deficits (Hale, 1981). The use of the WISC-R over the newer WISC-IV was decided on, as the WISC-R has received more use and attention within South African research (Skuy et al., 2001; Rushton, 2001; Rushton & Jensen, 2005; Rushton & Skuy, 2000) and therefore has a wider database of South African relevant normative data. Highlighting this, a literature search on low SES normative data for South Africa on the WISC-IV resulted in no publications, however there has been unpublished dissertations which have explored differences in quality of education on the results of the WISC-IV. Therefore the lack of published data reinforced the decision to employ the WISC-R in this research.

The Trail Making Test (TMT) is a test of visuomotor and visual conceptual tracking (visual scanning) that is split into two parts: Part A and Part B. The TMT requires the subject to connect, by making pencil lines, 25 encircled numbers randomly arranged on a page in numerical order (Part A), and 25 encircled numbers and letters in alternating order (Part B) (Strauss, Sherman, & Spreen, 2006). Both parts have a sample test for instruction and demonstration to ensure that the instructions are understood by the participant. Skuy and colleagues (2001) found significant differences between the international norms and the South African norm results. The international results give an average of 23 seconds to complete Part A and 47 seconds to complete Part B. The sample in Skuy et al's study took an average of 38.51 seconds on Part A (10th percentile), and an average of 85.72 seconds on Part B (below 10th percentile). Therefore is it hypothesised that both the test and control groups will take longer than the 5 minute average test time suggested for this test. The TMT is a well-known and internationally recognised test, with a history of use spanning since its creation in 1938 (Strauss et al, 2006). An integral factor when examining the TMT as a whole, is the importance of not using raw scores to make assumptions about the traits

ostensibly inherent to Part B without due consideration for the underlying abilities tapped in Part A.

The Grooved Pegboard (GPB) is a test which was initially designed to screen for neurological motor impairments, as the test requires considerable manual precision and dexterity in order to complete it (Strauss et al, 2006). The test consists of a board with a five by five matrix of holes that have randomly positioned slots. The pegs have a ridge or groove along one side, which must be rotated and aligned to match the slot in the hole before it can be inserted. The patient's task is to insert the pegs into the board in sequence as quickly as possible, with the dominant then non-dominant hand. The test is completed when all the pegs are placed in the board. The test is scored by the amount of time, in seconds, that the patient takes to complete the task for each hand. Although initially designed to be a screening assessment of motor functioning, research has shown that there is a large visuospatial (visuomotor) component to the Grooved Pegboard, specifically the required use of the Eye-hand coordination visuospatial ability (Grisham, Anderson, Poulton, Moffit & Andrews, 2009; Schear & Sato, 1989). The Grooved Pegboard had a moderate to high reliability (0.67 to 0.86) (Strauss et al, 2006), and has a moderately strong relationship with tests of visual acuity (Schear & Sato, 1989) which thereby highlight the tests strong visuospatial element.

The tests and subtests described above form the foundation of the battery examining the visuospatial abilities of HIV-positive adolescents on antiretroviral treatment. Some subtests are a purer measure of one specific visuospatial function (such as the Trail Making Test – part A which is an almost pure measure of Visual Scanning) (Strauss et al, 2006), whereas other subtests utilise, and therefore measure, more than one visuospatial ability (such as the Trail Making Test – part B, which can be used to measure Visual Scanning, Spatial Temporal Reasoning and the Visuospatial Sketchpad) (O'Donnell, McGregor, Dabrowski, Oestreicher & Romero, 1994; Shum, McFarland & Bain, 1990). It is therefore important to use a more holistic approach when examining the results, in order to be able to fully examine what functions each test measures, and thereby examine how these functions are affected by HIV as reflected in the assessment performance.

Research Questions

- What is the effect of vertically-transmitted HIV infection on visuospatial abilities in low-SES HIV-positive adolescents, in comparison to SES-Matched HIV-negative adolescents?
- Is there a statistically significant difference between different visuospatial abilities as a result of HIV-infection?
- Is the effect of HIV-infection with regards to visuospatial skills manifested differently in Males than in Females?
- Does the health of the participant with regards to HIV infection, as operationalized by CD4+ count at the time of assessment, have an effect upon visuospatial abilities?
- Does the current state of the HI-virus, as seen through the Viral Load count at the time of assessment, have an effect upon visuospatial functioning?
- Does the health of the participant at the onset of antiretroviral treatment, as displayed through CD4+ count at antiretroviral treatment start, have an effect on visuospatial functioning?
- Does the state of the HI-virus at the start of antiretroviral treatment, as measured by Viral Load count at antiretroviral onset, have an effect on visuospatial ability?
- What is the size of the effect of HIV upon visuospatial abilities?
- Does HIV effect males and females differently with regards to the size of the effect?

Chapter 2: Methodology

Instruments

A comprehensive neuropsychological battery was administered as part of the overarching project (see Appendix 1 – section 3.2, for the full list of tests administered in the battery). Only data from certain selected tests and subtests had relevance to visuospatial abilities, and therefore only this data was extracted from the results of the overall battery for use in this research. Tests and subtests examined by this research consist of the following: The Rey Osterrieth Complex Figure Test – Copy and Recognition Trials; Trail Making Test (Parts A and B); Delis-Kaplin Executive Function System – Colour Naming Test (Stroop); Grooved Pegboard (Dominant and Non-Dominant hand); and subtests of the WISC-R (Picture Completion, Picture Arrangement, Block Design, Object Assembly, Coding and Mazes).

Sample

The sample for this research consisted of 30 HIV-positive adolescents between the ages of 13 years 0 months to 15 years 11 months old; A healthy comparison group (Control group) consisted of 70 children who had similar socioeconomic status, operationalised by the area in which they live, and through quantification in a Socioeconomic Deprivation (SED) questionnaire. Given the ethical implications associated with formally testing to ensure the group was HIV-negative, the assumption of HIV-negativity was based on parental and school reports relative to the absence of regular medication and school absences.

The sex composition of the Research group was 14 Males and 16 Females, whilst the Control Group consisted of 33 Males and 33 Females and 4 whose sex was not recorded (see table 1 below for breakdown). The average age in both groups was 14 years 1 month old.

	Research (HIV-Positive) Group	Control Group	Total
Males	14	33	47
Females	16	33	49
Unknown		4	4
Total	30	70	100

Table 1: Sample Breakdown

The sample base for both groups consisted of Black, low socioeconomic teenagers, who have English as a second language. To minimise the extraneous impact of language proficiency in testing second language speakers, all participants were required to have completed at least four years of English medium schooling (criterion applied for both research and control group).

Participants for the Control group were obtained from the same schools in the Orlando area of Soweto reported on by Skuy and colleagues (2001). A sample comparable to the Research group was chosen with regard to age and socioeconomic status through the SED and demographic background questionnaire, (which were the same questionnaires used in the Skuy and colleagues article (2001)) from which the participants were quantifiably seen to be comparable to the Research group. A letter was sent home with the children explaining the research. Included in the letter was a request that should the child be on chronic medication, HIV positive, have experienced a head injury, have any neurological impairment, or is living outside of the nuclear family structure, a response to the request for participation was not necessary. In this way the exclusion criteria that applied to the HIV-positive group was operationalized in the HIV-negative control group. As testing was performed during the school holidays no specific insinuation would be inferred relative to no-participation with regards to the learners' peers.

Inclusion and Exclusion Criteria

There were strict exclusion criteria (head injury, have any neurological impairment such as meningitis or encephalitis, or is living outside of the nuclear family structure) for the Research Group, which were also applied to the Control Group, in an attempt to be able to isolate the exact effects of HIV through excluding possible extraneous variables. All participants needed to be within the age range of 13 years 0 months old to 15 years 11 months old. Within the research group, participants were chosen from adolescents where HIV infection occurred through vertical transmission (Mother-to-Child), as well as requiring the participants to still be on first-line antiretroviral treatment, with a history of good medication compliance, as discerned from the participants medical files (please see Appendix 12 for the biographical and demographic questionnaire).

Research Design

Although this research is inherently examining visuospatial abilities within the sample that may have been impaired (or failed to develop) over time due to the effect of HIV on the neurology underlying the abilities, the research aimed to explore the sample as they currently stand, not track the changes over time. These traits were examined in comparison to a control sample with similar socioeconomic status, selected by a screening process to attempt to ensure the participants are HIV-negative (as one cannot ethically enquire about their HIV status). This study purely examined variables, and did not attempt to manipulate them in any way. Therefore, this design was a non IV-manipulated cross-sectional quasi-experimental post-test only control group design.

Procedure

The data examined, to answer the questions posed in this research project, was collected as part of the overarching project (see Appendix 1 - section 3.4 for the full explanation of the overarching project's data gathering procedure). Data for the research group was gathered at an HIV clinic within one of the government hospitals in the Johannesburg area, whilst data for the comparison Group was gathered from a middle school in the Orlando-West district of Soweto.

Possible participants for the research group were initially screened from patients attending that day's clinic for their tri-monthly check-up, through examination of their medical files. Those adolescents who fitted into the inclusion criteria, and did not meet the exclusion criteria, were approached (together with their legal guardian) and invited to participate in the research. The procedure was explained to the participants and their guardians, together with explanations around confidentiality and anonymity (with regards to the written report). After the procedure was explained to the participant and their guardian, assent and consent forms were signed respectively. After this the participants accompanied administrators to complete the battery. Half way through the battery the participant was taken back to the clinic for their medical check-up (which also acted as a mid-administration break to avoid fatigue), after which the battery administration was completed. Psychometric assessment was conducted at the time of the regular scheduled clinic, to avoid the necessity that participants would be required to incur further school absences. Participants were specifically provided with refreshments in the form of a snack pack, and a stipend to reimburse for travel or any other

costs that may have been incurred relating to participation. Rotation of the assessment protocol was specifically designed to coincide with waiting times for the clinic to ensure that there was no interference with the clinic process. This also ensured that validity relating to cumulative data pertaining to a specific measure was not artefactually impacted upon by fatigue.

Data for the Control group was gathered at a secondary school in Orlando-West, Soweto, drawing learners of a comparable age and socioeconomic status, with clearance obtained from Gauteng Department of Education. Information letters, as well as consent and assent forms, were disseminated to learner's legal guardians and participants by the school principal. Learners were invited to participate during a two-week data collection time during the school holiday, which therefore ensured that there was no impact on contact teaching time.

The administration of the test battery consisted of a rotational administration. Test administrators each had separate sections of the entire battery and participants rotated between the administrators to complete the full battery. The rotational order of administration was planned so as to not cause specific subtests to be unduly subject to factors such as fatigue (by occurring at the end of the battery with all participants) or other factors such as lack of test wiseness, or rapport or nervousness (by occurring at the beginning of the battery with all participants). This also sought to improve inter-rater reliability by ensuring that the tests were administered equally among the administrators, and also therefore minimise intra-rater bias.

Ethical Considerations

The overarching research project was granted ethical approval by the University of the Witwatersrand Medical Ethics Board (Ethics Number M120268 – see Appendix 3 for Clearance Certificate) as well as having approval from the Gauteng department of Education (Reference Number D2012/235 – see Appendix 2 for GDE approval letter). See Appendix 1, section 3.6 for the overarching project's ethics section.

An explanatory letter was given to the research participant as well as their legal guardian, as well as face to face verbal communication, to ensure that the concepts (such as voluntary participation as well as right to withdraw at any time) were fully understood. Once agreement to participate was given, consent and assent forms were signed by the legal guardian and participant respectively, and then the test battery was administered (please see Appendices 4-

11 for all information sheets, consent and assent forms) Participants were given a snack pack (half-way through the battery so as not to unduly fatigue them) as well as a small stipend (at the completion of the test battery) to cover any incidental expenses resulting from participation.

Chapter 3: Results

Results

All data generated from the psychometric measuring instruments was in the form of interval or ratio data. All of the data were non-significant in the Levene's Test for Homogeneity of Variances, thereby indicating homogeneity of variances, and normality of the data was shown through examination of Skewness and Kurtosis values as well as the Kolmogorov-Smirnov Goodness-of-Fit test for Normal Distribution for each subtest comparison. Therefore all requirements for parametric tests were met. In the subtests where either homogeneity of variance was unequal, or where the data was not normal, an equivalent non-parametric statistical procedure was used in place of a parametric procedure.

An Analysis of Variance (ANOVA) was computed for the purpose of examining for significance in the differences of the results obtained from the research group and the results obtained from the control group (See table 2 below). All data used in the statistical analyses was the raw-score data from the various subtests. Within the WISC-R subtests significant differences were found in the measured performance on the Block Design subtest ($F=8.03$; $p=0.0056$) and the Object Assembly subtest ($F=10.85$; $p=0.0014$), with post-hoc testing, using the Bonferroni (Dunn) t-test, displaying significantly higher results in both subtests for the Control Group (higher results with regards to the WISC-R subtests display better proficiency in the task). In examination of the results of the rest of the battery containing specifically neuropsychological tests, significant results were found in the ROCFT copy trial ($F=17.92$; $p<0.0001$), ROCFT recognition trial ($F=7.42$; $p=0.0077$), TMT part A ($F=25.66$; $p<0.0001$), TMT part B ($F=13.94$; $p=0.0003$), Stroop Colour Naming Task Time ($F=18.45$; $p<0.0001$) and Error scores ($F=19.92$; $p<0.0001$), as well as the GPB dominant hand ($F=4.28$; $p=0.0413$) and non-dominant hand ($F-4.56$; $p=0.0353$). Post-hoc testing with the Bonferroni (Dunn) t-test displayed the Control Group having significantly better scores than the Research Group.

With regards to the GPB results, to ensure that the significant differences in the results reflected a visuospatial element (hand-eye co-ordination) instead of a motor element, the results of the Finger Tapping Test (FTT) were run. Unlike the GPB which has a large visuospatial element to the test (in hand-eye co-ordination), the FTT is a pure test of motor function in testing motor speed (Strauss et al, 2006). The results of the FTT displayed no

significant differences between the research and control groups for dominant hand (F=0.65; p=0.4205) and non-dominant hand (F=2.91; p=0.0913). It is therefore concluded that the GPB results reflect more on visuospatial ability than on motor function.

Comparisons were run with regards to the ROCFT immediate and delayed recall trials. Both the immediate recall scores (F=11.02; p=0.0013) and the delayed recall scores (F=12.94; p=0.0005) displayed significant results. However when the scores were converted into the percentage of retention relative to the initial Copy score, the results then became non-significant with regards to difference between the Research group and the Control group for both the immediate recall score (F=0.08; p=0.7875) and delayed recall scores (F=0.07; p=0.7867), with the raw scores being one percentage point apart between the two groups, for both the immediate and delayed recall percentage scores. This indicates that the scores for the immediate and delayed recall trials are not an indication of memory, but are rather a reflection of impaired visuospatial input at the original trial.

A comparison was also run on the scores of the part B and A when the Trail Making Test – part B was converted to a percentage of the Trail Making Test – part A. These results indicated that there was no significant difference (F=0.29; p=0.5939) between the results for the Research group and the Control group. The significance of this result will be discussed further below.

Subtest	Degrees of Freedom	F-Value	Pr > |F|
WISC-R Block Design	95	8.03	0.0056
WISC-R Object Assembly	94	10.85	0.0014
ROCFT Copy Trial	97	17.92	<0.0001
ROCFT Recognition Trial	94	7.42	0.0077
Trail Making Test – Part A	99	25.66	<0.0001
Trail Making Test – Part B	99	13.94	0.0003
Stroop Colour Naming Test – Time Score	99	18.45	<0.0001
Stroop Colour Naming Test – Error Score	100	19.92	<0.0001
Grooved Peg Board – Dominant Hand	97	4.28	0.0413
Grooved Peg Board – Non-Dominant Hand	97	4.56	0.0353

Table 2 – Subtests Displaying Significant Results

Initial results as presented above present disparities between the Research and Control groups that transcend sex. Considered separately both male and female HIV-positive cohorts demonstrated statistically significant deficits relative to the ROCFT copy trial (F=15.04, p=0.0003; F=6.15, p=0.0169 respectively), TMT part A (F=5.17, p=0.0278; F=22.16, p<0.0001), Stroop Colour Naming Task Time (F=13.71, p=0.0006; F=5.96, p=0.0185) and Error scores (F=9.94, p=0.0029; F=8.41, p=0.0056). Differences between Males and Females

were however found in other subtests. Males not identified as being HIV-positive performed significantly better than HIV-positive adolescent males in the Block Design subtest ($F=9.56$; $p=0.0035$), the TMT part B ($F=18.44$; $p<0.0001$) and the GPB dominant hand ($F=4.13$; $p=0.0484$) and non-dominant hand ($F=4.86$; 0.0329). With regards to the female cohort, females who were HIV-positive performed significantly worse than those females identified as being HIV-negative in the Object Assembly subtest ($F=7.97$; $p=0.0071$) and the ROCFT Recognition trial ($F=8.53$; $p=0.0054$), where Males displayed no significant differences in these subtests (See table 3 below for further details). Bonferroni (Dunn) post-hoc t-tests confirmed that in all cases the Control Group outperformed the Research Group. It must be acknowledged that the smaller sample size that was created in examination of sub-samples, may have had an effect on the results obtained statistically. Therefore all interpretations of the results must be made with caution.

Subtest	Sex	Degrees of Freedom	F-Value	Pr > |F|
ROCFT Copy Trial	Male	45	15.04	0.0003
	Female	47	6.15	0.0169
Trail Making Test – Part A	Male	46	5.17	0.0278
	Female	48	22.16	<0.0001
Stroop Colour Naming Test – Time Score	Male	46	13.71	0.0006
	Female	48	5.96	0.0185
Stroop Colour Naming Test – Error Score	Male	46	9.94	0.0029
	Female	48	8.41	0.0056
Block Design	Male	44	9.56	0.0035
Trail Making Test – Part B	Male	46	18.44	<0.0001
Grooved Peg Board – Dominant Hand	Male	44	4.13	0.0484
Grooved Peg Board – Non-Dominant Hand	Male	44	4.86	0.0353
Object Assembly	Female	45	7.97	0.0071
ROCFT Recognition Trial	Female	48	8.53	0.0054

Table 3 – Subtests Displaying Significant Results by Sex

When the subtest results were examined with regards to HIV-related medical/physiological considerations, three results indicated significance. This consisted of the research group being split into two groups in four different medical subgroups. The four subgroups were: Current CD4+ count (High [N=18] versus Low [N=12]), current HIV Viral Load (High [N=12] versus Low [N=18]), CD4+ count at HAART initiation (High [N=13] versus Low [N=17]) and HIV Viral Load at HAART initiation (High [N=21] versus Low [N=9]). Overall three of these subgroup comparisons displayed significant differences. Performance on the TMT-A

was statistically significantly poorer for the subgroup of HIV-positive adolescents who at time of assessment presented with a more compromised CD4+ count (T=-2.66; p=0.0128) and for those who presented with a higher viral load (T=-4.26; p=0,0007). Whereas performance on the Object Assembly subtest displayed statistically significant poorer results for those individuals whose CD4+ counts were compromised at the initiation of HAART (T=2.63; p=0.0146), supporting the above and suggesting that the development of Visuospatial construction could be compromise (See table 4 below for details).

Medical Subgroup	**Subtest**	**Degrees of Freedom**	**T-Value**	**Pr > |T|**
CD4+ count at HAART Initiation	Object Assembly	24	2.63	0.0146
Current CD4+ count	Trail Making Test – Part A	28	-2.66	0.0128
Current Viral Load Count	Trail Making Test – Part A	28	-4.26	0.0007

Table 4 – Medical Subgroups Significant Results

Supporting the assumption that these differences are not a consequence of economic availability, rather than the effect of HIV, no significant between group differences were recorded on measured performances when demographic effect of money for basic needs (is there enough money for basic needs such as food and clothing?) was examined as the Independent Variable. Both the research group and the overall sample were compared when split into two groups (yes and no with regards to money for basic needs). In both cases there were no significant differences in the results with regards to the variable of having money for basic needs, thereby suggesting the demographic variable of money had no effect.

Finally Factor Analyses were run on the data in an attempt to examine for specific communality in factors throughout the data. Unrotated Orthogonal Factor analyses were run with the data from the Research group and the Control group in an attempt to be able to find factors in each group which may help explain some of the results, or explain possible variances in the results. The number of factors in each analysis was decided upon by the eigenvalues, for which the cut-off for including the factor was an eigenvalue below 1. When comparing factors of the Control group in comparison to those found in the Research group, one can see how there are more factors in the Research group which overall account for 21%

more variance than in the Control group. The Factor Analysis by group revealed that the control group displayed three significant factors, explaining 53.66% of the variance in the results, whilst the research group displayed four significant factors explaining 74.22% of the variances in the elicited results (See table 5 below for details). These results therefore suggest that there are extra factors in the Research group which are causing a variation in the results, which are not present in the Control group. One could therefore hypothesise that the extra factors that explain more of the variance are HIV related factors, which are not present in the Control group.

	Control group			**Research Group**			
	Factor 1	Factor 2	Factor 3	Factor 1	Factor 2	Factor 3	Factor 4
WISC-R – Picture Completion	0.50394	0.24657	-0.03766	0.42489	0.45757	-0.50363	0.07381
WISC-R – Picture Arrangement	0.56675	0.01776	0.01134	0.72800	0.26848	0.28220	-0.05199
WISC-R – Block Design	0.76373	0.33755	0.28875	0.80054	-0.09150	-0.40726	0.04629
WISC-R – Object Assembly	0.68521	0.03733	0.12001	0.38322	0.39823	-0.30513	0.64655
WISC-R – Coding	0.67302	0.01169	-0.26019	0.64326	-0.07256	-0.04108	-0.42850
WISC-R – Mazes	0.54943	0.52258	0.27138	0.50060	0.49593	0.44857	-0.25623
ROCFT Copy Trial	0.39877	0.34213	0.58867	0.81732	0.11623	0.10516	-0.05677
ROCFT Recognition Trial	-0.21938	0.50619	-0.38716	-0.14482	-0.04478	0.74477	0.44952
TMT – A	-0.64840	-0.09706	0.52127	-0.24713	0.62277	0.17599	-0.48698
TMT – B	-0.75950	-0.06714	0.43868	-0.52757	0.52683	0.23209	0.38943
Stroop Colour Naming Task – Time	-0.52378	0.46844	0.17731	-0.79493	0.32391	-0.05222	-0.29954
Stroop Colour Naming Task – Errors	-0.28244	0.20505	0.10388	-0.22405	-0.81940	0.11180	-0.07278
GPB Dominant Hand	0.48066	-0.53248	0.20268	0.87390	-0.14784	0.22196	0.02447
GPB Non-Dominant Hand	0.46243	-0.63310	0.24239	0.75294	-0.18244	0.30652	0.06157
Variance Explained	4.386201	1.782711	1.343322	5.203739	2.211999	1.604160	1.371075
Final Communality Estimates	**7.512235**			**10.390975**			

Table 5 – Factor Analysis by Group

When a Factor Analysis was run with data grouped by Sex and Group, some interesting results were elicited. When the Control group male's results were examined with regards to the factors that displayed a significant impact on the results, five significant factors were realised in the data. These five factors explained 70.27% of the variance seen in the results of the males. Whereas in comparison, there were only four factors that were significant with the data from the females in the Control group. These four factors contributed to a total of 69.13% of the data variance within the results of the females in the Control group. As they are of direct interest, only the factor analyses run on the Research group males and females will be examined in further detail below. The data from the males in the Research group indicated that there were three significant factors. These three factors combined explained 79.36% of the variance in the results for the HIV-positive males. With regards to the females in the Research group, the analysis returned five significant factors, which overall explained 85.59% of the variance in the results of the HIV-positive female adolescents (see tables 6 and 7 below respectively for more details).

Research Group Males			
	Factor 1	Factor 2	Factor 3
WISC-R – Picture Completion	0.58208	0.70305	0.12387
WISC-R – Picture Arrangement	0.82324	0.35770	-0.15512
WISC-R – Block Design	0.90401	-0.05733	-0.15553
WISC-R – Object Assembly	0.69720	0.16827	-0.61832
WISC-R – Coding	0.67127	0.08686	0.30019
WISC-R – Mazes	0.20587	0.78159	0.27357
ROCFT Copy Trial	0.83999	0.19290	0.32797
ROCFT Recognition Trial	-0.70150	0.37110	0.06500
TMT – A	-0.45444	0.54946	0.60558
TMT – B	-0.39572	0.56378	-0.49020
Stroop Colour Naming Task – Time	-0.77197	0.28516	0.30914
Stroop Colour Naming Task – Errors	-0.28475	-0.85724	0.26734
GPB Dominant Hand	0.86141	-0.30868	0.30746
GPB Non-Dominant Hand	0.75092	-0.23356	0.36051
Variance Explained	6.356577	3.032938	1.721230
Final Communality Estimates	**11.110747**		

Table 6 – Factor Analysis Results – Research Group Males

Research Group Females					
	Factor 1	Factor 2	Factor 3	Factor 4	Factor 5
WISC-R – Picture Completion	0.22215	0.67299	-0.50159	0.28299	-0.28149
WISC-R – Picture Arrangement	0.67842	-0.02226	0.58346	0.07952	-0.21886
WISC-R – Block Design	0.74255	0.23654	-0.45029	-0.07434	0.19838
WISC-R – Object Assembly	0.10994	0.78744	-0.19397	0.42311	0.22633
WISC-R – Coding	0.68908	-0.17866	0.03202	-0.40393	0.07969
WISC-R – Mazes	0.60556	0.12881	0.58795	-0.01658	-0.23405
ROCFT Copy Trial	0.78940	0.16078	0.16516	-0.09928	0.50449
ROCFT Recognition Trial	0.15876	-0.57280	0.29510	0.54753	0.38392
TMT – A	-0.25079	0.58889	0.60002	0.02351	0.36843
TMT – B	-0.77502	0.19050	0.41801	0.09972	-0.27265
Stroop Colour Naming Task – Time	-0.87877	0.15846	0.23531	0.20094	0.06606
Stroop Colour Naming Task – Errors	-0.08544	-0.68174	-0.31050	0.44016	0.06147
GPB Dominant Hand	0.88406	0.03843	0.12419	0.24244	-0.18867
GPB Non-Dominant Hand	0.78537	-0.05747	0.07750	0.32434	-0.28313
Variance Explained	5.404418	2.409631	2.001443	1.152630	1.014728
Final Communality Estimates	**11.982852**				

Table 7 – Factor Analysis Results – Research Group Females

Chapter 4: Discussion

Discussion

HIV is a global pandemic that affects over 34 million people worldwide (Shisana et al., 2009), and with more than two thirds of HIV-infected people residing in in sub-Saharan Africa, it is a topic of immense importance in South Africa. Uncontrolled HIV has devastating physiological (Ellis et al., 2009), neurological and cognitive consequences (Civitello, 2003) as the virus directly effects the Central Nervous System. Children who are born HIV-positive through perinatal transmission often present with worse symptoms and a more rapid progression of symptoms than adults who contract the virus (Kovacs, 2009). Considering 87% of HIV-positive children under 15 years old are found in Sub-Saharan Africa (Wachsler-Felder & Golden, 2002), and due to the fact that adolescence is a period of critical physiological, neurological and consequently cognitive development, exploring the effects of HIV on this population is of vital importance.

Overall Visuospatial Abilities

The importance of visuospatial abilities in one's daily functioning cannot be overemphasised. As a person's visuospatial skills link into many (one may argue most) other cognitive domains, any impairment in visuospatial skills may have a greater impact than just in one singular domain (Mazzocco et al, 2006). As the development across the spectrum of visuospatial skills are reliant upon the neurological development that occurs throughout childhood, and critically through adolescence, the disruption that HIV causes on the neurology can therefore be devastating on those skills' development.

On analysis of the results comparing the research group to the control group, one can see that (other than in four of the WISC-R subtests) all tests which had a visuospatial component displayed significant differences between the two groups. Post-hoc tests confirmed that in all cases, even where the results were not significantly different, the control group displayed a superior performance to the research group. This suggests that, in comparison to those without HIV, adolescents with HIV have impaired visuospatial abilities. In line with what the research on the neurological effects of HIV suggests, one can see that HIV infection during adolescence impacts on neurological development responsible for the development of

visuospatial abilities, (Pomara et al, 2001; Stebbins et al, 2007). A closer examination of significant results will further illuminate the effects of HIV on specific visuospatial abilities.

As previously discussed, one of the most basic visuospatial abilities is that of visual scanning. This ability arguably underlies, or at least affects, all other visuospatial abilities. Results support the assumption that there was a significant difference between the Research group and Control group's results on the subtests that measure visuospatial scanning. The TMT-A is one of those subtests which provides a purer measure of visual scanning. Specifically it measures visual scanning speed and proficiency. Linked to this is the TMT-B, which is also a measure of visual scanning proficiency and speed. However the TMT-B does also employ the visuospatial sketchpad within working memory as well, and is therefore a useful measure of both. As both of these subtests, which measure visual scanning, are significantly different between the two groups, it suggests that the visuospatial ability of visual scanning is impacted upon by HIV. This is confirmed by the comparison run when the scores for part B were converted into the percentage of part A (B as a % of A). There was no significant difference between the two groups with this measure, which highlights a deficit in Visual Scanning. If either processing speed or working memory had been impacted upon by HIV, then the scores for part B as a percentage of part A would have been significantly higher for the Research group, as it would have indicated the effect of these domains upon the time in part B, and would thereby realise a significant different between the two groups in this measure. However, as there is no significant difference, it reinforces the finding that the deficit displayed is due to the negative effect of HIV upon Visual Scanning. This could have a myriad of possible effects upon the lives of those adolescents afflicted with HIV, such as being slower to locate visual stimuli. Whether it be a word in a book, or an approaching car on the street, the effects of this impairment may be far reaching. As this very basic visuospatial skill is impaired by HIV, the results indicating a host of other visuospatial abilities are impaired are therefore more logical.

Linked to the above, is the effect that impaired Visual Scanning would have on the ability of the adolescent to receive, understand and deal with visual information. To examine this, the results of the immediate and delayed recall trials of the ROCFT were examined. When the raw scores were compared, as they were, the results indicated that there were significant differences between the Research and the Control group. At first glance this suggests that there may be an impairment in visual memory. However when the scores for these two trials were converted into the amount of information retained with regards to the score in the initial

copy trial, both of these measures now realise no significant differences between the Research group and the Control group. This therefore indicates that the differences seen in the raw scores for the immediate and delayed recall trials are not a reflection of visual memory, but are rather an indication of the impaired ability of the adolescent to deal with visual information. Visual Scanning would thereby be an important factor to consider with regards to the impact that it could have on everyday functioning.

Another one of the more basic visuospatial abilities is that of eye-hand coordination. This ability underlies all basic-to-advanced visually guided motor activities, from picking up a glass to catching a ball in sports. The subtests that measured this ability were the Grooved Peg Board dominant and non-dominant hand tasks. To clarify that the deficits displayed were of a visuospatial nature rather than due to motor impairment, the results of the Finger Tapping Test were run, which is theoretically a test of pure motor function (Strauss et al, 2006) and would therefore also display impairment if there was a basic motor deficit. However there were no significant differences found for either the dominant hand or non-dominant hand on the Finger Tapping Test, which would imply that the deficits displayed by the Research group on the Grooved Peg Board subtests are the consequence of a visuospatial deficit and not a motor impairment. As with visual scanning, impairments to eye-hand coordination can have far reaching consequences for the life of an HIV-positive adolescent. There would theoretically be a underlying disadvantage to playing any sport which relied on eye-hand coordination (such as cricket or even arguably soccer with eye-foot coordination), as well as with tasks such as drawing and writing (which require a strong visual component), as well as essentially making the adolescent more clumsy with regards to day-to-day tasks such as picking up items, eating and drinking. Although many of these impairments may not be overtly noticeable in the everyday life (for example, some adolescents are naturally more clumsy), it is when they are put in perspective through comparison to control groups (such as in this study) that these impairments are fully brought to light and are thereby able to be examined, together with the consequences of the impairments.

Another thought of possible interest is the implication created by the combination of visual scanning and eye-hand coordination impairments. Theoretically this could give the appearance of slowed processing speed with regards to many visually-oriented tasks. The adolescent would be slower and less accurate to find and pick the specific visual stimuli, and then have difficulty in physically interacting with the stimuli. The result of this may be an unconscious or even purposively conscious slowing of actions in order to compensate for the

impairments, thereby allowing for more accurate interaction with the visual world for the adolescent. This however could possibly have the effect of portraying a picture of slowed processing and motor speed to the outside world. Although this is pure conjecture, it may warrant further investigation.

Spatial-temporal reasoning is the ability to visualise, hold, track and then manipulate or follow visual stimuli over a time-ordered series of events. This includes tasks as simple as being visually able to hold ones place and then follow through when reading a book, to being able to visually navigate oneself through a complex pattern or maze. HIV appears to impair the visuospatial ability of spatial-temporal reasoning, as the results of the subtests which display a measure of this ability in the Research group were significantly lower than in the Control group. The subtests that were the best reflection of this visuospatial ability were the Trail Making Test – Parts A and B and the Stroop Colour Naming Test. Both of these subtests require one to keep a visual place in space, whilst tracking and then moving onto the next spatial location, without moving to the incorrect location, and without losing one's place. This ability is obviously tied quite closely to the visuospatial ability of visual scanning, however it could be considered as an evolved form of visual scanning as it requires more advanced skills, as it requires integration of visual and verbal skills to maintain the visual tracking whilst verbally decoding. This has implications for the HIV positive adolescent, as it may impair their ability to seamlessly read, especially for example moving from one line of text to the next. This possible deficit could affect all aspects of their schooling, which would seriously hinder their ability to learn effectively.

The Visuospatial Sketchpad forms part of the visuospatial abilities spectrum, as well as falling into the domain of Working Memory. The visuospatial sketchpad allows for the temporary storage and manipulation of spatial and visual information, therefore assisting one in remembering shapes and the location of the shapes or objects in space. Again, one can see the negative effect of HIV on this visuospatial ability, as the Research group's scores for the subtests that measure this ability were significantly lower than the scores for the Control group. These subtests were the ROCFT Recognition Trial scores (specifically the true positives score) the Trail Making Test – Part B, and the Object Assembly subtest of the WISC-R. The Trail Making Test – Part B uses the visuospatial sketchpad to store locations of both numbers and letters, whilst allowing for scanning of the page to find the next position. This subtest does also engage with visual scanning as well as Spatial-Temporal reasoning, yet the utilisation of the visuospatial sketchpad would be crucial in the efficient completion of

this task. The ROCFT Recognition trial employs the visuospatial sketch pad in using stored visual information, recently accessed and refreshed from the 30-minute delay trial administered directly previously to the Recognition trial, in remembering and locating specific visual stimuli and manipulating them to match the whole figure that was initially seen. Finally the Object Assembly subtest would need to employ the Visuospatial Sketchpad to be able to facilitate Visuospatial Construction. It requires this by allowing one to remember the various parts as they are to enable one to mentally construct the whole from the parts, and then use then mental image of the whole (now stored in the Visuospatial Sketchpad) to enable one to recreate the whole picture with the use of the parts. Therefore all of these subtests suggest that the effect of HIV has caused the visuospatial sketchpad to have impaired functioning in HIV-positive adolescents. This could have the effect of disrupting the adolescents' lives with regards to visual stimuli, such as not being able to track and predict the direction, velocity and distance of a car coming towards them once they have looked away, or possibly battling to walk comfortably without looking directly at their feet, as they will not be as efficient at using the information in the sketchpad that is there from looking at the path ahead. However it must be considered that this ability is reliant upon the visual information gained through Visual Scanning. A deficit in Visual Scanning would impair the quality of the visual information being inputted into these abilities, subsequently translating in a deficit. Therefore it is important to consider that the deficit displayed here may be a consequence of the impairment in the foundation Visuospatial ability that this skill is based on.

Finally, Visuospatial Construction must be examined with regards to the effect of HIV on this visuospatial ability. Visuospatial Construction can be seen as the ability of being able to "see an object or picture as a set of parts and then to construct a replica of the original from these parts" (Mervis et al, 1999, p. 1222), or just being able to create a whole from parts without copying from another source. This ability also makes use of other mental faculties in its employment, such as the ability to mentally rotate objects as well as gestalt thinking. The results of the subtests that measure Visuospatial Construction illuminate the negative effect that HIV has on this visuospatial ability, as the Research group's results were significantly lower than the Control group's results. This was measured through three subtests: the ROCFT Copy Trial, Object Assembly and Block Design subtests of the WISC-R. The Object Assembly subtest uses the Visuospatial Construction ability to envision what the whole sum of the various parts of the object is, and then be able to create that whole. This therefore

involves gestalt thinking, by being able to see the whole picture in the parts. The ROCFT Copy Trial involves very similar requirements. Although the complex figure is not in separate pieces but in one whole, its innate design is such that the complexity of the figure can hide the whole and appear rather as a collection of parts. Therefore Visuospatial Construction is involved in recreating these parts into the whole. Gestalt thinking may be employed in the construction, by being able to see the whole aspect within the picture, with the details merely filling in the whole, rather than being entirely separate elements making a whole. This type of gestalt thinking would facilitate the Visuospatial Construction through the recognition of the whole. Block Design requires the use of Visuospatial Construction by creating a whole picture from individual parts. However an important aspect here, more so than in the other subtests measuring Visuospatial Construction, is the element of Mental Rotation.

Mental Rotation is part of the Visuospatial Constructive spectrum of abilities and refers to the ability to mentally rotate a visual stimulus. This is specifically important within the Block Design subtest, as all of the individual blocks need to be rotated to match the stimulus. However if this were to be done manually with each block during the trial, the participant would run the risk of running out of time, and of scoring lower. Therefore the ability to mentally rotate the blocks within one's mind is crucial to the smooth and effective facilitation of this task. Although the Object Assembly subtest does make use of the ability to Mentally Rotate, the more concrete nature of the constructions required within this subtest (shapes and objects found in the world) in comparison to the more abstract constructions required by the Block Design subtest (arbitrary patterns made up of two different colours and two different shapes), the Object Assembly subtest would thereby rely far more on the ability to recognise the shape required to be constructed than on Mental Rotation to fit the pieces of the shape together (suggesting that the Object Assembly subtest also makes use of the Visuospatial Sketchpad, as discussed above). HIV has created a notable deficit in the ability to mentally rotate, as the results between the Research and Control group highlight a significantly lower score within the Research group for the Block Design subtest.

Overall the impairment in Visuospatial Construction would affect the HIV-positive adolescents in everyday life, as their performance in tasks that require this visuospatial ability, such as the more mundane tasks of packing a shelf of groceries neatly and correctly or putting together a puzzle, to more complex tasks such as making clothes or designing a building, would be impaired due to the effects of HIV. Similarly when examining mental rotation specifically, tasks such as efficiently being able to read a map, dancing and playing

sports, specifically sports such as soccer, would be impaired due to the effects that HIV appears to have on the development of this visuospatial ability in adolescents.

When examining all of the results explored above, one can begin to clearly see the trend that seems to have been illuminated, that HIV has a serious negative impact on the development and subsequent use of visuospatial abilities in HIV-positive adolescents. The effect of HIV on visuospatial abilities seems to be very broad affecting essentially everything under the visuospatial spectrum, from basic visuospatial tasks such as Visual Scanning, to the most complex tasks such as Visuospatial Construction and Mental Rotation. This therefore lends strong evidence in support of previous research, as discussed previously, which explored how HIV has a significant negative impact on the white matter tracts (Stebbins et al, 2007), which all of the Visuospatial Abilities are inherently reliant upon (Mishkin et al, 1982; Woods et al, 2009), specifically during adolescence when these neurological areas, and the functions that then follow from these areas, are developed (Klingberg et al, 2002). However this is examining the results from an overarching perspective, without taking other factors into account. It is important therefore to examine what other factors, such as the very important factor of sex (which as was previously discussed, shows natural differences between males and females with regards to visuospatial abilities (Bellis et al, 2001)) and it is therefore important to explore how HIV would affect males and females differently.

The Different Expressions of HIV in Males and Females

As discussed previously, research has displayed that there is a marked difference in visuospatial abilities between healthy HIV-negative males and females during adolescence (Downing et al, 2008). These differences occur as a result of different neurological development which occurs differently in males and females during adolescence. Specifically with regards to visuospatial abilities, neuroimaging studies have found that during adolescence the important differences are that "males had more prominent age-related gray matter decreases and white matter volume and corpus callosal area increases compared with females" (Bellis et al, 2001, p. 552). Based on this observation is it logical to expect that the expressions of the neurological effects of HIV with regards to visuospatial abilities would be different for males than for females, due to the different neurology at the time of adolescence. Therefore it is important to examine the results of the tests with regards to sex so that these differences can be explored.

Firstly one must examine the similarities of the results between males and females so as to explore how they are alike with regards to the effects that HIV has on them, and thereby possibly begin to understand the differences that are seen. It is important to emphasise here that this is not a within group comparison where a male female difference would be expected as a factor of development, nor is this a comparison between HIV-positive males compared to a mixed gender control group, which would be skewed by the expected gender differences anyway. Rather this compares separately HIV-positive males against healthy males and HIV-positive females against healthy females The first and most basic visuospatial ability that displays no significant differences between the results of males and females, yet over all displayed a significant result when the Research group was compared to the Control group, is the Visual Scanning ability. The Trail Making Test part A results displayed no significant differences between males and females. From these results, one could make the inference HIV has an equal effect with regards to males and females on the visuospatial ability of Visual Scanning. As there is an equal effect on this basic ability, one could therefore infer that the neurological areas responsible for Visual Scanning are similar for males and females at this stage to display the same effects. The areas that research has suggested are responsible for Visual Scanning is the transverse occipital sulcus and the intraparietal salcus (Leonards, Suneart, Van Hecke & Orban, 2000; Nobre, Coull, Walsh & Frith, 2003). Both of these areas are grey matter sulci, located perpendicular to each other and leading into each other. Although there are age-related grey-matter differences between males and females, this could suggest that at this stage of adolescence (13 – 15 years old) the changes are not significantly different as of yet, therefore explaining how HIV is able to affect males and females equally with regards to this visuospatial ability.

The next visuospatial ability of importance due to its similarity between males and females is Spatial-Temporal Reasoning. The results of the Colour Naming subtest of the Colour Word Interference Test (with regards to the interaction between time and error scores) were significantly different between the Research group and the Control group, with the Research group scoring significantly lower than the control group. When these results were examined between groups with regards to significance between males and females, the results indicated that both males and females in the research group displayed significantly lower results for spatial-temporal reasoning, thereby indicating that there are no significant differences between males and females for this visuospatial ability. Essentially this means that both males and females took longer to visually process the colour, however once the colour was

”seen” had equal ability to transfer information forward for verbal expression The neurological areas that research has shown to be collated with spatial-temporal reasoning are the precuneus of the medial parietal lobe (specifically the posterior lobule of the precuneus), the superior temporal gyrus and areas of the dorsolateral prefrontal cortex (Wenderoth, Debaere, Sunaert & Swinnen, 2005). Again, one can see that the areas involved in the visuospatial ability of spatial-temporal reasoning here, consists of neurological areas that predominantly consist of grey-matter. As was postulated above, the lack of differences between males and females with regards to this visuospatial ability may be due to the lack of differences in the neurology between adolescent males and females at this stage of neurological development, specifically in regards to the stage of development of grey matter. As with the visuospatial ability of Visual Scanning, the neurology of adolescent males and females appears to facilitate HIV in affecting males and females equally in this regard.

Finally the visuospatial skill of Visuospatial Construction must be examined due to the lack of differences between males and females. The ROCFT Copy trial displayed significant differences between the results of the Research group and the Control group, with the Research group’s results being significantly lower than the Control group’s results. When the results were examined with regards to comparing the Research and Control groups by sex, both males and females in the Research group displayed significantly lower results than the males and females in the Control group, thereby indicating that there is no differences between males and females in this subtest. Research has displayed that the neurological areas that are engaged when performing the ROCFT Copy trial are the posterior temporal-parietal cortex and areas of the right lateral prefrontal cortex (Melrose, Harwood, Khoo, Mandelkern & Sultzer, 2013). As with the three visuospatial abilities discussed above, these neurological areas that are employed in the use of Visuospatial Construction are areas that consist almost predominantly of grey-matter, which as suggested above, may be the reason for HIV affecting males and females equally in this regard.

When one examines the above information on the visuospatial abilities that are similarly effected by HIV between males and females, on can see that a pattern begins to emerge. All of the visuospatial abilities discussed above appear to be reliant upon neurological areas that essentially all consist of grey-matter. However research indicates that males have less grey-matter due to the natural neurological development during adolescence (Bellis et al, 2001), thereby suggesting that with the visuospatial abilities explored above, all of which are reliant upon grey-matter, one would expect a greater deficit in males than in females in these

abilities. However both HIV-positive males and females both display deficits in these abilities. This therefore could suggest various other possibilities. One possibility is that one of the long-term effects vertically transmitted HIV may be a slowing of the natural neurological development, which would thereby explain why a difference in abilities that employ grey-matter is not observed in males and females. Another possibility is that due to having HIV for over 10 years, much of which was uncontrolled by antiretroviral treatment (as was prevalent in the sample for this research), the neurological effect of HIV could have moved from a more white-matter targeted effect to a more global effect in this population. With either of these two theories, more research would be required, specifically research that employed imaging-scans so as to examine the actual neurology of a similar sample. However with regards to this research, a closer examination of the subtests that displayed a difference between males and females is vital to further understanding the neurological differences as well as the differences of the effects of HIV on adolescent males and females respectively.

When examining which of the results displayed significant differences for the females between the Control and the Research group and not for the males, only two subtests were revealed as being significantly lower for the Research group females than for the Control group. These subtests are the Object Assembly subtest from the WISC-R, and the ROCFT Recognition trial. These subtests are linked in that they both make use of the Visuospatial Sketchpad in their completion. The ROCFT Recognition trial requires the use of the Visuospatial Sketchpad to hold in mind the complex figure drawn three times previously, and then use that image held on the sketchpad to identify aspects of that complex figure from a selection of choices. The Recognition trial is also dependant on the quality of the information available, as gained through Visual Scanning. The Object Assembly subtest of the WISC-R uses the Visuospatial Sketchpad to hold in mind the constructed object made from the pieces sitting in front of the person, and then using that whole object on the sketchpad to recreate it using the individual pieces. However again Object Assembly is reliant upon the quality of the information gained through visual scanning to enable the recreation. The Object Assembly subtest logically also makes use of the Visuospatial construction ability in order to enable proper completion of the task. However use of the sketchpad is a vital part of the process to enable the formation and subsequent construction of the overall object.

Of important consideration would be the neurological areas that are involved in the employment of the Visuospatial Sketchpad. Research by Sala and Courtney (2007) worked on a triangular model of Visuospatial Working Memory (Sketchpad). Their research

postulated that visuospatial working memory was used in three distinct ways: What (identifying visual stimuli and holding it in mind), Where (where in the spatial domain a visual stimulus is located), and finally employing both the Where and When domains simultaneously (identifying What a visual stimulus is, and Where in space it is located). Their research located three independent (though partially overlapping) set of neurological networks depending on which of the three domains was employed. In both the ROCFT Recognition trial and the Object Assembly subtest of the WISC-R, the What domain of the Visuospatial Working Memory would have been the specific domain employed. In the ROCFT Recognition trial identifying the specific pieces of the whole complex figure would have employed the What domain, as no spatial information was required in the completion of the task. Similarly with the Object Assembly subtest, employment of the What domain in Visuospatial Working Memory would be required to complete the task. Identification of what the individual pieces would create when placed in the whole would be what is required from Visuospatial Working Memory, as all the pieces are placed in the same spatial area, therefore bypassing the need to use the Where domain of Visuospatial Working Memory. Sala and Courtney's imaging research (2007) found that the What domain of Visuospatial Working Memory employed a system of neurological networks spanning from the Frontal Lobe, consisting of the left middle frontal and inferior frontal gyri, along the cingulate to the superior occipital area. From the occipital area the networks touched dorsally to the inferior parietal areas, and extended along to the medial and ventral temporal areas, and specifically the parahippocampal gyrus (Han, Berg, Oh, Samaras & Leung, 2013; Sala & Courtney, 2007). These neurological areas are made up of grey-matter, however they make extensive use of white-matter tracts in their function. However as the What domain would need to be employed, this domain is fully reliant upon the quality of the visual information inputted from Visual Scanning. Therefore the deficit displayed in Visual Scanning would lower the quality of the information and thus hinder the What domain from being fully functional. This thereby suggests that the deficits here are due to the impairment in the foundation visuospatial skill rather than in a visuospatial skill that requires higher cognitive functions.

Therefore this suggests that when tasks are engaged that make use of visuospatial abilities that employ neurological areas of both grey and white matter, the effect of HIV is felt by the female adolescents more than the male adolescents. As previously stated, imaging research suggests that during adolescence males have an increase in white matter, specifically an increase in white matter density along the various white-matter tracts in the brain (Bellis et al,

2001). Assuming that this normal neurological development has progressed properly with the HIV positive adolescent males (unlike, in the theory postulated above, with the same age-related grey-matter changes in males), males would have denser white-matter network tracts to rely on. Therefore with Visuospatial abilities that employ neurological areas consisting of both grey and white matter, males have a more developed white matter network to rely upon. This could mean that when HIV affects these areas, the denser white matter tracts in males would help lessen the effect that HIV has on this Visuospatial ability thereby preserving some of the ability. This could therefore translate into the neuropsychological tests, whereby a significant difference is not seen in males due to the dense white-matter's ability to help compensate for the deficit. As the females would not have had developed as advanced a white-matter system as of yet, the effect of HIV on these networks could therefore translate into the significant differences displayed between the Research and Control group's females in the subtests that measure the Visuospatial Sketchpad. The effect that HIV has on this specific neurology, due to the diffuse mode of action of the virus, may be a contributing factor, however as mentioned above, the lack of coherent visual information due to the deficits in Visual Scanning may pre-empt the above and thus explain the deficit seen here. This again suggests the underlying deficit in the foundation skill of Visual Scanning may help explain much of the deficits seen.

However, when one moves attention to examine the subtests whose results displayed significant differences between the Research group and the Control group for the male sample, four subtests appear as significant. This is double the amount of subtests that displayed significant results in comparison to the females. These subtests were the Block Design subtest from the WISC-R, the Trail-Making-Test part B, and the Grooved Peg Board Dominant Hand and Grooved Peg Board Non-Dominant Hand. These tests represent a range of visuospatial abilities, and thereby suggest that the effect of HIV on males is far more severe than the effect of HIV on females with regards to visuospatial functioning. The visuospatial abilities these tests employ in their use are Eye-Hand Coordination, Visuospatial Construction (but more specifically Mental Rotation), Visual Scanning and the Visuospatial Sketchpad. Unlike with regards to female HIV-positive adolescents, where only one visuospatial ability was affected (the What domain of the Visuospatial Sketchpad), male HIV-positive adolescents have a wide range of visuospatial abilities that appear to be affected by HIV. This evidence may support the argument that the effects seen are due to developmental differences. It is the more advanced skills that males, but possibly not females

to the same extent, should have developed. The HIV group is equally poor on the more basic skills, which both genders should have developed, however on the slightly more sophisticated skills, that only the healthy males but not the females may have more fully developed, the impact of the virus is more apparent in the males. One could argue that if one tested an older age group where females would have matched the development in these abilities, then both male and female HIV-positive groups should display a deficit when compared to the control.

The Grooved Peg Board subtests (Dominant Hand and Non-Dominant Hand) employ the visuospatial ability of Eye-Hand Coordination, as it requires one to quickly and efficiently line up the peg in one's hand with the hole in the board, and good employment of Eye-Hand Coordination would be essential for this process to go smoothly. One could also make the argument that Mental Rotation could also be employed in the completion of the Grooved Peg Board, as the groove on the peg needs to be lined up with the groove in the board. For this process to be efficient, Mental Rotation could occur to allow the person to know how they need to rotate the peg in order for it to fit. Without Mental Rotation in play, the task could take longer as manual rotation of the peg would have to occur until the grooves line up and the peg fits into the hole. The Block Design subtest of the WISC-R employs the visuospatial ability of Visuospatial Construction in its completion. However, as discussed above, facilitation of the ability to Mentally Rotate visual objects is an imperative aspect of this task, as the individual blocks would need to be rotated mentally in order to place the blocks correctly. Finally the Trail-Making-Test part B requires the use of both Visual Scanning as well as the Visuospatial Sketchpad for its completion. The Trail-Making-Test part B would use visual scanning to scan through the visual stimuli in order to locate the next objective. Its use of the Visuospatial Sketchpad would differ from its use in the ROCFT Recognition trial as well as the Object Assembly subtest, which employed purely the What domain of the Sketchpad. The Trail-Making-Test part B would use the Both domain (What and Where information), with regards to Sala and Courtney's research (2007), as it would require knowing What the visual stimulus is (is it a number or letter, and what number or letter it is), as well as holding Where in space it is, as well as the previous and the next stimuli's locations, as well as what they are (number or letter, and which). Again it must be emphasised that this is all reliant upon the visual information gained through visual scanning. Therefore the deficits seen in Visual Scanning would initially hinder the subsequent visuospatial skills ability to function fully, as is highlighted when examining the results of

part B as a percentage of part A, suggesting the greater focus is on the deficit in visual scanning.

Again, it is important to examine the neurological areas and/or networks used in the facilitation of these visuospatial abilities. Beginning with the Visuospatial Sketchpad, research has shown that use of the Both domain of visual working memory makes use of mainly white-matter areas of the brain (Sala & Courtney, 2007). Specifically, the neurological areas activated are: Superior Frontal Sulcus, Inferior and Middle Frontal Gyrus, Cingulate, Superior Motor Area, Precentral Sulcus, Cuneus, Superior Parietal Lobule and the Middle Occipital Gyrus area. With regards to all of these areas, it is the white-matter tracts within these areas that displays activation when the Both domain is activated within visual working memory. With regards to Visual Scanning, similar neurological areas are activated in its use. The Superior Parietal Lobule and Cinculate areas are activated, as well as the Intraparietal Sulcus as well as Ventral Prefrontal Cortex areas (Nobre et al, 2003). When examining the areas used for Eye-Hand Coordination, again a similar pattern appears to emerge in that activation is shown in mainly white-matter areas of the brain. These areas are the Primary Motor Cortex, Lateral Premotor Cortex, Supplementary Motor Area, V1 along the Calcarine Sulcus and the Extrastriate Cortex (V5) (Grefkes, Eickhoff, Nowak, Dafotakis & Fink, 2008). Specifically, the specific activations within these areas were, as defined by research "M1 coordinate had to be located in the precentral gyrus/ central sulcus near the "hand knob"; PMC in lateral precentral cortex/sulcus; SMA in the dorsal medial wall within the interhemispheric fissure; V5 at the occipitotemporal junction near the ascending branch of the inferior temporal sulcus" (Grefkes et al, 2008, p. 1384). Finally with regards to Mental Rotation the pattern so far displayed is again repeated in that areas of importance with regards to this visuospatial ability are centred around white-matter areas. Areas of peak activation during tasks of Mental Rotation are posterior Superior Parietal Cortex, Inferior Parietal Cortex, leading on to the head of the Caudate Nucleus and the Intraparietal Area (Alivisatos & Petrides, 1996; Jordan, Heinze, Lutz, Kanowski & Jancke, 2001). As HIV has a very diffuse effect, the range of areas affected here is expected, and would therefore contribute to the overall picture of the effect of HIV.

Overall a clear pattern appears to have emerged when examining the neurology related to the subtests that had significantly different results between the Research group and the Control group with regards to the HIV-positive adolescent males. The neurology associated with the visuospatial abilities of the males that appear to be impaired are all centred around areas of

the brain that consist of white-matter. This differs to the results displayed by the females, where visuospatial abilities that are reliant upon areas or networks of both grey and white matter appear to be affected more strongly by HIV. Males appear to be more vulnerable to the effects of HIV on visuospatial abilities that are based on white-matter areas and white-matter tracts.

When all the results with regards to sex are examined holistically, one may begin to see some patterns emerging. When grey-matter is affected by HIV, abilities that are reliant upon areas of grey-matter, whether alone or together with white-matter, females suffer the effect of this the most severely. This may be due to the natural neurological development of females during adolescence, as in comparison to males, they have not fully developed the white-matter tracts to rely on when using visuospatial abilities. Therefore when the grey-matter that females are relying on is disrupted, the visuospatial abilities are therefore disrupted. As to why there is no significant differences with regards to abilities that are more reliant upon white-matter, one could hypothesise that due to the not-yet-developed white-matter, these visuospatial abilities in females are therefore also not yet developed fully. Therefore a disruption to those abilities would not be as noticeable when compared to a control. With regards to males, the effect of HIV on visuospatial abilities appears to be most disruptive on abilities that either use white-matter or grey-matter. Abilities that appear to use both grey- and white-matter seem to be more resilient in males, possibly due to the further-developed white-matter, and as postulated above, the grey matter that may not yet have begun to be pruned. However abilities that rely purely on white-matter appear to be particularly vulnerable in males. This can possibly be attributed to the natural development of, and subsequent reliance on, white matter. Due to the advanced development of white matter, abilities that are reliant upon white matter are also more advanced in males (Downing et al, 2008). Therefore any disruption to the white matter would have devastating effects upon these visuospatial abilities (which is displayed in the results). Conversely, as has been discussed, the possible slowing of the grey-matter pruning may have resulted in some visuospatial abilities being more reliant upon some grey-matter areas, and therefore disruption to those areas would also have an impairing effect upon those abilities. However when abilities are focused on areas of both grey and white matter, these abilities appear to be more resilient in males, in comparison to females. Again this may possibly be attributed to the advanced white matter, and the under-pruned grey-matter. Overall this is conjecture and

would require further research using neuroimaging research to be able to fully confirm the above discussion.

HIV Particulars

As the HI-Virus is a highly adaptive and resilient virus, specifics around its effect on the human body as a whole are important to consider, and with regards to those who are HIV-positive, important to monitor regularly. The two most important factors with regards to someone who is infected with HIV is to monitor the Viral Load of the HI-Virus in the Blood, as well as the strength of the immune system by examining the CD4+ levels within the blood (a measure of white blood cells). In consideration of this the World Health Organisations latest recommendations on viral load and CD4+ count are important to consider. As of 2009, the World Health Organisation made recommendations around threshold CD4+ levels in HIV-positive persons, and when to start antiretroviral therapy with regards to the CD4+ count. Their recommendations moved the antiretroviral therapy initiation threshold from a CD4+ count of 200, to a CD4+ count of 350 (WHO, 2009). With regards to this, the research group was split into two separate group with regards to their CD4+ count at HAART initiation, as well as split into two group with regards to their current CD4+ count. The groups were divided according to the latest WHO guidelines. This enabled comparison of those whose CD4+ counts were above 350 to those whose CD4+ counts were below 350, at both HAART initiation as well as currently. The same principle was held with regards to splitting the Research group in respect of their Viral Load count, both at HAART initiation, as well as currently. These groups were split along the principles of a Viral Load count, comparing those with a Viral Load of 40 or below (undetectable) with those that had a Viral Load above 40 (WHO, 2009). Again this was performed for the current Viral Load as well as retrospective groups with regards to Viral Load count at HAART initiation.

This essentially allowed for four within group comparisons with regards to the Research group. These being: CD4+ count at HAART Initiation, Current CD4+ count, Viral Load count at HAART Initiation, and current Viral Load count. Out of these four comparisons, three displayed significant results. The three significant comparison groups were the CD4+ count at HAART initiation, and the Current CD4+ count and Current Viral Load count groups. With regards to these three groups, there was one subtest in each group, two subtests overall, whose results were significantly different between those individuals being compared. With regard to the CD4+ count at HAART initiation comparison, the Object Assembly

subtest form the WISC-R indicated significant results between the two groups, whereas for both the Current CD4+ Count as well as the Current Viral Load Count comparisons, the Trail Making Test – Part A's results were significantly different between the two groups for each comparison respectively. Further examination of these results may further highlight the effect of HIV on the Central Nervous System.

Examination of the effects of current CD4+ and Viral Load counts are illuminating with regards to the effects of HIV. As the sample were all on first-line antiretroviral treatment through HAART, the effects of HIV have theoretically been tempered by the antiretrovirals (Govender, Eley, Walker, Petersen, & Wilmshurst, 2011; Robertson et al., 2004; Shanbhag et al., 2005). Therefore the deficits displayed when examining the current effects of HIV are indicative of the initial effect of the virus, due to the tempering effects of the antiretrovirals. It is therefore of interest that the subtest that displays significance is the Trail Making Test – part A. As discussed above, the Trail Making Test – part A is one of the purer measures of the most basic of the visuospatial abilities being Visual Scanning. Here one can see that a high Viral Load count and a low CD4+ count (as per the group splits) after a period of being on antiretrovirals results in the disruption of the most basic visuospatial ability. One could therefore say that this effect will eventually evolve to disrupt all visuospatial abilities, as even the most complex visuospatial abilities have foundations in this most basic of abilities. This thereby demonstrates the destructive effect HIV can have on visuospatial abilities from a grassroots level. Building on this idea, would be to examine the effect of HIV after a long period where it will have been able to have an effect on the central nervous system. This can therefore be seen through examination of the subtest affected in the CD4+ count at HAART initiation. This would thereby give some illumination into the raw untempered effect of HIV upon the neurology. As previously discussed, the Object Assembly subtest of the WISC-R requires strong engagement of Visuospatial Construction in order to complete it. This therefore suggests that the effect of HIV has moved beyond affecting the basic visuospatial abilities, and now the difference demonstrated between a high and a low CD4+ count is with the more advanced abilities. One could postulate by the fact that basic abilities are not significantly different at this point, highlighting the previously mentioned fact that it is the basic abilities that are first impaired, that now at the later stage, the differences are seen with the advanced abilities.

A factor that must be taken into account with regards to the above, is that when splitting the Research group for these analyses, the sample sizes in each subgroup were small. The results,

and subsequent discussion, should therefore be examined in this light with a mind frame of an educated hypothesis rather than empirical fact. However, with this in mind, the results do begin to suggest a pattern to the neurological progression of HIV on the central nervous system. It appears that HIV begins by first affecting the basic foundation visuospatial abilities, and from there progresses to affecting the advanced abilities. Whether this is due to progression of the virus itself, or due to the progression of the disruption of the foundation abilities the advanced abilities are based on, or a combination of both of these factors is unknown within the context of this research. This would therefore require further research, possibly with research involving neuroimaging, to confirm or deny these results.

Factors in Play

As has been discussed above, when one is dealing with the subject of HIV, as well as that of adolescence, there are a multitude of factors which may come into play with regards to having effects on the results, or causing variations in the results. It is therefore important that one is able to examine what factors are significant with regards to the results, and to examine what these factors may be.

The research group's factor analysis arrives at four significant factors which account for 74.22% of the variance in the results. When examining how the total variance explained is split across the four factors, there is an interesting result. Factor one of the four factors accounts for 50.08% of the total variance (which is 37.17% out of the 74.22% total) being the strongest factor out of the four. Factors two, three and four represent 21.29%, 15.44% and 13.19% of the total variance respectively. Although what these factors actually are is not actually known. Educated hypotheses may be made by examining the correlation patterns of the individual subtests on each factor. Factor four may be postulated to be the influence of developmental difference relative to a specific skill between males and females. The subtests that are significant in female adolescents only, have a high correlation to factor four, whereas those shared significant subtests and those significant for males only, have lower correlations. Thus due to the neurodevelopmental differences between males and females at this age, the difference in skill development (due to neurological differences) would be a significant contributing factor. By this pattern, it is suggested that factor four indicates the effect of sex. Factor two is suggested to represent the effect of the participant's current state health with regards to HIV, specifically their current CD4+ count and current Viral Load count. The Trail Making Test – part A has the strongest positive correlation of all the subtests with this factor.

As that was the subtest which displayed significance with regards to the current counts of CD4+ and Viral Load, it can therefore be postulated that the loading on this factor therefore represents those effects. Factor one, being the strongest of the factors, is suggested to represent the overall cumulative effect of HIV upon the adolescent's central nervous system, as it impacts upon the ability to analyse basic visual input. This hypothesis is made by examining the pattern of the loadings of the subtests upon this factor. The subtests where a lower score represents the better performance display a negative correlation to this factor, whereas those subtests in which a high score is the better score, realise a positive correlation to the factor. The loadings also seem to be representative of the subtests that displayed significance with regards to comparisons between the Research group and the Control group. Those subtests appear to generally have the higher loadings with this factor. Therefore the overall subtest loading pattern with this factor appears to represent the cumulative effect of HIV upon the central nervous system in HIV-positive adolescents on antiretroviral treatment. The pattern with regards to Factor three is unclear, and no clear factor emerges from the analysis. It may be possible that factor three represents some demographic factor, or possibly that is the effect of the antiretrovirals upon the central nervous system, or another such factor.

When one examines the factors for each sex in the Research group, some marked differences between males and females can be noted with regards to the factors. Due to the size of each group after having split the Research group into males and females, the strength of the statistical procedure is relatively weak, and is specifically sensitive to any outlying data. Therefore all discussion pertaining to this is merely conjecture on the apparent pattern that emerges, and should be interpreted with caution.

The males in the Research group realised three factors that explained a total of 79.36% of the variance in their results. This appears to be significantly different to the females whose results indicated five factors explaining 85.59% of the variance within their results. Although the number of factors with significant are different for males than for females, there does appear to be a marked similarity with regards to the subtest loadings on one of the factors in both. This is most evident in respect of Factor one in both the males and the female's results. Factor one is postulated to be the cumulative effect of HIV upon the central nervous system which impacts upon the basic visuoperceptual ability. As above, the subtest loadings on this factor in both males and females represent the patterns seen in the group comparisons, with regards to positive and negative correlations as well as loading strengths. The patterns and relative strengths appear to be fairly similar for males and females, thereby suggesting that

Factor one is a common factor. With males Factor one accounts for 57.21% of the total variance whereas Factor one in females accounts for 45.11% of the total variance explained. As the strength of the effect of HIV is stronger in males as it explains over 10% more of the variance seen than in females, this does agree with the results above, which suggest that males are more sensitive to the effects of HIV upon visuospatial abilities, as they have further developed visuospatial skills due to different neurodevelopment, and deficits upon those skills would therefore have more of an impact, and thereby be more noticeable. The rest of the factors in the males and females are different enough to suggest that there is not another factor that is similar enough in both to be counted as another common factor. The rest of the factors for both males and females therefore account for different variables with regards to variations in the results. Due to the current sample size, further research expanding upon the sample size would be needed to attempt to make accurate hypotheses upon what the remaining factors represent.

Limitations and Directions for Future Research

As with all research, this study had elements in it that limit the efficacy of the obtained results. First and foremost one of the most significant weaknesses in the study is the sample sizes. Specifically with regards to the Research group, where there were only 30 participants. This small sample size may have had an effect on the reliability of the statistical findings, lessening their power. This effect was possibly intensified in the subgroup comparisons where the Research group numbers were split, thereby becoming even smaller. Future research should attempt to increase the sample sizes of both the Research group, as well as the Control group, so as to increase the power and reliability of the statistical procedures performed. Although attempts were made to control for fatigue during the test administration, in some cases this may not have been entirely successful. This may have affected the some adolescent's results due to the overall effect of fatigue. Therefore future research should attempt to control for this, possibly by breaking the battery administration up into smaller sections, which may possibly extend the administration.

Future research should attempt to expand upon the results obtained here. Specifically research should attempt to repeat this study so as to examine whether the results obtained are replicable and therefore externally valid. Future research may also seek to examine different age bands, so as to be able to further examine the male female developmental anomalies. Future research should also attempt to incorporate neuroimaging, specifically using MRI

scanning due to the higher resolution with regards to white-matter tracts. This will allow for actual examination of the neural networks, and thereby how HIV is affecting the actual brain matter. Future research should also attempt to incorporate a longitudinal element. This will allow for closer examination of the changes over time, specifically allowing one to examine the step-by-step effect that HIV has upon the central nervous system. A possible limitation in this research was the possible effect of the different clades of the HI-Virus. This was not tested in the participants in the Research group, as it was assumed they all had the same clade (HIV-1 clade C) due to the prominence of this clade in South Africa (Rao et al, 2008). Future research could therefore attempt to control for the clade of HIV through identification of the specific HI-virus in each participant. This would both allow for control of the extraneous variable of the different clades of virus, as well as allow for a closer examination of how each virus clade affects the central nervous system differently.

Conclusions

Overall the results presented in this report come to the conclusion that HIV has a detrimental effect upon the visuospatial abilities of HIV-positive adolescents currently on first-line antiretroviral treatment.

It was discovered that HIV had a detrimental effect upon most of the visuospatial abilities. Of most importance was the effect on Visual Scanning, one of the most basic visuospatial abilities, and the ability that arguably underlies all other visuospatial abilities. Therefore the deficit on the other visuospatial abilities due to the Visual Scanning deficit comes as a logical conclusion. However it can be argued that the impairments displayed in the other visuospatial abilities are not just as a result of a Visual Scanning deficit, but are rather a reflection of the state of the underlying neural networks as a whole. Therefore examination of the specific impairments of the other visuospatial abilities is of vital importance, as it allows for exploration of the manner in which the HI-virus affects the central nervous system.

As an overview, the following visuospatial abilities displayed a deficit as reflected in the results of the neuropsychological assessment: Visual Scanning, Spatial Temporal Reasoning, Eye-hand Coordination, Visuospatial Construction and Mental Rotation. These visuospatial abilities, as reflected in the literature, are all reliant upon various white-matter tracts in the brain. As HIV has been proven to have a detrimental effect upon white matter, the deficits in the abilities that utilise these tracts therefore comes as a logical conclusion, and thereby adds a new dimension, with regards to the neurocognitive domain, to the existing literature. The outcome of the combination of all the deficits within the Visuospatial domain are important factors to consider with regards to the future of HIV-positive children and adolescents, as the effects have the possibility to be far reaching, with possible effects being seen in all elements from daily living to implications in schooling.

There are many factors that impact upon how HIV affects the neural pathways that govern the various visuospatial abilities. Possibly the most prominent would be the effect of the sex of the adolescent. The results indicated significant differences in many of the visuospatial abilities between males and females. This not only is an indication of the differing neurological and developmental state due to the natural neurodevelopmental process, but is also theorised to be a reflection of the manner in which HIV effects male's and female's neurology differently. Another important factor that comes into play with regards to how HIV

affects neurology, is the actual physiological state of the adolescent with regards to CD4+ count and the HIV Viral Load. This is important both at the initiation of HAART as well as at the time of testing. The effects displayed when the factors of CD4+ and Viral Load counts at HAART initiation and the current counts were taken into account are an indication of the raw effects of HIV upon the central nervous system, as well as a reflection of the tempering effects of antiretrovirals respectively. These factors indicated that HIV starts by affecting the most basic visuospatial abilities (Visual Scanning) and then moving to affecting the more complex abilities. Factors such as demographic variables (poverty) and age (within the range of the sample in this research) were shown to not have any significant effect upon the results, and therefore on the progression of HIV upon neurology.

These results in their entirety display the detrimental effect that HIV has upon the central nervous system, and thereby on the various abilities that utilise the various neural networks that are affected by HIV. This research highlighted the specific, and worrying, affects that HIV has on the spectrum of visuospatial abilities. This should be an important consideration with regards to the future of both treatment of HIV, as well as for the requirements of those adolescents afflicted with HIV due to the vital role that visuospatial abilities play in everyday life. Therefore the implications of this research suggest that HIV may have more far reaching effects on the HIV-positive adolescents than has been considered in both the neurological as well as the psychosocial domains. This study therefore highlights the importance of future research on this topic, as well as a call for an examination of the policies around the treatment of HIV in the adolescent population as well as the implications on their daily functioning.

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Appendices

Appendix 1: Overarching Research Proposal

The Neuropsychological Profile of HIV Positive Adolescents on Anti-Retroviral Treatment in Johannesburg, South Africa

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The Neuropsychological Profile of HIV Positive Adolescents on Anti-Retroviral Treatment in Johannesburg, South Africa

Abstract

In 2007 it was reported that an estimate of 33 million people were living with the Human Immuno-Deficiency Virus (HIV). Of this global population 35% live in South Africa. The most prominent form of transmission of HIV in South Africa is from mother to child. From 1997 until 2004, South Africa had limited access to ARV treatment at and after birth due to the government legislation. As a consequence, treatment of HIV may only have been initiated after clinical presentation of immune deficiency. This study investigates the consequence of this delay in treatment on the neurocognitive profiles of young, low socio-economic seropositive adolescents that are currently on a managed anti-retroviral programme and how they compare to a control group in South Africa (matched for age, demographics and educational system). More specifically, the study focuses on changes in memory, executive function, visuospatial abilities and motor function as a factor of cortical thinning associated with HIV. The relative impact of variables such as duration of ARV treatment, drug regimen, WHO stage at diagnosis and $CD4^+$ count have all been considered.

Introduction

Globally 33 million people were estimated to be living with the human immuno-deficiency virus (HIV) in 2007 (Shisana et al., 2009). Sub-Saharan Africa is still the most affected with over two thirds of the world population who are living with HIV (UNAIDS, 2009) - 35% of whom live in Southern Africa (Shisana et al., 2009). Women and children are the most at risk for infection (Wachsler-Felder & Golden, 2002) with vertical mother to child transmission being the primary mode of transmission in South Africa (Shisana et al., 2005).

While the association between HIV and cognitive function has been well documented in adult populations (Toborek, M, et al., 2005; Melrose et al., 2008; Singh et al., 2010; Lawler et al., 2010), studies have also explored HIV in paediatric populations (Govender et al, 2011; Sherr, Mueller & Varrall, 2009; Koekkoek, S., de Sonneville, Wolfs, Licht, & Geelan, 2008) – in many of these cases, a key limitation has been either the smaller sample sizes or the broad age group of the population ranging from neonates to adolescents (Wachsler-Felder & Golden, 2002; Govender et al, 2011). Results on neurocognitive profiles are consequently generalised across age groups with within group differences being rather diverse. For the most part, studies on HIV in children have emerged from the USA and Europe (Tardieu et al., 1995; Wachsler-Felder & Golden, 2002; Martin, et al., 2006; Koekkoek, et al, 2008) focusing on the Clade B specific strain of HIV, while recent studies in Thailand have begun to look at the Clade C specific neurocognitive profile (Puthankit et al., 2010). In the Thai study, peri-

natally acquired HIV positive children had limited access to ARV treatment at and after birth largely as a consequence of the high cost of anti-retrovirals (ARV). In Thailand, treatment may therefore only have been initiated after clinical presentation of immune deficiency (Puthankit et al., 2010), a point of similarity to South Africa. In South African, however, unlike Thailand, preference policy decisions during the 1994 – 2004 period level, resulted in low HIV coverage for the vast masses of HIV positive people. In 2004, following increased pressure from the international scientific communities, this policy was changed, with proactive preventative mother to child transmission (PMTCT) being effected and ARV rollouts implemented into the public sector (Butler, 2005). Against this background, it is therefore envisaged that many adolescents who were born prior to policy change in 2004 may have been ARV-naïve and only been placed onto ARV's after presenting symptomatically. The aim of this study is therefore to examine whether and how the neurocognitive profiles of young seropositive adolescents that are currently on a managed anti-retroviral programme differ from an uninfected group in South Africa - matched for age, demographics and educational system. The study will also examine the effect of duration of ARV treatment, type of drug regimen, WHO stage at diagnosis and $CD4^{+}$ on specifically motor functioning, visuospatial functioning, memory and executive functioning.

It is hoped that these insights will be used to stimulate further research and better advise appropriate interventions to address the needs of these children.

Literature Review

The human immuno-deficiency virus (HIV) epidemic is a global public health issue. In 2007, approximately 33 million people worldwide were estimated to be living with HIV (Shisana et al., 2009). Sub-Saharan Africa still remains the region most affected by HIV with over two thirds of all people worldwide living with HIV and accounting for 72% of Autoimmune Deficiency Syndrome (AIDS) related deaths in 2008. Despite exhaustive efforts to reduce the prevalence of HIV, the rate of new infection is still extensive. During this time for instance approximately 1.9 million new infections were reported in sub-Saharan Africa alone with South Africa being home to the largest population of HIV-infected people in the world (UNAIDS, 2009). Furthermore, 87% of HIV-infected children under the age of 15 are found in sub-Saharan Africa (Wachsler-Felder & Golden, 2002).

Since the 1970s, approximately 30 million people worldwide have died due to illnesses related to AIDS (UNAIDS, 2010). According to Wachsler-Felder and Golden (2002), women and children are the most vulnerable to HIV infection in developing countries. “Children are often the hardest hit due to the fact that HIV usually affects infants and children faster and more devastatingly than adults” (UNAIDS, 2010, p.442).

In South Africa, the primary mode of infection in children is through vertical mother to transmission. Vertical transmission can involve pre-natal, peri-natal or post-natal transmission (through breastfeeding) (Shisana et al., 2005). In 2003, it was estimated that 96 228 babies were infected with HIV through vertical transmission (Department of Health, 2003). Initial predictions indicated that more than half of these infections would result in fatalities within two years (Newell, Coovadia, Cortina-Borja & Rollins, 2004), however,

subsequent studies by Shisana et al. (2005) showed fairly even distributions across different age groups of seropositive children suggesting better survival rates than was initially predicted. It was also shown that of the three different forms of vertical transmission; post-natal transmission was associated with better survival rates (Newell et al., 2004).

HIV and Anti-Retroviral Treatment in South Africa

The diagnosis of HIV positive is associated with a great deal of concern. Prior to 1995, the prognosis was dismal with disease progression rapidly leading to death. The advent of triple combination anti-retroviral treatment (cART), also referred to as highly active anti-retroviral treatment (HAART), and when combined with treatment compliance, dramatically increased life expectancy (Woods, Moore, Weber, & Grant, 2009). Individuals with HIV-1 are now expected to live more than 20 years after initial infection and diagnosis (Skinner, Adewale, DeBlock, Gill, & Power, 2009). In the case of adults, HAART improved life expectancy and reduced the prevalence of HIV-associated central nervous system disorders – particularly HIV-associated encephalopathy (HIVE) and other neurological opportunistic infections (Patel et al., 2009; Martin et al., 2006; Civitello, 2003). According to the UNAIDS fact sheet (2009), 44% of adults and children in sub-Saharan Africa had access to anti-retroviral (ARV) treatment by the end of 2008.

While morbidity rates have dropped substantially since the introduction of anti-retrovirals, HIV-induced disabilities have become of prime importance for both psycho-social and socio-economic reasons (Butler, 2005). In countries such as North America, ARV administration was initiated and controlled from birth for seropositive neonates, but in South Africa the

scenario was different. Policy decisions fuelled by unsubstantiated fears of AZT toxins and the high cost of ARV's at the time prevented the blanket ARV rollouts in the public sector (Bulter, 2005). Many children may only have been placed on ARV treatment based on the severity of clinical symptomology and/or viral loads with effective PMTCT programmes curtailed (Coovadia, 2009). Epidemiological studies in South Africa subsequently reported that infant mortality was at its peak between 1997 and 2002 (Bourne, Thompson, & Brody, 2009). The Western Cape was the only province that failed to mimic the national peak (attributed largely to the effective preventative mother to child treatment (PMTCT) initiated in that province from 1999) (Boulle, et al., 2011). But for the Western Cape, the situation in South Africa was similar to the situation in countries such as Thailand where the lack of resources also prevented early initiation of ARV treatment (Puthanakit, et al., 2010).

Studies from the US show that ARV-naïve children who were placed onto HAART after presenting symptomatically; show greater neurocognitive deficits as compared to children who are placed on ARV's from birth (Laughton et al., 2010). Consequently, it can be expected that South African children who were born HIV positive during this period (1994 – 2004/5), and who emerge from environmentally impoverished areas with low coverage of HAART, would be inclined to greater amounts of neurocognitive deficits (Smith, Adnams, & Eley, 2008) despite being placed on HAART several years after vertical acquisition.

In order to understand the effects of HIV on cognition, it is important to first gain some insight into its pathogenesis.

Neuropathology of HIV

The HI-virus is a retrovirus, belonging to the family of lentiviruses, which leads to acquired immunodeficiency syndrome (AIDS). Immune deficiency in HIV manifests once the virus has entered the body through fluids, infecting the CD4+ lymphocytes (T-cells) and macrophages of the immune system (Ellis, Calero & Stockin, 2009). The virus overrides the programming of these host cells and causes the manufacture of reverse transcriptase to convert the viral RNA into DNA (Ellis et al., 2009). In so doing, the viral DNA is able to invade the host cell's genetic material. In the central nervous system (CNS), HIV collects in the cerebrospinal fluid (CSF). It doesn't affect neurons directly but rather through viral factors, host factors and co-factors (Civitello, 2003; Ellis et al., 2009).

Ellis et al. (2009) describe the mechanisms of HIV-associated injury in the CNS as an accumulation of these factors damaging the intricate networking of neurons at the synaptodendritic site. Viral factors are neurotoxic proteins produced by the HIV genome. gp120 is one of these proteins produced by infected, activated glial cells that "alter(s) glutamate pathway signalling and induce(s) cytokine production that can injure neurons and affect the activation state of microglia and astrocytes" (Ellis et al., 2009, p.147). Pathological changes associated with gp120 include "synaptodendritic injury, reactive astrocytosis, and microgliosis, and loss of large pyramidal neurons" (Ellis et al., 2009, p.147). Complex synaptodendritic networks are the underlying basis for higher cognitive functions thus injury to these would result in cognitive dysfunction. Another viral factor involved in neuronal injury is transactivator of transcription (Tat) which is associated with "mitochondrial dysfunction, dendritic loss and cell death" (Ellis et al., 2009, p.147). Host factors are part of the secondary effect of HIV infection and involve pro-inflammatory cytokines and

chemokines (Ellis et al., 2009). Thus, activation of their receptors, found in microglia, astrocytes, oligodendrocytes and neurons, results in structural and functional neuronal changes and apoptosis is facilitated (Ellis et al., 2009; Koekkoek et al., 2008; Toborek et al., 2005). Opportunistic infections, HIVE and HAD, as well as reduced CD4+ cells are consequently some of the key clinical markers for a positive Stage IV – AIDS diagnosis (Sherr, 2005). Lipton (1998) argues that "neuronal injury may result in reversible dysfunction rather than inevitable demise" (p.160) suggesting opportunity for treatment. Cofactors are co-morbidities of the infected individual that may exacerbate pathogenesis of HIV such as drug and alcohol abuse.

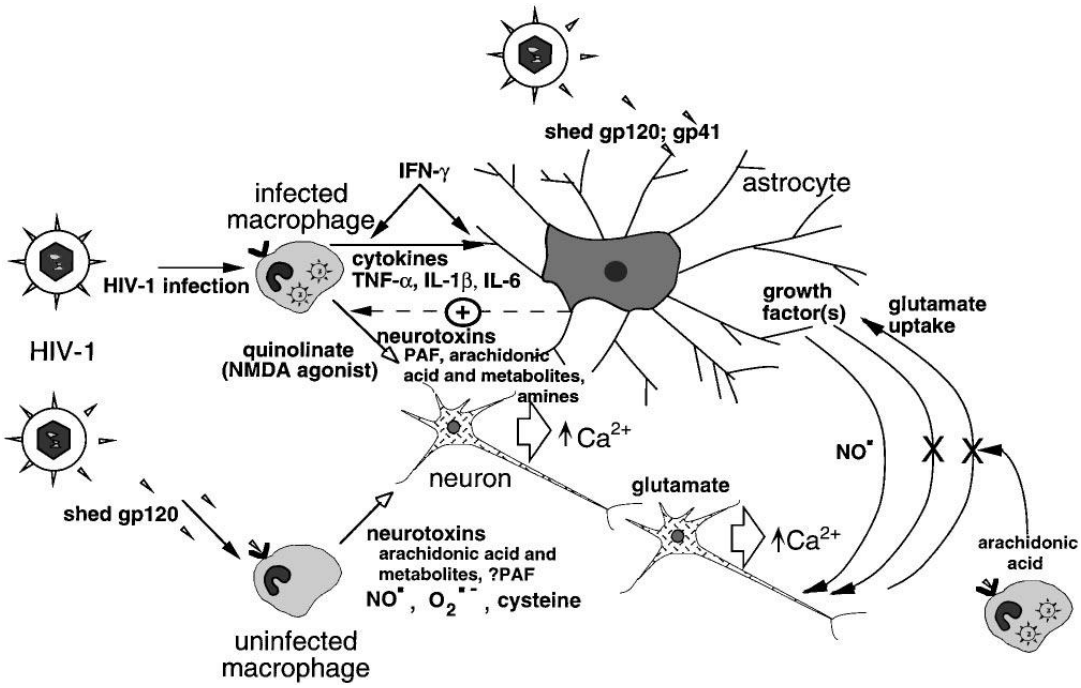

Image reproduced from: Lipton, 1998, p.162.

According to Civitello (2003), the characteristic pathological finding in infants with aids is calcification in the basal ganglia, and some of the white matter, as seen on CT scans. Studies have shown that asymptomatic HIV positive children do not show overt changes in everyday

functioning however, with disease progression, neurological deficits emerge as cognitive, motor and behavioural impairments (Wachsler-Felder & Golden, 2002).

The lack of specific neuropathologies in HIV infection is not unexpected given that CSF is distributed within the ventricles and around the meninges of the brain. Clinical symptoms of primary infection are thus diffuse rather than focal (Koekkoek et al, 2008). In their review, Wachsler-Felder and Golden (2002) conclude that the lack of a standardised neuropsychological battery for HIV testing, the small sample sizes as well as the large age differentials within studies (ranging from newborns to 16 years), transmission history, environmental issues and immunological states in the various studies has added to the lack of clarity of the precise neuropathology and hence contributes to the 'mixed' neuropsychological profiles. In this respect, it was suggested that tests be conducted on larger groups with a narrower age band so as to adjust for age differentials (Wachsler-Felder & Golden, 2002). With this in mind, this study therefore aims to focus on a demographically homogeneous group of 13 – 15 year olds on a managed ARV programme.

Clade-Specific Neuropathology

HIV infection can be classified according to the different subtypes, or clades. HIV-1 clade C is the predominant subtype in South Africa. In Western countries, however, the most common subtype is HIV-1 clade B (Ellis et al., 2009). In their systematic review of the literature, Sherr, Mueller and Varrall (2009) reported that 63% of the 111 studies on HIV and child development were performed in North America. Clearly, the majority of the literature available on HIV and child development is regarding HIV-1 clade B infection.

Within the literature on paediatric HIV, there is consensus that neuropsychological impairments do exist in seropositive HIV children (Sherr et al., 2009; Wachsler-Felder & Golden, 2002) however clinical symptomologies have been shown to differ from region to region (Rao, et al., 2008). The incidence and severity of problems such as HAD, for instance, revealed that HAD severity and morbidity rates were more severe in North America when compared to parts of Asia and sub-Saharan Africa. Further studies suggested that the different clades of HIV affected the brain differently. HAD was found to be typical of HIV-1 clade B infection (North America) yet this was not as common in HIV-1 clade C infection (South East Asia and sub-Saharan Africa). Even where HAD was suspected in clade C affected individuals, the clinical cases were milder than in clade B affected individuals revealing clade-specific neuropathogenicity (Rao et al, 2008).

One cannot, however, generalise the results of HIV-1 clade B infection to a South African population of predominantly HIV-1 clade C infection. Therefore, South African-specific research regarding HIV infection and the effects on child development and adolescence is required.

Neurocognitive Development and HIV

In order to understand how HIV affects neurocognitive development, it is important to understand healthy brain development. Although much research has documented emotional, behavioural and cognitive differences in children, adolescents and adults the neuroanatomical

substrates that underlie these differences have been more evasive. This may be because the structure of the brain at any given time is simply a product of the genetic epigenetic and environmental (including both internal physiological environment as well as the external environment) interactions (Casey et al, 2000).

Neurocognitive Development in the Healthy Human Brain

According to Lenroot & Giedd, (2006) specific events are key in brain development. These key events include the development of the neural tube, the differentiation of the neural tube, the myelination of the neurons, the proliferation and organisation of the synapses and lastly the formation of the gyri and sulci (Lenroot & Giedd, 2006).

The development of the nervous system begins at 18 days into gestation, but is far from complete at birth (De Luca & Leventer, 2008; Kolb & Whishaw, 2009). The development of the nervous system is a product of the integration of several synchronised processes some of which are completed during gestation, whereas others continue into adulthood. The initial key event occurring in the development of the central nervous system, is the formation of the neural tube which is specialised fold of the ectodermal tissue. The development of the neural tube is completed 3-4 weeks into gestation and forms the basis for the development of the nervous system development. Abnormalities in the development of the neural tube have been seen to cause birth defects such as Spina Bifida as well as Meningomyelocele (Victor et al, as cited in Lenroot & Giedd, 2006).

In the subsequent 4-12 weeks of gestation this neural tube separates into what eventually develops into the different parts of the nervous system. One end of the tube develops into the forebrain and facial structure, the opposite end develops into the spinal cord and the hollow gap in the middle eventually develops into the brain from the ventricles. Proliferative zones are formed near the ventricles and these regions give rise to young neurons (Lenroot & Giedd, 2006).

From 12 -20 weeks of the neurons migrate to their pre-determined destinations along the scaffolding of the glial cells where they then differentiate and mature to form a canvas of cortical organisation upon which post-natal environmental stimuli and genetic programming can build (De Luca & Leventer, 2008; Kolb & Whishaw, 2009 ; Rackie et al, 1990 as cited in Lenroot & Giedd, 2006).After the migration, the number of neurons is dramatically reduced by half in the period between 24 weeks gestation to 4 weeks after birth when a period of rapid cell death occurs. The cell bodies of the neurons form the gray matter of the brain and the white matter is formed by the myelinated axons of the brain (Lenroot & Giedd, 2006).

The myelination of the neurons begins at 29 weeks and this process occurs regionally, beginning with the brain stem. Post-natally the Myelination proceeds in an orderly way "from inferior to superior and posterior to anterior" (Lenroot & Giedd, 2006 pg 719) and "proximal pathways tend to myelinate before distal, sensory before motor, and projection before association" (Volpe, 2000, cited in Lentroot & Giedd, 2006). Although many of the major tracts have virtually completed the myelination process in early childhood, axons within the cortex in certain regions such as a white matter bundle located near the temporal lobe as well as arcuate fasiculus continue to myelinate into the second and the third decades of life. (Yarkovlev & Lecours, 1967 as cited in Lenroot & Giedd, 2006).

Another key event in the brain development includes the proliferation and organisation of synapses begins in the 20th week of gestation (Lenroot & Giedd, 2006). Synaptogenesis involves the proliferation and organisation of synapses to increase synaptic density (Lenroot & Giedd, 2006; De Luca & Leventer, 2008). By the age of 2 years, this should reach a level that is 50% of those in adults (Huttenlocher, 1979, cited in Lenroot & Giedd, 2006). Following this, there is a loss in synaptic connections – a pruning of these connections in a use it or lose it manner. The loss in synaptic connections occurs regionally with maximum synaptic density occurring in the visual cortex at approximately 4 months after birth yet in the prefrontal cortex this peak is only seen at four years of age (Lenroot & Giedd, 2006).

The formation of the sulci and the Gyri begins by the surface of the growing brain folding at 15 weeks of gestation (Levine and Barnes, 1999 as cited in Lenroot & Giedd, 2006). With the exception of the occipital lobe all other major sulci are in place by 28 weeks of gestation which is further followed by the elaboration of the secondary and tertiary sulci allowing for virtually all Gyri to be present by birth. The patterns of the sulci and Gyri gain complexity after birth and this change has been related to the maturation of the subcortical tracts and the cell packing density changes. (Lenroot & Giedd, 2006).

fMRI and MRI studies have been useful in tracking human brain development. A longitudinal MRI study by the Child Psychiatry Branch at the NIMH revealed peaks in cortical grey matter volume at different ages in childhood, according to specific regions, and then a decline (Lenroot & Giedd, 2006). The first areas to mature are the primary cortical motor and sensory

regions – these regions undergo a burst in synaptogenesis and myelination during the first two years of life (De Luca & Leventer, 2008).

In a study conducted by Casey, Giedd and Thomas (2000), the findings of MRI based anatomical that preceded the study were collaborated and the authors stated that the most consistent findings were recorded. "a lack of significant change in cerebral volume after 5 years in age...A significant decrease in the cortical gray matter after 12 years...An increase in cerebral white matter throughout childhood and young adulthood." (Casey, Giedd & Thomas, 2000, p.243)

The study also reported that the subcortical gray regions such as the basal ganglia decreases during childhood and this is found particularly in males while the cortical gray matter in the parietal and frontal cortices does not appear to decrease until puberty. More specifically there seems to be a an increase in the white matter in the dorsal prefrontal cortex yet not in the ventral prefrontal regions (Reiss et al, 1996 as cited in Casey et al, 2000). Whereas the temporal lobe volume appears to remain stable from the age of 4-18years of age and the hippocampal formation volume increase with age for females and the amygdale increases with age for males (Giedd et al, 1996 as cited in Casey et al, 2000). In summary the brain seems to change across age according to the region with the prefrontal cortex maturing last and specifically the dorsolateral prefrontal cortex (Casey et al, 2000).

It is generally accepted that as specific brain regions develop, so does behaviour (Kolb & Whishaw, 2009). Piaget described four stages of cognitive development: sensorimotor (birth

to 18 – 24 months); pre-operational (2 – 6 years); concrete operational (7 – 11 years); and formal operational (12+ years) (cited in Kolb & Whishaw, 2009). De Luca and Leventer, 2008, describe these different stages of neurodevelopment.

Major gains are seen in motor and language development in the first two years. From 2 – 6 years, white and grey matter volumes continue to increase. This results in "the ability to form meaningful connections between temporally sequenced events" (De Luca & Leventer, 2008, p.31) and so this period is characterised by the question "why?" Their level of processing improves although they lack the inhibitory and distractibility control of developed prefrontal connections. Whilst white matter volume continues to develop steadily during preadolescence (≈8 – 12 years), there is a spurt in cortical grey matter volume which peaks at 11 in girls and 12 in boys (Rapoport et al., 1999, cited in De Luca & Leventer, 2008). From then on, grey matter volume gradually decreases. During this period, executive functions such as cognitive flexibility, working memory and goal-directed behaviour begin to mature.

Several fMRI studies have investigated the prefrontal activity in children during memory and attention tasks, with one of the first paediatric fMRI studies examining prefrontal cortical activity during a working memory task (Casey et al,1995 as cited in Casey et al, 2000). These studies have noted that the investigation into the frontal lobe is important as there is considerable organisation and development in the frontal lobe in childhood and adolescence; the prefrontal cortex has been associated with higher cognitive processes such as memory and attention which tend to develop during this period and the prefrontal cortex is implicated and affected in a number of developmental disorders (Casey et al, 2000).

During adolescence, considerable changes occur in the cerebral cortex, particularly the frontal lobes. White matter volume continues to increase whilst grey matter volume decreases and fMRI studies have implicated that more advanced frontal lobe circuits are used rather than amygdala-based circuits (Killgore, Oki & Yurgelun-Todd, 2001, cited in De Luca & Leventer, 2008). It is during this period that continued maturation and refinement of executive functions occurs and this may be as a result of the prolonged development of the frontal lobes. "PET studies of glucose metabolism suggest that maturation of local metabolic rates closely parallel the time course of overproduction and subsequent pruning of synapses with the prefrontal cortex showing a prolonged maturation relative to the visual cortex" (Chugani et al, 1987 as cited in Casey, Giedd & Thomas, 2000). It must be noted however that PET studies are more likely to be performed using clinical population and for this reason may have limited application in healthy subjects.

The development of the nervous system is therefore a process that works towards developing a healthy, optimally functioning brain that can cope with all the higher cognitive demands of human life. If one stage is disrupted, it may have future detrimental consequences. The frontal lobe as previously mentioned is the last to mature however it has been shown to be the most susceptible in aging as measured with MRI (Svenner-holm et al, 1994 as cited in Casey et al, 2000). This finding has perturbed researchers as too why the last brain to mature was the first to be affected? Casey et al (2000) suggested that this may be that brain regions are most plastic whilst they are developing and thus may be affected by environment factors.

Neurocognitive Development and HIV

It is well-known that the brain is vulnerable to disease in vitro, e.g. spina bifida, rubella etc. (Zillmer, Spiers & Culbertson, 2008). Thus, one can assume the HI virus affects this early stage of neurodevelopment (Gay et al., 1995). Radiological studies with seropositive children have revealed some CNS abnormalities such as cortical atrophy and calcification, especially in the basal ganglia and frontal cortex white matter (Belman et al., 1985; Belman et al., 1986; Epstein, Berman, Sharer, Khademi & Desposito, 1987; Civitello, 2003), and myelinopathy (Gay et al., 1995). As previously described, myelination undergoes a significant burst during the first two years of life and continues throughout adolescence into adulthood. It is a critical process to ensure the efficient and rapid communication between the complicated networks of neurons. Wachsler-Felder and Golden (2002) state that "disruption of myelination processes in young children can cause delays in language, sequencing and integration" (p.449). Consequently it would be expected that if the HI virus disrupts the unmyelinated nervous system still in the process of development, there would be disruptions in the development of future cognitive functions.

As mentioned previously, the progression of HIV is faster in children than in adults due to its effect on the developing immune and nervous systems (Belman, 1997; Brouwers et al., 1996). Once the virus has infected the central nervous system (CNS), motor, cognitive and behavioural features are seen (Wachsler-Felder & Golden, 2002). Englund et al., (1996) argue that "the most frequent neurologic abnormality is motor dysfunction" (cited in Wachsler-Felder & Golden, 2002, p.444). This is to be expected as the basal ganglia are necessary for motor function. Features of HIV-associated progressive encephalopathy in children include "progressive corticospinal tract signs with concomitant loss of previously

acquired motor milestones, or a markedly deviant rate of acquiring motor skills" (Wachsler-Felder & Golden, 2002, p.444).

Earlier studies have explored the neuropsychological sequelae of HIV positive children (Koekkoek, S., de Sonneville, Wolfs, Licht & Geelan, 2008; Martin, et al., 2006; Patel, et al., 2009; Smith, Adnams & Eley, 2008; Wachsler-Felder & Golden, 2002). In the pre-HAART era, deficits included a broad range of disorders arising from HIVE induced pervasive CNS dysfunctions and neurodevelopmental delays (which has a slow onset) to CNS opportunistic infections. In older school-going children, the first signs were usually declining academic performances, behavioural changes, psychomotor impairment with eventual progressive cognitive impairment and the emergence of new pyramidal tract signs (Civitello, 2003). It is understood that the age of starting HAART is an important predictor for neuropsychological outcome (Smith, Adnams, & Eley, 2008). Nevertheless, Sherr et al. (2009) describe several methodological issues with the HIV paediatric literature such as population sample, risk factors, age range and tests used.

Given the evidence presented on HIV, combined with neurodevelopmental theory, it is has been shown that specific areas of the brain have been and are affected by HIV in the developing brain. In their report Brouwers et al (1995) indicated that in Europe, more children are diagnosed with neurological impairments compared to adolescents. This issue begs the question of Clade specificity, appropriate ART adherence and whether adequate educational support facilitated a better prognosis in Europe. For South Africa, however, these very questions need to be addressed. Unlike the European situation, not only is the Clade different, but the South African *context* is considerably different. Against this background

(which includes the extrinsic and intrinsic factors to HIV infection), the neurocognitive profile collected needs to be evaluated in terms of how each of the key functional areas of the brain are affected by HIV.

HIV and Motor Functioning

Although one could argue that the majority of the nervous system functions to move the body, the "motor system" includes the somatosensory cortex of the parietal lobe, the motor cortex of the frontal lobe, the subcortical basal ganglia, the cerebellum, the brain stem and spinal cord, and the motor neurons (Kolb & Whishaw, 2009). Different types of movement disorders, such as akinesias and apraxias, occur as a result of damage or disease in any part of the motor system, although it isn't always easy to determine which area is damaged (Lezak, 2004).

HIV predominantly infects the pathways between the frontal cortex and the basal ganglia – two areas critical for intact motor function. In the basal ganglia, calcifications are seen which, in addition to neuronal loss and tissue necrosis, are a result of a build-up of infected macrophages (Tardieu, 1998). The striatal complex of the basal ganglia receive information from the somatosensory areas which is then projected through the globus pallidus to the thalamus. The thalamus then projects the information to the premotor and prefrontal areas where motor skills are integrated for action (Lezak, 2004; Zillmer, Spiers & Culbertson,

2008). Lesions to this fronto-striatal loop disrupt this integration of motor skills and so result in impaired or uncoordinated movements (Lezak, 2004). Thus, this type of motor impairment would be expected in an HIV population.

Nozyce, Hittelman, Muenz, Durako, Fischer and Willoughby (1994) reported gross and fine motor developmental delays in HIV infected infants. In addition, Gay et al. (1995) reported motor developmental delays in seropositive infants. Blanchette, Smith, King, Fernandes-Penney and Read (2002) found fine motor and motor strength deficits in vertically infected school-age children. In addition, they concluded that those children with structural abnormalities in the brain were at risk of visual-motor deficits.

If a function such as motor ability is delayed, it would have an impact on future emerging skills as the development of the brain and central nervous system is a sequential process. As the majority of this literature has been with young children and infants, it would be interesting to investigate the motor function of young adolescents to determine to what extent it has been affected through HIV infection. With the introduction of ARVs, improvement in patients' processing speed, memory, motor skill and overall cognitive ability has been seen (Brouwers et al., 1997; Martin et al., 1999; Suarez et al., 2001). It would be of interest to investigate the motor skills of HIV vertically infected South Africa adolescents on HAART as motor function is an integral part of everyday social and vocational life.

In order to measure motor function, the Finger Tapping Test and Purdue Pegboard Test are widely used measures of fine motor co-ordination and speed (Lezak, 2004). Burton, Sepehri, Hecht, VandenBroek, Ryan and Drabman (2001) argue that motor speed can be used as an indicator of cognitive ability. This will be further explained in the methodology section.

HIV and Visuospatial Functioning

Visuospatial ability in humans impacts broadly, affecting everything from simple processes such the ability to walk or pick up objects, to more complex and advanced mechanisms such as engineering, most sports, science, and art, to the basics of everyday life such as judging the distance and speed of an approaching car when crossing the street. Visuospatial abilities are governed by the white-matter tracts in the parieto-preoccipital subareas of the cerebral cortex (Mishkin, Lewis & Ungerleider, 1982), but rely very heavily on the fronto-striato-parietal networks (Woods et al, 2009), especially during the development of these areas (specifically the frontal lobe) that occurs at the onset of adolescence (Klingberg, Forssberg &Westerberg, 2002). Therefore any disruption to the white-matter tracts, or to the development of the fronto-striato-parietal networks, would results in deficits to the visuospatial abilities. Visuospatial abilities are also closely linked to motor functioning. For example one's visuospatial ability allows one to see where in relation to one's self a glass of water is, which then links to one's motor functioning informing where to move one's hand to reach the glass.

HIV has been shown to negatively affect the white-matter of the brain, specifically causing a direct loss of axonal integrity, as well as a loss of complexity to the underlying axonal matrix of the white matter (Stebbins, Smith, Bartt, Kessler, Adeyemi & Martin et al, 2007). This

disruption to the white matter has been shown to be specifically prevalent within the frontal lobe (Pomara, Crandall, Choi, Johnson & Lim, 2001).

Research has illustrated the disruption of white matter, specifically within the frontal lobe, due to HIV. Therefore due to the disruption of this white matter, one could assume that visuospatial ability would be negatively affected as a consequemce. The effect that HIV has on visuospatial ability is therefore important, specifically in the age group for this research, where network development is strengthened and frontal lobe maturation is supposed to be beginning (Klingberg, Forssberg &Westerberg, 2002). Therefore the effect that HIV has on this development, and on the functions that result from this development, are of interest. Consequently to explore this affect the results from the Rey Osterrieth Complex Figure Test and subtests from the WISC-R (Picture Completion, Block Design, Object Assembly, Coding and Mazes) will be examined, as all of these tests require some greater or lesser use of one's visuospatial abilities to complete.

HIV and Memory

Memory deficits are common in children with vertically acquired HIV infection (Boivin, 2010). A markedly poor presentation has been found in children with HIV CNS disease, specifically on verbal learning and recall (Gendelman, 2005). Thus, neurocognitive deficits associated with HIV infection have a significant impact on the academic performance of these children. In particular, working memory is preferentially affected by HIV due to the effect of the infection on the fronto-temporo-thalamocortico system (Bassel, Rourke, Halman, & Smith, 2002). As a result of this, the individual's ability to manipulate, as well as

temporarily store, verbal and visuospatial information declines dramatically (Goldman-Rakic, 1995; Petrides, 1995, 1998). The child therefore has difficulty with the modulation of attention. Chang et al. (2001) suggests that the fronto-straital brain impairment caused by the HIV infection necessitates supplementary attentional modulation of the neural circuits. Since additional activation of the frontal lobes is required for the performance of tasks, greater use of the brain's reserves are consequently utilized for the selection of attentional stimuli as well as information processing (Bassel, et al., 2002).

The HIV infection targets neural systems found in the striatum and basal ganglia (Gendelman, 2005). Subcortical atrophy in these regions gives an indication of deficits in procedural memory. This has a pronounced effect on an individual's ability to perform psychomotor tasks necessary for everyday life, such as driving (Boivin, 2010). Furthermore, it has been found that episodic memory is compromised by HIV due to the effect of the virus on the integrity of the hippocampal-prefrontal regions of the brain (Castelo, Sherman, Courtney, Melrose, & Stern, 2006). As the hippocampus has an important role in declarative memory, verbal memory deteriorates because of the damage to this memory system. Furthermore, the decline in the integrity of the fronto-striato parietal circuits has a direct effect on visuospatial memory, which relies on the intact functioning of these neural correlates (Chang et al., 2001). However, studies have postulated that deterioration of the memory processing systems may not be targeted themselves, but rather suggest that the decline in general cerebral deficiency is responsible for memory processing impairment (Bassel et al., 2002). Nevertheless, HIV has a severe and widespread effect on the neural systems upon which memory processing rely.

HIV and Executive Functioning

The frontal lobes are thought to be the seat for executive function. Executive function is considered to incorporate decision-making; planning, goal directed behaviour and self-regulation. As such it facilitates the adaptation to novel situations – a functionality that is intrinsically associated with optimal cognitive, social and emotional behaviour (Lezak, Howieson, & Loring, 2004). Because of its integrative role, executive functioning is affected cortically (through damage to the frontal lobes); sub-cortically via the circuitry connecting the deeper subcortical parts of the brain to the frontal lobes or if indeed those subcortical areas are in themselves affected preventing any communication to the frontal lobes (Gazzaniga, Ivry, & Mangun, 2009).

As alluded to earlier in the review, HIV affects multiple areas in the brain with neurotoxic effects being noted in the basal ganglia, the frontal neocortex and the white matter tracts in between (Woods, Moore, Weber, & Grant, 2009). Frontal dysfunction in HIV affected individuals is therefore not atypical but is usually indicated in the latter stages of HIV disease and indicated by cognitive decline and attributed to disruptions of the frontostriatal loops (Melrose et al, 2009)

It is acknowledged that the later stages of HIV have been associated with deficits in executive function in adults who have had fully developed executive functioning prior to infection. Neurodevelopmentally speaking, the failure to develop earlier more basic functions may compromise the development of later more complex functions even where the anatomical structures ostensibly responsible may still be intact. For an adolescent population who were

exposed to environmentally poor conditions (poor socio-economic and/or socio-educational systems), who were ARV-naïve following birth and who may only have been placed on ART following symptomatic presentation; the extent to which executive function has been compromised is of prime concern.

Based on evidence presented on cognitive dysfunction in ARV-naïve populations (Laughton et al, 2010) and for the complexities raised by the South African scenario, we predict, for this sample, that HIV positive adolescents on HAART will have poorer executive function than a matched control group of HIV negative adolescents. From this perspective, the study will examine which of the variables within the HIV positive adolescents predict a better overall executive function outcome. In this case, within group comparisons based on the socio-demographic and the clinical variations as outlined earlier as well as between group comparisons to the control group (HIV positive vs Control) will be examined. Selected tests from the WISC-R viz the information subtest (which explores environmentally expectant vs environmentally determinant aspects) the picture arrangement test (to test planning functionality); the comprehension subtest (which evaluates social intelligence). Since working memory is of extreme importance for executive function in its' entirety (ie. it affects decision making, planning, purpose driven action as well as self- regulation); the memory for digits subtest will also be conducted to assess working memory functionality. Tests such as the Wisconsin card sorting test will be applied to evaluate deficits in abstraction, set shifting and novel problem solving (Lezak, Howieson, & Loring, 2004), while the Stroop Colour Word Test will be used to measure attention and response inhibition abilities (Strauss, Sherman, & Spreen, 2006). Once again, further elaboration will be provided in the methodology section of this paper.

External and Internal Factors on Neuropsychological Functioning

Grant et al, (1987) and Woods and Grant (2005) documented a flow chart which detailed the relationships between the neuromedical, psychiatric, environmental and tests characteristics which affect the neuropsychological test performance. The flow chart can be seen below.

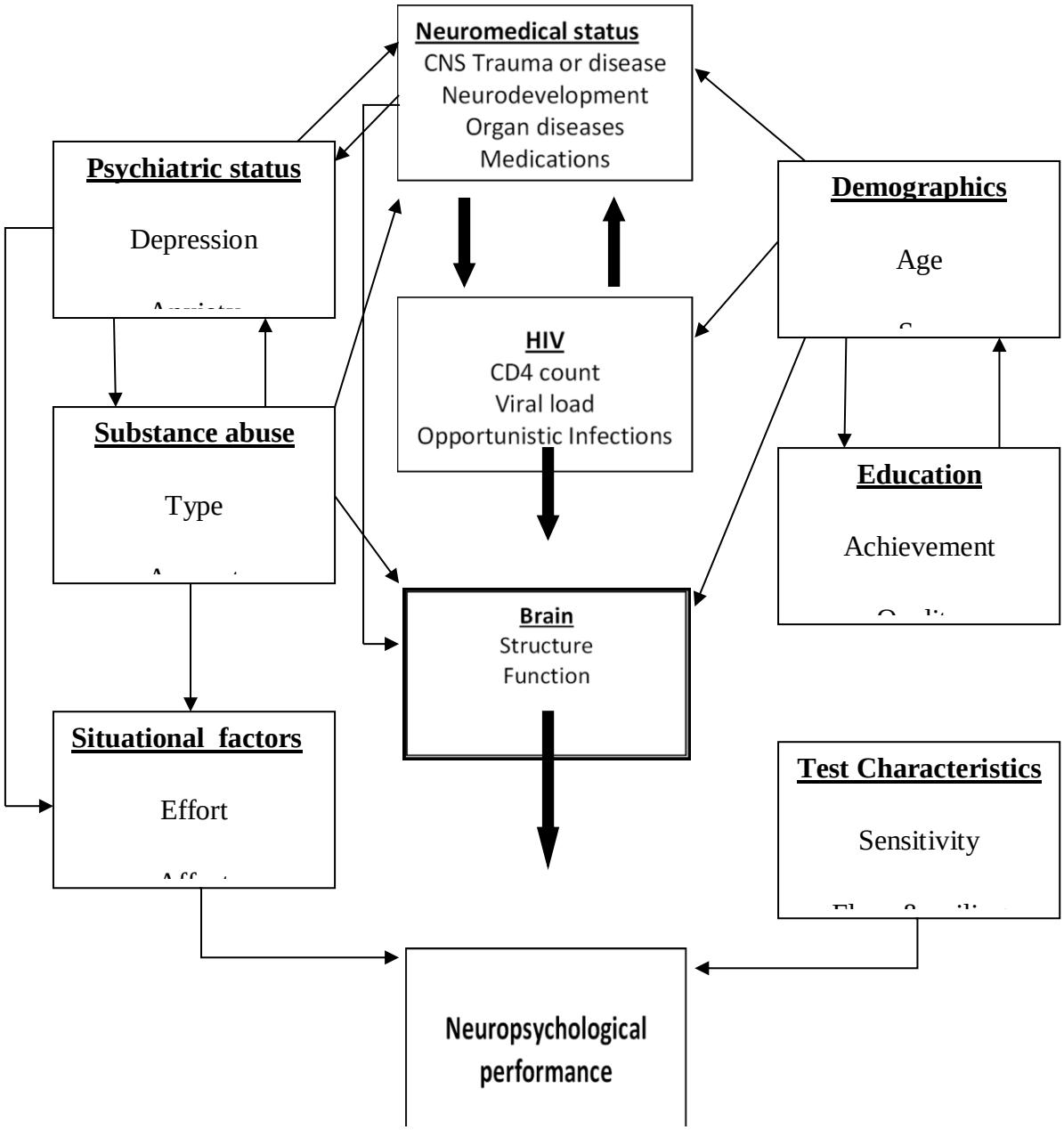

Fig 2 Flow chart depicting the relationships between neuromedical, psychiatric, environmental, person-specific and test characteristics on neuropsychological test performance, SES, Socioeconomic status: ADHD, attention-deficit, hyperactivity disorder. (Adapted from Grant et al. 1987 as cited in woods & Grant , 2005).

A multitude of social, medical, psychiatric factors may influence the performance on neuropsychological tests (Fig 2). This increases the difficulty of assessing whether the neurocognitive deficits found in research are in fact due to the HIV infection. Certain factors

within this flow chart affects neuropsychological performance directly namely the Demographic Factors such as Age, sex, race and socio-economic status (Woods & Grant, 2005). It is therefore essential that these factors are matched when comparing the neuropsychological performance of HIV positive versus HIV negative individuals.

Neuropsychological tests are often reliant on education systems and levels - specifically those testing semantic memory. Gender differences have been identified in research for some neuropsychological tests such as grooved pegboard and verbal fluency tests however research has too shown that men and woman perform comparatively on measures of global cognitive ability. Ethnicity disparities have been found where the results tend to favour the majority race (Woods & Grant, 2005). Disparities also need to take socio-economic status, education and mainly culture differences into account.

Neuromedical factors can also severely affect the performance. These factors incorporate premorbid or co-morbid diseases such as central nervous system diseases, trauma, psychoactive medications, substance abuse, systemic illnesses, psychiatric conditions and learning disabilities. Substance abuse has notably high co-morbid rate in HIV infected persons, this may be a result of the risky lifestyle behaviors that are well documented for substance abuse as well as HIV infection. The known impact of various licit and illicit substances on the brain and cognitive functioning, these disorder arise as a strong confound of the neuropsychological performance on tests (Woods & Grant, 2005).

These factors need to be carefully considered when identifying disparities in results. Woods and Grant (2005) propose that the neuropsychological findings will additionally be varied according to the disease characteristics such as the disease markers (viral load in the cerebrospinal fluid), effectiveness of treatment and opportunistic infections.

Internal factor influencing neuropsychological performance includes mood, fatigue and effort. As a result of the progression of the disease, the patient may suffer fatigue and a lack of motivation specifically in the later stages of the disease. This factor plays a major role in affecting the patient's ability to complete and excel on many of the tasks in the neuropsychological battery. Mood disturbances is another theoretical confound in neuropsychological assessment of HIV individuals specifically that of depression. The prevalence of major depression is elevated in HIV positive persons as well as seronegative individuals that have a high risk for HIV infection (Woods & Grant, 2005). Despite several studies suggesting a correlation between mood and Neuropsychological majority of studies have not yet established such an association (Grant et al, 1993).

Since both external and internal factors play such a vital role in performance, due consideration will be taken to ensure that a fairly homogeneous sample is obtained while accounting for the within group differences.

Rationale for the study

What the literature review hoped to provide is an overview of the complexities surrounding HIV. Not only do the neuropathological pathways differ leading to very diffuse CNS

disorders, but the effects of both external and internal stressors cannot be ignored (Wachsler-Felder & Golden, 2002).

From a practical perspective, anecdotal evidence from medical practitioners and educators alike suggest that learning difficulties are indicated in HIV positive children. Moreover, given the historical South African scenario, ARV-naïve children are also suspected to have the added disadvantage of only being placed onto an anti-retroviral regimen on presentation of clinical symptom as alluded to in the literature review (encephalitis, tuberculosis or pneumonia). By this time, some CNS functionalities may have already been compromised.

Given the lag in treatment the aim of this research is to provide a neuropsychological impression of those HIV positive adolescents currently on a managed ART programme. It is hypothesised that HIV positive adolescents on HAART will have poorer neuropsychological profiles than a matched control group of unaffected HIV negative children. To facilitate a more holistic study, those mediating factors that predict a better overall neurocognitive outcome will also be investigated. This will involve exploring group comparisons based on the socio-demographic data. Within group clinical variations such as duration of ARV treatment, drug regimen, WHO stage at diagnosis and $CD4^+$ counts will also be considered in the final analysis as will the between group comparisons to the control group (HIV positive versus the Control group).

The larger research question attempts to establish the neurocognitive profile of HIV positive *adolescents* on ART in Johannesburg, South Africa (within the context alluded to earlier). This question will be addressed by collaboratively enriching the statistical differences (that

are hypothesised to emerge between the groups) with a more comprehensive analysis of specific neurocognitive functionalities. These are as follows:

- Motor Functions in HIV Positive Adolescents on Anti-Retroviral Treatment in Johannesburg, South Africa
- Visuospatial Functions in HIV Positive Adolescents on Anti-Retroviral Treatment in Johannesburg, South Africa
- Memory in HIV Positive Adolescents on Anti-Retroviral Treatment in Johannesburg, South Africa
- Executive Functions in HIV Positive Adolescents on Anti-Retroviral Treatment in Johannesburg, South Africa

It is also envisaged that this research forms the foundation upon which further studies for psycho-therapeutic or psycho-educational interventions can be explored so as to optimise the psychological functioning and potential of the child.

Methods

3.1 Sample

The sample will consist of 40 HIV-positive children between the ages of 13 to 15 years old. A control group of 40 HIV-negative children will also be tested for comparative purposes, and will be matched for socioeconomic status, operationalised by the area in which they live.

Following communication with staff at the clinics and hospitals from which the sample will be drawn, our sample base will consist of Black, low socioeconomic teenagers, who have

English as a second language. To minimise the extraneous impact of language proficiency in testing second language speakers all participants will be required to have completed at least four years of English medium schooling. South Africa has eleven official languages. This creates logistical difficulties (Adler, 2001), which, together with the widespread preference for education in English (Vesely, 2000), result in the Revised National Curriculum Statement's (RNCS) (Department of Education, 2002) language policy only being partially implemented. This language policy uses an additive approach to bi- or multi-lingualism, whereby the first language is maintained and used as a basis for the learning of another language (Chick & McKay, 2001; The Advisory Panel on Language Policy, 2000). This approach has benefits for the learner as "continued development of both languages into literate domains ... is a precondition for enhanced cognitive, linguistic, and academic growth" (Cummins, 2000, 37). Due to the partial implementation of the language policy, South African educators face the challenges of large numbers of ESOL learners in their classes (PANSALB, 2000). Cummins (2000, 59) distinguishes between basic interpersonal communication skills (BICS) and cognitive academic language proficiency (CALP), "the registers of language that children acquire in school and which they need to use effectively if they are to progress successfully through the grades". Although learners may be able to use English competently among peers and in social settings (BICS), they may not be proficient in the type of language expected in the classroom (CALP) (Cummins, 2000). While it takes ESOL learners approximately two years to become competent in English BICS, it takes them five to seven years to reach the same level as their first-language peers in terms of CALP (Hall, 1996; Cummins, 2000).

Not only for ethical reasons but also based on the strong support found in the literature that institutionalisation brings with it its own set of neurobiologcal sequalae, children without a parent or guardian will be excluded from the study. Based on similar neurobiological

reasoning, additional exclusion criteria will include any form of neurological compromise such as Epilepsy, Meningitis, Traumatic Brain Injury and so on. This is to keep the integrity of the internal validity so that the results of the instruments reflect the deficits caused by HIV and not any other confounding cause.

Participants for the control group will be obtained from the same schools in the Orlando area of Soweto reported on by Skuy et al. (2001). They will be matched for age and socioeconomic status. A letter will be sent home with the children explaining the research. Included in the letter will be a request that should the child be on chronic medication, HIV positive, have experienced a head injury, have any neurological impairment, or is living outside of the nuclear family structure a response to the request for participation is not necessary. In this way the exclusion criteria that apply to the HIV-positive group can be operationalized in the HIV-negative control group.

3.2 Instruments

The first test to be administered will be the Rey Auditory Verbal Learning Test (RAVLT). The test consists of a group of 15 words read out to the subject at a prescribed rate. The subject is instructed that they must memorise these and will be required to recall them in an order of their own preference, commonly known as free-recall (Senior, 2000). This procedure is performed a total of five times (trials I-V) with the subject instructed that they must include words recalled in previous trial as well as additional words remembered on each subsequent trial. On completion of the fifth recall of the target words, an interference word list is presented once in accordance with the same presentation procedure. This trial is to ascertain

the amount of proactive interference occurring from the original word set to the new word set. Immediately following the recall of the interference word list the participant is asked to recall the words from Target word list A without the word set being read out. This trial is to ascertain the amount of retroactive interference that has occurred from the new word set. Administration time for this procedure is approximately seven to ten minutes. Following a 20-30 minute delay trial VIII, which is exactly the same as trial VII, is performed to measure degradation of memory over time. Trial IX, a recognition test, is the last trial and is carried out directly after trial VIII. A list of 45 words is read out aloud to the subject, one at a time, who then has to identify the word as a target word (set A) or not (Senior, 2000).

The reliability and validity scores of the RAVLT are in the range of 0.70-0.88 dependant on a number of factors, such as environment and the rate at which the list is presented (Groth-Marnat, 2003; King, Gfeller, & Davis, 1998). Having been created in 1941 (Senior, 2000), this test has, after a few minor modifications, stood the test of time as being at the forefront of memory and verbal learning tests.

The Rey Osterrieth Complex Figure Test (ROCFT) evaluates the participant's visuospatial constructional ability, visual memory and executive function mediated by the prefrontal lobe (Shin, Park, Park, Seol & Kwon, 2009). The ROCFT is made up of three conditions. In the initial phase, the participant is given the Complex Figure to copy.

Five minutes later, the second phase requires the participant to draw what they remember of the Complex Figure. Finally, following a delay of thirty minutes, the participant is asked to draw the Complex Figure. The way in which the administrator scores the tests is related to the location, accuracy, and organisation of the figure at each of the three stages.

A study conducted by Skuy, Schutte, Fridjhon and O'Carroll (2001) found that the mean standard of the copies on a South African Soweto sample yielded lower scores (31.27; Sd: 3.14) than the American norms (35.1; Sd:1.5), while the reproduction scores after a lapse of thirty to forty-five minutes resulted in a mean score of 19.9 for the Sowetan sample and 23.2 for the American norm. Thus the administrator should expect the scores by South African children to be lower than the norm before accounting for the effects of HIV. However, the scoring system evaluates fragmentation, planning, organisation, presence and accuracy of various features, placement, size distortions, perseveration, confabulation, rotation, neatness, symmetry and immediate and delayed retention and results in a score for each category. This provides a reliable method for scoring the ROCFT, nevertheless good inter-rater reliability is essential in order to produce reliable scores (Stern et al, 2007).

The next test to be employed in the study is the Wisconsin Card Sorting Test (WCST). The WCST has been proven to be an exceptionally good test at identifying frontal lobe abnormalities, with a reliability of 0.84 (Heaton, Chelune, Talley, Kay & Curtiss, 1993).

The test consists of 128 cards with varying colours (blue, green, red, or yellow), shapes (circle, triangle, square or cross), and numbers (one, two, three or four). The subject has to sort out the pile of cards according to either number, shape or colour (see Appendix B for an example of WCST). The subject is not told any rules, but rather told to sort the cards and then work on feedback given by the researcher ("correct" or "incorrect"). One rule will apply initially (for example: sort according to number), and after ten correct consecutive responses (called a set) the rule will then change (for example: sort according to shape). The subject is not told when the rules change, but has to figure out the changes according to responses from the researcher (Greve et al., 2005). The test is terminated once the subject completes six sets, or when all 128 cards have been used. Scores derived from the WCST (specifically

conceptual level response scores) provide insights relevant to many aspects of frontal lobe functionality including self-monitoring, working memory, attention span, learning curve, and of course frontal lobe functions (with regards to their overall score having a relationship to overall frontal lobe function).

The Stroop Colour-Word Test is a measure of cognitive flexibility and executive function, as well as a measure of focused attention (Moering, Schinka, Mortimer, & Graves, 2003). The participant is given a list of the names of colours and is asked by the administrator to read them aloud. The test administrator keeps a record of the time it takes for the participant to complete the list. The participant is then given an analogous task, however, this time the participant is asked to name the ink colour that is incompatible with the name of the colour that the words spell, thus suppressing the participant's habitual response. Once again the administrator records the time spent on naming the colours (Lezak et al, 2004).

The test-retest reliability for the Stroop is high with the Word item coefficient at 0.83, the Colour coefficient at 0.74 and the Colour-Word coefficient at 0.67 (van der Elst, van Boxel, and van Breukelen, 2006). Lezak (1985) maintains that the Stroop is very reliable – a testament to its wide use.

The Purdue Pegboard Test (PPT) measures the dexterity primarily for fingertips but also the gross movement of the arms and hands. The PPT was originally standardised in an industrial environment but has been found to be reliable in clinical settings (Magee, 2006).

The PPT consists of four parts. The first of which is a measure of the dexterity of the dominant hand (Lezak, 2004). The participant places small pins into holes on the board with their dominant hand. The test administrator counts the number of pins that were placed successfully in the holes after thirty seconds. In the second phase, the participant repeats this exercise using their non-dominant hand and the pins are subsequently counted. The third phase requires the participant to place the pins into two rows of holes simultaneously within thirty seconds. The administrator then counts the total number of pins placed in the holes. Finally, the participant assembles sequences of pins, collars and washers using both hands for sixty seconds. The administrator then makes one final count (Gallus & Mathiowetz, 2003). Research has shown that reliability for the PPT is higher with the three trial administration, than with the one trial administration (Lezak, 2004)

The Finger Tapping Test (FTT) is a pure measure of motor speed. Impairments in motor functioning can be detected using the FTT (Shimayama, Ninchoji, & Uemura, 1990). The participant is required to tap as fast as possible using the index finger of their dominant hand for ten seconds. This procedure is then repeated until five consecutive trials within five taps are obtained. This exercise is subsequently replicated with the non-dominant hand. The resultant score for each hand is the average of the five consecutive trials (Morrison, Gregory, & Paul, 1979). Should the non-dominant hand yield a speed of <80% than that of the dominant hand, impairment in the contralateral hemisphere is indicated. Should the speed of the dominant hand equal or be slower than the non-dominant hand, impairment is suggested in that contralateral hemisphere.

The FTT generally shows high reliability coefficients (0.9), with men generally displaying a higher coefficient than women (0,94 and 0.86 respectively) (Lezak, 2004). Combined reliability coefficients in both dominant and non-dominant hands are also shown to be high at 0.8 (Prigatano & Hoffmann, 1997).

The Controlled Oral Word Association (COWA) test, also known as the FAS, is a test of verbal fluency, displaying the speed and ease of verbal production. The test consists of three word-naming trials where the participant is required to name as many words beginning with a single letter in one minute (Lezak, 2004). The first letter is F, the letter for the second trial is A, and the last letter is S (thereby also being known as the FAS test). Proper nouns, numbers, and the same word with a different suffix are not allowed.

Research has shown that reliability is generally moderately high averaging around 0.7 (Lezak, 2004). The performances of participants with lower education (specifically levels below high school) should be interpreted with caution, due to high variability at lower educational levels.

The Wechsler Intelligence Scale for Children Revised (WISC-R) has ten scales, and two additional supplementary scales which have been combined in such a way that the WISC-R is a measure of Verbal IQ (VIQ), Performance IQ (PIQ), and Full Scale IQ (FSIQ) (Franzen, 2000). VIQ is comprised of the Information, Similarities, Arithmetic, Vocabulary and Comprehension subtests and PIQ is comprised of the Picture Completion, Coding, Picture

Arrangement, Block Design and Object Assembly subtests. The FSIQ is based on both the VIQ and PIQ subtests. The WISC-R is an individual test that does not require the participant to engage in any reading or writing. The test administrator sits with the participant and facilitates the completion of each of the ten subtests. The VIQ subtests are verbal questions that the administrator asks and are without time limits, the exception being the Arithmetic subtest. The PIQ subtests are nonverbal problems that the participant solves while being timed by the test administrator (Slate & Jones, 1992).

Overall internal consistency reliability coefficients have been generated where PIQ has a reliability coefficient of 0.90, VIQ of 0.94, and FSIQ of 0.96 respectively. Correlation coefficients for the Verbal subtests range from 0.63 for Similarities to 0.80 for Digit Span, while correlation coefficients for the Performance subtests range from 0.59 for Picture Completion to 0.80 for Object Assembly (Franzen, 2000). The validity of the use of the WISC-R in a sample with neural impairment is high as the results of the WISC-R delineate profiles of skills and deficits (Hale, 1981). The use of the WISC-R over the more modern WISC-IV was decided on as the WISC-R has received more use and attention within South African research (as seen in Skuy et al., 2001) and therefore has a wider database of South African relevant normative data that can be used for comparison.

3.3 Research Design

Although this research is inherently examining traits within the sample that have changed (or failed to develop) over time due to the effect of HIV, it aims to explore the sample as they currently stand, and not track the changes. These traits will be examined with regard to a

control sample of HIV-negative participants matched for socioeconomic status. This study is only examining variables and is not attempting to manipulate them in any way. Therefore, this design is a non IV-manipulated cross-sectional quasi-experimental post-test only control group design.

3.4 Data Gathering

Data gathering will occur at the Rahima Moosa Mother and Child Hospital, one of the University of the Witwatersrand Medical School's three teaching hospitals. The hospital holds clinical check-up days on Tuesdays, Wednesdays, and Thursdays. Patients who fit the inclusion criteria will be approached to participate in the study. A neutral party, an employee at the Rahima Moosa Hospital, will invite the child and guardian to participate in the study while they wait for their check up with the doctor. This will be implemented to ensure that the patients and their guardian feel they can decline without the fear of negative consequences. Consenting participants will be taken for testing directly after their regular clinical check-up.

Quiet venues for the testing process have been organised within the psychiatry ward of the hospital. There will be seven testers at each session who have all received the same training in the administration of the test battery. Testers include four Masters students in Clinical Neuropsychology and three psychometric interns.

Participants will have the process of the research explained to them and then they will be asked to complete an assent form (see Appendix 2). Their legal guardian will be asked to fill in a consent form. Should the guardian not be either literate or proficient in the English language a medical professional at the Rahima Moosa Hospital will assist in translation. The order in which the test battery will be administered will be as follows: the RAVLT part one, the ROCFT part one, the WCST, the Stroop, the RAVLT part two and then the ROCFT part two, the Purdue Pegboard, and the Finger Tapping Test. This section should take approximately one hour. Participants will then be given a fifteen minute break, in which light refreshments lunch will be provided for both the participants and their guardians. Testing will then recommence with the WISC-R being administered. This section should take approximately one and a half to two hours to administer. Therefore the total time required for each participant will be approximately three to three and a half hours

The same procedure will be implemented for the data gathering of the control group at the school. Control group participants will be tested with as little disruption to the school timetable as possible, preferably after school and in the school holidays

3.5 Data Analysis

Data obtained from all the tests will be in the form of interval data. Assuming all the requirements for parametric tests are met, parametric analyses will be used. A Matched-pairs T-test will be run to compare the data for the test group with that of previously gathered normative data from the same age group in South Africa. A Multivariate Analysis of Variance (MANOVA) will be run to compare the test group with themselves to examine for individual differences.

A CHAID (Chi Square Automatic Interaction Detection) procedure (Kass,1980) will be run to examine for the effects of other demographic details, such as gender, specific age, time on antiretroviral, type of antiretroviral, and so on. These results will be used to examine the effects of these variables on the results.

3.6 Ethical Considerations

Participants will be above the age of assent, but not above the age of consent. Participants will therefore be required to fill in an assent form (see Appendix 2) and their legal guardians will be required to fill in a consent form (See Appendix 1). The children in the HIV-positive sample all attend an HIV clinic and are on ARV's, as such each should be aware of their HIV status. Nevertheless, due to the sensitivity surrounding HIV, the participant will be informed that the research investigates the effect of the treatment of HIV and the effects of HIV itself will not be elaborated on.

Confidentiality will be kept with the utmost importance and should the participant require any further information this will be done in collaboration with the medical officer consulting on the case. However, as the participants need to be physically present for the testing, there cannot be anonymity. If any participant, for any reason, experiences distress, they will be provided with the contact details of free counselling services.

All of the tests being performed are non-invasive, manual, pen-and-paper style tests and therefore no foreseeable harm can befall the participants from participating. As the testing process will take a few hours, lunch and refreshments will be provided for the participants and their guardians (if present). If the participants travel to the hospital for the purpose of testing, rather than routine check-ups, their travelling costs will be reimbursed. In these instances, participants will be asked to attend testing sessions that occur during the school holidays so that no school is missed.

Permission for testing the HIV group will need to be obtained from the Empilweni Clinic while permission for testing the control group will be obtained from the Department of Education and the school itself.

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Appendix 2: GDE Research Approval Letter

education
Department: Education
GAUTENG PROVINCE

For administrative use:
Reference no. D2012/235

GDE RESEARCH APPROVAL LETTER

Date:	**15 March 2012**
Validity of research Approval:	**15 March 2012 to 30 September 2012**
Name of Researcher:	**Holland K.**
Address of Researcher:	**2 Gardenia Road**
	Primrose
	Germiston
	1401
Telephone Number:	**011 021 6112 / 083 449 6416**
Email address:	**kelly.holland149@gmail.com**
Research Topic:	**Neurophysical profile of HIV positive adolescents on antiretroviral treatment in Johannesburg**
Number and type of schools:	**THREE Secondary Schools**
District/s/HO	**Johannesburg South**

Re: Approval in Respect of Request to Conduct Research

This letter serves to indicate that approval is hereby granted to the above-mentioned researcher to proceed with research in respect of the study indicated above. The onus rests with the researcher to negotiate appropriate and relevant time schedules with the school/s and/or offices involved to conduct the research. A separate copy of this letter must be presented to both the School (both Principal and SGB) and the District/Head Office Senior Manager confirming that permission has been granted for the research to be conducted.

The following conditions apply to GDE research. The researcher may proceed with the above study subject to the conditions listed below being met. Approval may be withdrawn should any of the conditions listed below be flouted:

1. *The District/Head Office Senior Manager/s concerned must be presented with a copy of this letter that would indicate that the said researcher/s has/have been granted permission from the Gauteng Department of Education to conduct the research study.*
2. *The District/Head Office Senior Manager/s must be approached separately, and in writing, for permission to involve District/Head Office Officials in the project.*

1

Making education a societal priority

Office of the Director: Knowledge Management and Research
9th Floor, 111 Commissioner Street, Johannesburg, 2001
P.O. Box 7710, Johannesburg, 2000 Tel: (011) 355 0506
Email: David.Makhado@gauteng.gov.za
Website: www.education.gpg.gov.za

3. *A copy of this letter must be forwarded to the school principal and the chairperson of the School Governing Body (SGB) that would indicate that the researcher/s have been granted permission from the Gauteng Department of Education to conduct the research study.*
4. *A letter / document that outlines the purpose of the research and the anticipated outcomes of such research must be made available to the principals, SGBs and District/Head Office Senior Managers of the schools and districts/offices concerned, respectively.*
5. *The Researcher will make every effort obtain the goodwill and co-operation of all the GDE officials, principals, and chairpersons of the SGBs, teachers and learners involved. Persons who offer their co-operation will not receive additional remuneration from the Department while those that opt not to participate will not be penalised in any way.*
6. *Research may only be conducted after school hours so that the normal school programme is not interrupted. The Principal (if at a school) and/or Director (if at a district/head office) must be consulted about an appropriate time when the researcher/s may carry out their research at the sites that they manage.*
7. *Research may only commence from the second week of February and must be concluded before the beginning of the last quarter of the academic year.*
8. *Items 6 and 7 will not apply to any research effort being undertaken on behalf of the GDE. Such research will have been commissioned and be paid for by the Gauteng Department of Education.*
9. *It is the researcher's responsibility to obtain written parental consent of all learners that are expected to participate in the study.*
10. *The researcher is responsible for supplying and utilising his/her own research resources, such as stationery, photocopies, transport, faxes and telephones and should not depend on the goodwill of the institutions and/or the offices visited for supplying such resources.*
11. *The names of the GDE officials, schools, principals, parents, teachers and learners that participate in the study may not appear in the research report without the written consent of each of these individuals and/or organisations.*
12. *On completion of the study the researcher must supply the Director: Knowledge Management & Research with one Hard Cover bound and an electronic copy of the research.*
13. *The researcher may be expected to provide short presentations on the purpose, findings and recommendations of his/her research to both GDE officials and the schools concerned.*
14. *Should the researcher have been involved with research at a school and/or a district/head office level, the Director concerned must also be supplied with a brief summary of the purpose, findings and recommendations of the research study.*

The Gauteng Department of Education wishes you well in this important undertaking and looks forward to examining the findings of your research study.

Kind regards

Dr David Makhado 2012/08/16

Director: Knowledge Management and Research

Making education a societal priority

Office of the Director: Knowledge Management and Research

9th Floor, 111 Commissioner Street, Johannesburg, 2001
P.O. Box 7710, Johannesburg, 2000 Tel: (011) 355 0506
Email: David.Makhado@gauteng.gov.za
Website: www.education.gpg.gov.za

Appendix 3: Medical Ethics Clearance Certificate

UNIVERSITY OF THE WITWATERSRAND, JOHANNESBURG
Division of the Deputy Registrar (Research)

HUMAN RESEARCH ETHICS COMMITTEE (MEDICAL)
R14/49 Miss Kelly Holland

CLEARANCE CERTIFICATE	**M120268**
PROJECT	Neuropsychological Profile of HIV Positive Adolescents on Anti-retroviral Treatment in Johannesburg, South Africa
INVESTIGATORS	Miss Kelly Holland .
DEPARTMENT	Department of Psychology
DATE CONSIDERED	24/02/2012
+DECISION OF THE COMMITTEE*	Approved unconditionally

Unless otherwise specified this ethical clearance is valid for 5 years and may be renewed upon application.

DATE 20/04/2012 **CHAIRPERSON** .....
(Professor PE Cleaton-Jones)

*Guidelines for written 'informed consent' attached where applicable
cc: Supervisor : E Schutte et al

DECLARATION OF INVESTIGATOR(S)
To be completed in duplicate and **ONE COPY** returned to the Secretary at Room 10004, 10th Floor, Senate House, University.
I/We fully understand the conditions under which I am/we are authorized to carry out the abovementioned research and I/we guarantee to ensure compliance with these conditions. Should any departure to be contemplated from the research procedure as approved I/we undertake to resubmit the protocol to the Committee. **I agree to a completion of a yearly progress report.**

PLEASE QUOTE THE PROTOCOL NUMBER IN ALL ENQUIRIES...

Appendix 4: Parental Information Sheet (Research group)

School of Human and Community Development

Private Bag 3, Wits 2050, Johannesburg, South Africa

Tel: 27 (0)11 717 4524/5 Fax: 27 (0)11 717 4556

Dear Parent/Guardian,

Our names are Daniel Greenslade, Urvashi Chiba, Shona Fraser, Stephanie MacIlwaine, Cindy Van Wyk, Jessica Rice and Kelly Holland. We are conducting research for the purpose of obtaining a Masters degree in Neuropsychology at the University of the Witwatersrand. Our area of focus is young adolescents attending the Empilweni Clinic for treatment. We would like to invite your child/ward to take part in this study.

We are doing neuropsychological evaluations of adolescents attending the Empilweni Clinic. A neuropsychological evaluation involves using standardised tests to be able to describe an individual's cognitive strengths and weaknesses pertaining to mental processes such as memory, judgement, processing and reasoning.

If you, as the guardian/parent agree to allow your child/ward to participate, they will be required to complete some neuropsychological tests which are made up of drawing tasks, repeating lists of words and numbers, identifying colours as well as trying their hand with some cards. This may take between four to five hours to complete with rests in between. Your child will be provided with light refreshments half way through the tests.

Participation is voluntary, and no individual will be advantaged or disadvantaged in any way for choosing to, or not to, participate.

Please be assured that confidentiality about the results between the researcher and your child as the participant is guaranteed. The information from the tests will be coded and names will not be assigned to the information. The information we receive from the tests will only be seen by us and our research supervisors. No individual feedback can be given as the participants are on a managed treatment programme therefore test results will be supplied to the medical practitioner to be used at their discretion. The grouped data collected may be

used in publications or conference presentations, but no data that identifies your child will be used.

Please note that your child is free to stop the procedure at any time and no negative consequences will follow. He/she may simply say they would no longer like to participate. The information your child provides will be kept confidential in a locked cabinet according to the regulations set out by the Health Professions Council of South Africa. The regulations state that the information must be kept for two years if there is a publication and six years if the research is not published.

The tests will be administered in a room provided by the Psychology department at Rahima Moosa Mother and Child Hospital after your child/ward has seen the doctor at the Empilweni Clinic.

This research project was approved by the Human Research Ethics Committee (HREC) at the University of the Witwatersrand. If you have any complaints, compliments or queries you can address them to the HREC on 011 717 1234.

In order to facilitate the smooth running of our research, we need your permission to access your child/ward's file at the clinic so as to obtain the duration, as well as the type of treatment your child/ward is currently on and the other treatments they have been on in the past.

If your child/ward seems to be suffering from any psychological stress as a result of the testing they will be referred to the Emthonjeni Centre at the University of the Witwatersrand. You may additionally contact the centre for psychological services after the research is complete if your child is suffering any psychological stress. For referral to one of the training psychologists at the Emthonjeni Centre please contact Ntabiseng Modikane on 011-717-8663 or 011-717-4513.

Should you have any further questions, please feel free to contact any of us, or our supervisors at the below mentioned telephone numbers and we will be happy to assist.

Thank You and Kind Regards,

Daniel Greenslade, Urvashi Chiba, Shona Fraser, Stephanie MacIlwaine, Cindy Van Wyk, Jessica Rice, Kelly Holland, 0118722372

Supervisors: Enid Schutte, Kate Cockcroft, Marilyn Lucas, Aline Ferreira Correia 0117174524

Medical Ethics number: ***M120268***

Appendix 5: Parental Consent Form (Research Group)



UNIVERISTY OF THE WITWATERSRAND, JOHANNESBURG

School of Human and Community Development
Private Bag X3, Wits, 2050, Johannesburg, South Africa
Tel: (011) 717 4500 Fax: (011) 717 4559
Medical Ethics number: ***M120268***

I, Mother/Father/Legal Guardian of _____, give consent for my child/ward to participate in this study

I understand that:

- There is no risk or harm that could come to my child/ward from taking part
- Participation is voluntary
- My child/ward, or I, may choose to stop the testing at any time for any reason with no penalty or loss of benefits
- My child's/ward's results will remain confidential
- No positive or negative consequences will follow from choosing to, or not to, participate

By allowing my child/ward to participate I state that:

- My child/ward has no history of Epilepsy, Meningitis, or have suffered a serious head injury
- All the relevant information about this research has been explained to me and my child/ward clearly and simply and I understand the information
- The researchers have access to my child's file at the clinic in order to get the demographic and medical information they require

Signed: _____ Date: _____

Assigned Participant Number: _____

Appendix 6: Participant Information Sheet (Research Group)

School of Human and Community Development

Private Bag 3, Wits 2050, Johannesburg, South Africa

Tel: 27 (0)11 717 4524/5 Fax: 27 (0)11 717 4556

Hello,

Our names are Daniel Greenslade, Urvashi Chiba, Shona Fraser, Stephanie MacIlwaine, Cindy Van Wyk, Jessica Rice and Kelly Holland. We are conducting research for the purpose of obtaining a Masters degree in Neuropsychology at the University of the Witwatersrand. Our area of focus is young adolescents attending the Empilweni Clinic. We would like to invite you to take part in this study.

Your parent/guardian has to give consent to let you take part in the study and you will also need to give us assent (your permission) to participate in the study.

We are doing neuropsychological evaluations of adolescents attending the Empilweni Clinic. A neuropsychological evaluation involves using standardised tests to be able to describe an individual's cognitive strengths and weaknesses in mental processes such as memory, judgement, processing and reasoning.

You will be asked to complete some drawing tasks, repeat some lists of words and numbers, identify some colours as well as try your hand with some cards. This may take between four to five hours to complete with rests in between. You will be provided with light refreshments half way through the tests.

Participation is voluntary and you won't be advantaged or disadvantaged in any way for choosing to, or not to, participate.

Please be assured that confidentiality about the results between the researcher and you as a participant is guaranteed. Your name will not be on any of your information from the study. The information we receive from the tests will only be seen by us and our research supervisors. No individual feedback can be given. The grouped data collected may be used in publications or conference presentations, but no data that identifies you will be used.

Please note that you will be free to stop the procedure at any time and no negative consequences will follow. You can simply tell the test administrator that you do not want to continue anymore. The information you provide will be kept confidential according to the rules and regulations of the Health Professions Council of South Africa. The regulations state

that the information must be kept for two years if there is a publication and six years if the research is not published.

In order to facilitate the smooth running of our research we would like to have permission to have access to your file at the clinic to find out the type of treatment you are on and how long you have been using it and other treatments you have had in the past.

While we are doing the different tests, if you feel sad, uncomfortable or scared or nervous we will refer you to see a training psychologist at the Emthonjeni Centre at the University of the Witwatersrand. You can also call the Emthonjeni Centre at any time after you have participated and speak to Ntabiseng Modikane on 011-717-8663 or 011-717-4513.

This research project was approved by the Human Research Ethics Committee (HREC) at the University of the Witwatersrand. If you have any complaints, compliments or queries, you can address them to the HREC on 011 717 1234.

Should you have any further questions, please feel free to contact any of us, or our supervisors at the below mentioned telephone numbers and we will be happy to assist.

Thank You and Kind Regards,

Daniel Greenslade, Urvashi Chiba, Shona Fraser, Stephanie MacIlwaine, Cindy Van Wyk, Jessica Rice, Kelly Holland, 0118722372

Supervisors: Enid Schutte, Kate Cockcroft, Marilyn Lucas, Aline Ferreira Correia 0117174524

Medical Ethics number: ***M120268***

Appendix 7: Participant Assent Form (Research Group)

UNIVERISTY OF THE WITWATERSRAND, JOHANNESBURG

School of Human and Community Development

Private Bag X3, Wits, 2050, Johannesburg, South Africa

Tel: (011) 717 4500 Fax: (011) 717 4559

Hello,

We (Kelly, Daniel, Shona, Stephanie, Urvashi, Cindy and Jessica) are all students at Witwatersrand University and we are doing a study on adolescents attending the Empilweni Clinic for treatment.

We are doing neuropsychological evaluations of adolescents attending the Empilweni Clinic. A neuropsychological evaluation involves using standardised tests to be able to describe an individual's cognitive strengths and weaknesses of their mental processes such as memory, judgement, processing and reasoning

We would like you to take part in the study. If you agree to join in, you will be asked to complete some drawing tasks, repeat some lists of words and numbers, identify some colours as well as try your hand with some cards.

If you are happy to take part we would like you to please sign below to say if you would like to participate. If you decide not to, that is okay and no one will be upset. If you decide to join and then later change your mind and want to stop, this is okay too.

Would you like to participate (*Tick **one** box*)

☐ Yes, I am willing

☐ No, I do not want to

Signing at the bottom of this form means that you agree to take part in this research.

Thank you very much,

Signed (You can just write your name): _____

Date: _____

Assigned Participant Code: _____

Medical Ethics number: ***M120268***

Appendix 8: Parental Information Sheet (Control group)

School of Human and Community Development

Private Bag 3, Wits 2050, Johannesburg, South Africa

Tel: 27 (0)11 717 4524/5 Fax: 27 (0)11 717 4556

Dear Parent/Guardian,

Our names are Daniel Greenslade, Urvashi Chiba, Shona Fraser, Stephanie MacIlwaine, Cindy van Wyk, Jessica Rice and Kelly Holland. We are conducting research for the purpose of obtaining a Masters degree in at the University of the Witwatersrand. Our area of focus is young adolescents. We would like to invite your child to take part in this study.

We are doing a Neuropsychological evaluation of Children attending the school. A neuropsychological evaluation involves using standardised tests to be able to describe an individual's cognitive strengths and weaknesses pertaining to mental processes such as memory, judgement, processing and reasoning.

If you, as the guardian/parent agree to allow your child/ward to participate, they will be asked to complete some neuropsychological tests which include drawing tasks, repeat some lists of words and numbers, identify some colours as well as try their hand with some cards. This may take between two to three hours to complete with rests in between. Your child will be provided with light refreshments half way through the tests.

Your child's Participation is voluntary, and no individual will be advantaged or disadvantaged in any way for choosing to, or not to, participate.

Please be assured that confidentiality about the results between the researcher and your child as the participant is guaranteed. The information from the test will be coded and names will not be assigned to the information. The information we receive from the tests will only be seen by us and our research supervisors. No individual feedback will be given. The grouped data collected may be used in publications or conference presentations, but no data that identifies your child will be used.

Please note that you will be free to stop the procedure at any time and no negative consequences will follow. Your child may simply say that he/she no longer wishes to participate. The information your child provides will be kept confidential for in a locked cabinet according to the regulations set out by the Health professions' Council of South Africa. The regulations state that the information must be kept for 2 years if there is a publication and 6 years if the research is not published

The tests will be administers at a room provided at the school. The test will be conducted after school and will not interrupt learning

While we are doing the different test, you feel sad, uncomfortable or scared or nervous we will send you to see some people at the Emthonjeni Centre at the University of the Witwatersrand. They will help manage your feelings. You can call the Emthonjeni Centre and speak to Ntabiseng Modikane on 011-717-8663 or 011-717-4513.

This research project was approved by the Human Research Ethics Committee (HREC) at the University of the Witwatersrand. If you have any complaints, compliments or queries you can address them to the HREC on 011 717 1234.

Should you have any further questions, please feel free to contact any of us, or our supervisors at the below mentioned telephone numbers and we will be happy to assist.

Thank You and Kind Regards,

Daniel Greenslade 0835605017, Urvashi Chiba 0829049867, Shona Fraser 0827468865, Stephanie MacIlwaine 0844449917, Kelly Holland 0834496416, 0118722372 , Cindy van Wyk 072 279 7828, Jessica Rice 082 376 2980

Supervisors: Enid Schutte, Kate Cockcroft, Marilyn Lucas, Aline Fereirra-Correia

Medical Ethics number: ***M120268***

Appendix 9: Parental Consent Form (Control Group)



UNIVERISTY OF THE WITWATERSRAND, JOHANNESBURG

School of Human and Community Development

Private Bag X3, Wits, 2050, Johannesburg, South Africa

Tel: (011) 717 4500 Fax: (011) 717 4559

Medical Ethics number: ***M120268***

I, Mother/Father/Legal Guardian of

_____, give consent for my child/ward to participate in this study

I understand that:

- There is no risk or harm that could come to my child/ ward from taking part
- Participation is voluntary
- My child/ward, or I, may choose to stop the testing at any time, for any reason, with no penalty or loss of benefits.
- My child's/ ward's results will remain confidential
- No positive or negative consequences will follow from choosing to, or not to, participate

By allowing my child/ward to participate I state that:

- My child/ward has no history of epilepsy, Meningitis, HIV infection, Neurocognitive impairment , serious head injury nor or they taking chronic medication and does not live outside a nuclear family unit
- All the relevant information about this research has been explained to me and my child/ward, clearly and simply, and I understand the information

Signed: _____ Date: _____

Assigned Participant Number: _____

Appendix 10: Participant Information Sheet (Control Group)

School of Human and Community Development

Private Bag 3, Wits 2050, Johannesburg, South Africa

Tel: 27 (0)11 717 4524/5 Fax: 27 (0)11 717 4556

Hello!

Our names are Daniel Greenslade, Urvashi Chiba, Shona Fraser, Stephanie MacIlwaine, Cindy van Wyk, Jessica Rice and Kelly Holland. We are conducting research for the purpose of obtaining a Masters degree in at the University of the Witwatersrand. Our area of focus is young adolescents. We would like to invite you to take part in this study.

Your parents have to give consent to let you be part of the study and you will also need to give us assent (your permission) to participate in the study.

We are doing a Neuropsychological evaluation of Children attending the school. A neuropsychological evaluation involves using standardised tests to be able to describe an individual's cognitive strengths and weaknesses pertaining to mental processes such as memory, judgement, processing and reasoning.

If you, agree to join in you will be required to complete some drawing tasks, repeat some lists of words and numbers, identify some colours as well as try your hand with some cards. This may take between two to three hours to complete with rests in between. You will be provided with light refreshments half way through the tests.

Participation is voluntary, and you will not be advantaged or disadvantaged in any way for choosing to, or not to, participate.

Please be assured that confidentiality about the results between the researcher and you as a participant is guaranteed. The information we receive from the tests will only be seen by us and our research supervisors. No individual feedback can be given.. The grouped data collected may be used in publications or conference presentations, but no data that identifies you will be used. This means nothing will have your name on.

Please note that you will be free to stop the procedure at any time and no negative consequences will follow. You can simply tell the test administrator that you do not want to continue anymore. The information you provide will be kept confidential according to the rules and Regulations of the Health Professions' Council of South Africa. The regulations state that the information must be kept for 2 years if there is a publication and 6 years if the research is not published

While we are doing the different test, you feel sad, uncomfortable or scared or nervous we will send you to see some people at the Emthonjeni Centre at the University of the Witwatersrand. They will help manage your feelings. You can call the Emthonjeni Centre and speak to Ntabiseng Modikane on 011-717-8663 or 011-717-4513.

The tests will be administers at a room provided at the school. The test will be conducted after school and will not interrupt your learning

Should you have any further questions, please feel free to contact any of us, or our supervisors at the above mentioned telephone numbers and we will be happy to assist.

This research project was approved by the Human Research Ethics Committee (HREC) at the University of the Witwatersrand. If you have any complaints you can report them to the HREC on 011 717 1234.

Thank You and Kind Regards,

Daniel Greenslade 0835605017, Urvashi Chiba 0829049867, Shona Fraser 0827468865, Stephanie MacIlwaine 0844449917, Kelly Holland 0834496416, 0118722372 , Cindy van Wyk 072 279 7828, Jessica Rice 082 376 2980

Supervisors: Enid Schutte, Kate Cockcroft, Marilyn Lucas, Aline Fereirra-Correia

Medical Ethics number: ***M120268***

Appendix 11: Participant Assent Form (Control group)

UNIVERISTY
OF THE
WITWATERSRAND,
JOHANNESBURG

School of Human and Community Development

Private Bag X3, Wits, 2050, Johannesburg, South Africa

Tel: (011) 717 4500 Fax: (011) 717 4559

Medical Ethics number: ***M120268***

Hello,

We (Kelly, Daniel, Shona, Stephanie, Urvashi, Cindy and Jessica) are all students at Witwatersrand University and we are doing a study on adolescents at your school.

We are doing a Neuropsychological evaluation of Children attending your school. A neuropsychological evaluation involves using standardised tests to be able to describe a person's cognitive strengths and weaknesses. Meaning, your strengths and weaknesses of your mental processes such as your memory, judgment, processing and reasoning

We would like you to take part in the study but need your permission to do so. If you agree to join in you will be required to complete some drawing tasks, repeat some lists of words and numbers, identify some colours as well as try your hand with some cards.

If you are happy to take part we would like you to please sign to say you would like to join us. If you decide not to, that is okay and no one will be upset. If you decide to join and then later change your mind and want to stop, this is okay too.

Would you like to participate (*Tick **one** box*)

☐ Yes, I am willing

☐ No, I do not want to

Signing at the bottom of this form means that you agree to take part in this research.

Thank you very much,

Signed (You can just write your name): _____

Date: _____

Assigned Participant Number: _____

Appendix 12: Biographical Questionnaire

PART A: Participant Screening

To be completed by Case Manager/Doctor

(Only if all boxes ticked, proceed to details below)

Criteria for inclusion	
Age 13.5 upto but less than 16 years	
Vertically acquired	
First Line HAART	
No Traumatic Brain Injury, Meningitis or co-morbid conditions such as Downs Syndrome, Autism, Epilepsy *(* Note ADHD and HIVE **not** excluded)*	
Non-institutionalised (in family-type setting)	
Minimum of 4 years of schooling in English medium (includes repeated grades)	

Date…… Code……..

1. Gender: Male [1] Female [2]

2. D.O.B:…… 3. Age:…….(to confirm D.O.B)

4. Home Language: Sotho [1] Zulu [2] Xhosa [3] English [4] Afrikaans [5] Other [6]

5.	Age at which HAART initiated	
6.	WHO stage of HIV at diagnosis	
7.	CD4 T-cells count at time of HAART initiation	
8.	Viral load at time of HAART initiation	
9.	Current CD4 T-cell Count	
10.	Current Viral Load	
11.	Also add names of HIV medication details – dosage and names Any other chronic medication (eg. Ritalin etc).	

PART B: Biographical Questionnaire

Collateral/Home Information

I am going to ask you some questions about the home and family

12. Where does your ward/child live?.....

13. Can you talk about the type and number of rooms in the house?

	Yes	No
Bedroom?	1	0
If yes, how many?		
Bathroom?	1	0
Kitchen?	1	0
Living room?	1	0

14. Who lives at home with the child?

	Yes	No	
Mother ?	1	0	
Father?	1	0	
Grandmother?	1	0	
Grandfather?	1	0	
Mother's boyfriend?	1	0	
Father's girlfriend?	1	0	
Brothers?	1	0	How many?
Sisters?	1	0	How many?
Aunts?	1	0	How many?
Uncles?	1	0	How many?
Other?			

15. Who is the person that takes care of your ward/child most of the time?

Mother	1
Father	2
Grandmother	3
Grandfather	4
Aunt	5
Uncle	6

Sister	7
Brother	8
Mother's boyfriend	9
Father's girlfriend	10
Other	11……

16. Do the parents or guardians work?

	Yes	**No**	**If Yes: What kind of work do they do?**
Mother / female guardian only	1	0	
Father /male guardian only	1	0	
Both parents (mother and father)	1	0	

		Yes	**No**	**Don't know**
17	Have at least one of the parents/guardians passed grade 8?	1	2	3
18.	Are there more than 20 hardcover booked in the home?	1	2	3
19.	Does at least one of the parents/guardians read a newspaper or magazine once a week?	1	2	3
20.	Does the child/ward usually receive a present from their parents/guardians on their birthday?	1	2	3
21.	Is the attitude of the parents/guardians towards schooling positive or at least neutral?	1	2	3
22.	Is there enough money at home for basic things like food, clothes?	1	2	3
23.	Is there enough money to buy expensive things? (e.g. plasma TV)	1	2	3

	Is there:	**Yes**	**No**
24.	a TV that is working at home?	1	0
25.	a radio that is working at home?	1	0
26.	a hot water tap inside your home?	1	0
27.	a flush toilet?	1	0
28.	a parent/guardian who has their own car?	1	0
29.	a vegetable garden at home?	1	0
30.	electricity in the home?	1	0
31.	gas at home?	1	0
32.	a fridge at home?	1	0
33.	a bed that the child/ward sleeps on by himself/herself?	1	0
34.	a bedroom that the child sleeps in?	1	0

	If not, in what room does he/she sleep in?		
35.	Is he child sleeping alone in the bedroom?	1	0
	If not, who do you share it with?		

Does the child eat:

	Yes	No	What does he/she usually eat?
36.1 Breakfast?	1	0	
36.2 Lunch?	1	0	
36.3. Dinner?	1	0	

		Yes	No	Don't know
37.	Did the mother have any problems during her pregnancy with the child?	1	2	3
38.	Were there any problems during the birth?	1	2	3
39.	Did the child learn to walk, talk etc at an around the right age?	1	2	3
	Comments			

		Yes	No	If so, when and for what?
	Has the child/ward ever received:			
40.	psychotherapy?	1	0	
41.	physiotherapy?	1	0	
42.	occupational therapy?	1	0	
43.	speech therapy?	1	0	
44.	had your eyes tested?	1	0	
45.	had any other forms of treatment?	1	0	
	If so, what?			

Could you tell me about the languages spoken at home.

46. Language Context Information

Languages Used	Home	School	Friends	Mom	Dad	Grandparents
English						
Afrikaans						
Zulu						
SeSotho						
Xhosa						

(Tshivenda) Venda						
(Setswana) Tswana						
Siswati						
Ndebele						
(Xitsonga) Tsonga						
(Sepedi) Northern Sotho						

PART C: Participant Questions:

I need some background information before we start. I am going to ask you some questions about you starting with the languages you speak

47. Participant languages:

Languages	**Read**	**Write**	**Speak**
English			
Afrikaans			
Zulu			
SeSotho			
Xhosa			
(Tshivenda) Venda			
(Setswana) Tswana			
Siswati			
Ndebele			
(Xitsonga) Tsonga			
(Sepedi) Northern Sotho			

I'm going to ask you some questions about your school

48. What language do you learn in at school? ……(should be English but check)

49. What grade are you currently in? ……

50. Have you ever repeated a grade at school?

Yes	1	Which Grade?
No	0	

51. Have you been absent from school this year?

Yes	1	Why?
No	0	

52. What do you do straight after school?.……

53. What do you do when you get home from school?

……

……

		Yes	No	Don't know
54.	Do you smoke?	1	2	
55.	Do you drink alcohol?	1	2	
56.	If so, how much in a week?			
57.	Do you take drugs?	1	2	
58.	If so, how often and what?			
59.	Do you exercise regularly?	1	2	
60.	Are you in a relationship?	1	2	

Now I'm going to ask some questions about which hand you use to do things

		Left	Right	Both	Not sure
	Which hand do you usually use…				
61	To write a letter legibly				
62.	To throw a ball				
63.	To cut with scissors				
64.	To deal playing cards				
65.	To hammer a nail into wood				
66.	To turn a door handle				
67.	To unscrew a jar				
68.	To hold your toothbrush				
	Which foot do you use				
69.	To kick a ball				
70.	To step on a bug				
	Which eye do you use				
71.	To look through a vuvuzela				
72.	To look through a hole				

Clinical Impressions:

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