

Memory Functioning in HIV Positive Adolescents Receiving Anti-Retroviral Treatment.



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**Research Report submitted in fulfilment of the requirements for a Master
of Arts by coursework and research in Neuropsychology**

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Declaration

I hereby declare that this research report is my own independent work, and has not been presented for any other degree at any other academic institution, or published in any form.

It is submitted in partial fulfilment of the requirements for the degree of Masters of Arts in Psychology by Coursework and Research Report at the University of the Witwatersrand, Johannesburg.

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Abstract

In 2007 it was reported that an estimated 33 million people worldwide were living with the Human Immunodeficiency Virus (HIV). Of this, 35% (approximately 11.5 million) live in South Africa, most of whom were infected with HIV by mother to child transmission. Due to government legislation, until 2004, South Africans had limited access to Antiretroviral (ARV) treatment at and after birth. As a consequence, treatment of HIV was, at this time, only in government facilities, initiated after the clinical presentation of immune deficiency. This study compared the memory functioning of low socio-economic seropositive adolescents that were on a managed anti-retroviral programme to that of a contrast group that were HIV negative. The groups were matched for age, gender, demographics and educational level. The relative impact of variables such as duration of ARV treatment, drug regimen, WHO stage at diagnosis and CD4⁺ count were all considered.

Performance on a comprehensive neuropsychological battery was compared between the HIV positive group and their typically developing counterparts both in terms of memory functions as well as other cognitive processes that may have an effect on memory. The HIV positive group performed significantly below their HIV negative peers in processing speed, holistic processing, and spatial processing as well as specific visual functions such as visual constructional skills, visual recall ability, disruptions in both storage and retrieval of visuospatial information, and visual spatial working memory. No significant differences were found between the groups on tasks measuring verbal memory and verbal learning ability indicating that the neurocognitive profile of clade C HIV has a different presentation from the other clades.

The findings suggest that the preferential effect HIV has on the frontostriatal circuits in the brain impacts memory processes due to the destructive impact of the virus on the myelination of these circuits. As a result of the higher degree of white matter tracts in the right hemisphere, holistic and integrative processing is impaired and visuospatial functions are affected whereas verbal processes are largely spared. The resulting neurocognitive profile is similar to that of nonverbal learning disorders and may benefit from similarly constructed interventions such as placing more emphasis on verbal learning strategies and limiting dependence on visual information for HIV positive pupils.

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Chapter 1: Introduction and Literature Review

In 2007, an estimated 33 million people were living with the human immuno-deficiency virus (HIV) (Shisana, Rehle, Simbayi, Zuma, Jooste, & Pillay-van-Wyk, 2009). Sub-Saharan Africa is the most affected area, with over two thirds of the infected population worldwide living in this region (UNAIDS, 2012). 35% of this population lives in Southern Africa and are infected with clade C HIV (Shisana et al., 2009). Women and children are the most at risk for infection with vertical mother to child transmission being the primary mode of transmission in South Africa (Shisana et al., 2009; Wachslar-Felder & Golden, 2002). It has been estimated that 90% of children orphaned by AIDS worldwide live in Sub-Saharan Africa (UNAIDS, 2010).

The association between HIV and cognitive function has been well documented in adult populations (Andras, Wylegala, & Nath 2005; Lawler, Mosepele, Ratcliffe, Seloilwe, Steele, Nthonatsang, & Steenhoff 2010; Melrose, Tinaz, Castelo, Courtney, & Stern 2008; Singh, Joska, Goodkin, Lopez, Myer, Paul et al., 2010; Toborek, Woo Lee, Flora, Pu, 2005); fewer studies have explored HIV in paediatric populations. In addition, results are inconclusive due to either the smaller sample sizes or the broad age group of the population ranging from neonates to adolescents (Govender, Eley, Walker, Petersen, & Wilmshurst, 2011; Koekkoek, de Sonnevile, Wolfs, Licht, & Geelan, 2008; Sherr, Mueller, & Varrall, 2009; Wachslar-Felder & Golden, 2002). Results on neurocognitive profiles in children are consequently often generalised across age groups despite the diverse group differences. For the most part, studies on HIV in children have emerged from the USA and Europe, focusing on the clade B specific strain of HIV (Koekkoek, et al, 2008; Martin, Pitrak, Novak, Pursell, & Mullane, 2006; Tardieu, 1998; Wachslar-Felder & Golden, 2002).

In South Africa the lack of access to antiretroviral (ARV) treatment from birth between 1994 and 2004 was a result of government policy decisions based on misinformation about the toxicity of such treatment and resulted in low ARV treatment coverage for the majority of HIV positive people that accessed public healthcare. 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). However, many adolescents who were born prior to the policy change in 2004 may have been ARV-naïve and only been placed onto ARV's after presenting symptomatically. The aim of the current study was therefore to examine whether and, if so, how the memory profiles of young seropositive adolescents, currently on a managed anti-retroviral programme differ from those of an uninfected group of

typically developing adolescents. Both groups were matched as far as possible for age, gender, demographics and educational level.

Literature Review

Despite efforts to reduce the prevalence of HIV, the rate of new infection is still extensive, especially in sub-Saharan Africa with approximately 1.9 million new infections reported between 2007 and 2009. South Africa is home to the largest population of HIV-infected people in the world, which was believed to be 5.6 million in 2011 (UNAIDS, 2011). 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 the most affected by HIV due to the speed at which their immune systems are compromised, as well as the devastating effect the virus has on their development (UNAIDS, 2010).

In South Africa, the primary mode of infection in children is through vertical mother to child transmission. Vertical transmission can involve pre-natal, peri-natal or post-natal transmission, through breastfeeding, which has the highest survival rate (Newell, Coovadia, Cortina-Borja, & Rollins, 2004).

HIV and Anti-Retroviral Treatment in South Africa.

Prior to 1995, the prognosis for individuals with HIV in South Africa was dismal with disease progression rapidly leading to death. The advent in 1995 of triple combination anti-retroviral treatment (cART), also referred to as highly active anti-retroviral treatment (HAART), when combined with treatment compliance, dramatically increased life expectancy (Woods, Moore, Weber, & Grant, 2009). Individuals with HIV 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 (Civitello, 2003; Martin et al., 2006; Patel, Ming, Williams, Robertson, Oleske, & Seage, 2009). According to the UNAIDS fact sheet (2012), 2 million adults and children in South Africa had access to anti-retroviral (ARV) treatment by October 2012.

While morbidity rates have dropped substantially since the introduction of anti-retrovirals, HIV-induced disabilities have become of prime importance for both psychosocial and socio-economic reasons. 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 were only placed on ARV treatment based on the severity of clinical symptomology and/or viral loads with effective preventative mother to child treatment (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 effective PMTCT) initiated in that province from 1999 (Boulle et al., 2011).

Studies from the United States show that ARV-naïve children who were placed onto HAART after presenting symptomatically show greater neurocognitive deficits when compared to children who are placed on ARV's from birth due to the restrictive impact the treatment has on the progression of the disease (Laughton et al., 2010). Consequently, it is that South African children who were born HIV positive during this period (1994 – 2004/5), and who did not immediately receive HAART, would be inclined to widespread neurocognitive deficits that result from HIV on the developing brain, despite being placed on HAART several years after vertical acquisition (Smith, Adams, & Eley, 2008).

Neuropathology of HIV.

HIV 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 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 does not affect neurons directly but rather through viral factors (neurotoxic proteins produced by the HIV genome), host factors and co-factors (co-morbidities of the infected individual that may exacerbate pathogenesis of HIV such as drug and alcohol abuse) (Civitello, 2003; Ellis et al., 2009). 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).

Gp120 is a protein that is produced by infected glial cells that are responsible for the alteration of the glutamate pathway which results in the stimulation of the production of cytokines. It is this process that results in synaptodendritic damage of neurons, leading to cognitive dysfunction, as well as negatively affecting the activation of microglia and astrocytes (Ellis et al., 2009). In addition, transactivator of transcription (Tat) is another viral factor involved in neuronal injury and is specifically associated with mitochondrial dysfunction, dendritic loss, and cell death (Ellis et al., 2009).

Host factors are part of the secondary effect of HIV infection and involve pro-inflammatory cytokines and chemokines (Ellis et al., 2009). The activation of their receptors, which are 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, HIV encephalopathy (HIVE) and HIV associated dementia (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 injury or damage sustained to the neural networks may not inevitably result in death, but rather in reversible dysfunction. This suggests opportunity for treatment.

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 attention and executive functioning deficits, motor, and behavioural impairments (Wachsler-Felder & Golden, 2002).

Clade-Specific Neuropathology.

HIV infection can be classified according to different subtypes, or clades. As indicated in the introduction, 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 review, Sherr, Mueller and Varrall (2009) reported that 63% of the 111 studies on HIV and child development were performed in North America. This suggests that the majority of the literature available on HIV and child development focuses on HIV-1 clade B infection and there is a paucity of research on the developmental effects of clade C.

The incidence and severity of cognitive deficits, such as HAD, is more severe in North America when compared to parts of Asia and sub-Saharan Africa. Studies have suggested that the different clades of HIV affect the brain differently. HAD was found to be typical of

HIV-1 clade B infection, yet this was not as common in HIV-1 clade C infection, predominantly found in 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). It has been found that the clade C subtype is highly virulent as it is more effective at binding to immune cells (Kanki, 1999). As a result, the more virulent an effect a specific clade has on the immune cells of the body, the more severe and rapid the progression of the virus, and its associated illnesses, will be.

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 country to country (Rao et al., 2008). Some research has been conducted on the effect HIV has on neurocognitive development; however, there has been very little verification on the specific outcomes these effects have on children, who have been vertically exposed to the virus, in South Africa. The next section reviews the neurocognitive effects of HIV in childhood.

Neurocognitive Development and HIV.

It is well-known that the brain is vulnerable to disease in vitro, examples of these include spina bifida and rubella (Zillmer, Spiers & Culbertson, 2008). Thus, one can assume that HIV affects this early stage of neurodevelopment (Gay et al., 1995). Radiology studies with seropositive children have revealed some CNS abnormalities, such as cortical atrophy and calcification, especially in the basal ganglia and white matter in the frontal cortex (Belman et al., 1985; Belman et al., 1986; Civitello, 2003; Epstein, Berman, Sharer, Khademi & Desposito, 1987), as well as some evidence of myelinopathy (Gay et al., 1995).

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, deficits present in motor, cognitive and behavioural functioning (Wachsler-Felder & Golden, 2002). Englund et al. (1996) established that the neurological abnormality that appeared the most frequently in HIV positive children is motor dysfunction, which is consistent with the calcification and atrophy in the basal ganglia. HIV-associated progressive encephalopathy in children exhibits a loss of previously acquired motor achievements associated with corticospinal tract signs. In younger children, the acquisition of motor skills is noticeably abnormal and slower due to calcifications found in the basal ganglia (Wachsler-Felder & Golden, 2002).

In addition, myelination undergoes a significant burst during the first two years of life and continues throughout adolescence into adulthood. It is a critical process that ensures rapid and efficient communication between neural networks. There are different cytoarchitectural differences that exist between the two hemispheres (Goldberg & Costa, 1981). The left hemisphere has a higher ratio of gray matter to white matter while the right hemisphere has greater white matter to gray matter ratios. This indicates that there is an uneven distribution of white matter in the brain and there is a greater density of myelination within the right hemisphere (Rourke, 1989). According to Wachsler-Felder and Golden (2002), consequences of a disturbance in the process of myelination in the initial development of the child's central nervous system involve delays in language, sequencing and integration of information; resulting in quite diffuse cognitive impairment.

The extent to which neurocognitive development is compromised due to HIV is difficult to determine due to the plethora of heterogeneous environmental variables that contribute to each child's resulting neurocognitive profile. In this regard, Sherr et al. (2009) identified several methodological shortcomings with the local HIV paediatric literature, such as small samples with large age ranges, failure to document or homogenise the mode of HIV transmission, diverse demographics, and differences in the assessments used. The matter is complicated by the fact that there are no well established locally standardised assessment batteries for younger South African children. As a consequence, test interpretation, test appropriateness, and the accuracy of normative data often invalidate the understanding of the test results. Due to the absence of a standard local neuropsychological assessment battery, researchers employ different tests in their studies with the result that the research is not comparable (Wachsler-Felder & Golden, 2002). It has been suggested that tests be conducted on groups with a narrower age band so as to adjust for age differentials (Wachsler-Felder & Golden, 2002). With this in mind, the current study focused on a demographically homogeneous group of 13 – 15 year olds on a managed ARV programme. However, there were difficulties obtaining a large sample due to the exclusionary criteria selected for this study, as well as the logistical challenges experienced with individual testing.

Possibly due to the difficulties that arise in the methodology of such research, a limited number of earlier studies have explored the neuropsychological sequelae of HIV positive children (Koekkoek, de Sonnevile, Wolfs, Licht & Geelan, 2008; Martin, et al., 2006; Patel, et al., 2009; Smith, Adnams & Eley, 2008; Wachsler-Felder & Golden, 2002). During the time that preceded HAART treatment in South Africa, HIV induced dysfunctions, as well as opportunistic infections of the central nervous system, resulted in pervasive

neurodevelopmental delays in HIV positive children. Markers of these delays included behavioural changes, psychomotor impairment, and progressive cognitive deterioration associated with a decline in academic performance (Civitello, 2003). In order to explore possibilities for the prevention of rapid further progression of this impairment, research was undertaken which indicates that the age of commencing HAART is an important predictor for neuropsychological outcome and that the earlier a child is treated for HIV the better their neurocognitive prognosis (Smith, Adnams, & Eley, 2008).

Since differences in the brain develop at different times, they will be differentially affected by HIV. According to Brouwers et al. (1995), significantly more adolescents are diagnosed annually with neurological impairments in South Africa when compared to adolescents in Europe, which is possibly a function of greater infection rates. Unlike the European situation, not only is the clade of HIV different, but the South African context is also considerably different, specifically in the low socio-economic bracket. Against this background, this includes the extrinsic and intrinsic factors to HIV infection, memory functioning needs to be evaluated in terms of how it may be affected by HIV. This knowledge is fundamental given the broad involvement memory has on many other cognitive functions, especially for learning and development. Thus the focus of the effects of this research was on the effects of HIV on one aspect of neurocognitive functioning, namely memory.

Memory.

Memory, as a cognitive construct, covers a broad base; it is in no way a unitary function. The neurological and conceptual diversity of memory function and its processes has prompted a need to organise the systems in such a way so as to facilitate understanding. The following section will briefly explain the neural and cognitive mechanisms of these systems as well as the purpose and functions of the memory systems themselves.

Perception of the world enters the memory system through the initial selection, recording, and processing of information by the sensory receptors (Lezak, 1995). This sensory memory encompasses iconic memory, which is primarily visual and echoic memory, which is predominantly auditory. Other types of sensory memory include kinaesthetic memory, which is primarily tactile, and olfactory memory, which is related to smell. Once this information is registered, it is further processed into short-term memory storage. Short-term memory retains information that is currently in use (Cameron, Haarmann, Grafman, & Ruchkin, 2005). The function of short-term memory is to temporarily store a limited amount of information; this includes names, digits, or thoughts that, once internalised, guide behaviour (Lezak, 1995;

Purser, et al., 2012). Although the term “short-term memory” is often used interchangeably with that of “working memory”, the two are actually separate, but related, processes. Working memory is the active component of short-term memory that allows one to manipulate and process information for a limited period (Purser et al., 2012). Short-term memory refers to the passive, temporary storage of information without any processing.

The most popular model of working memory is that of Baddeley (2000) which specifies that working memory has several working parts, rather than being a unitary entity. The core of this model is the central executive, which may be likened to an accomplished processor that is able to monitor and regulate general activity and control resources (Alloway, Pickering, & Gathercole, 2006). Temporary storage of verbal information is made possible by the phonological loop, while the preservation and manipulation of visual and spatial depictions is mediated by the visuospatial sketchpad. Information across each of the domains, as well as information maintained in long-term memory systems, is integrated by the episodic buffer (Baddeley, 2000). The capacity of working memory is measured by tasks that necessitate short-term memory storage while concurrently processing additional information, an example of which is mental arithmetic. Performance on such tasks is a reflection of the functioning in either verbal or visuospatial ability and is subject to individual variation and developmental differences (Alloway, Pickering, & Gathercole, 2006). Short-term memory tasks differ from those of working memory as the former only draw on basic passive storage skills, thus limited requirement is placed on information processing as opposed to the complex and demanding processing required by working memory tasks (Alloway, 2006). Consequently, short-term memory tasks are often referred to as simple memory tasks and working memory tasks as complex memory tasks. Thus the term working memory is used to encompass all of these processes.

The relative capacity of working memory differs between individuals; this has an effect on the potential of the child to acquire knowledge and their ability to learn new skills (Alloway, 2006). Working memory affects academic performance both in terms of reading and mathematical ability. Reading achievement may be predicted by both working memory tasks and verbal short-term memory tasks independently of one another (Swanson, 2003). Rather than a processing impairment in verbal short-term memory, this dissociation may be due to the limited capacity for the processing and storage of information in working memory. Should this be the case, the reading disabilities associated with working memory deficits in typically developing children do not spontaneously improve (Swanson & Sachse-Lee, 2001). Furthermore, differential mathematical deficits may be attributed to poor working memory

skills (Alloway, 2006). Verbal short-term memory is responsible for temporary number storage while the child is attempting a mathematical sum. Visuospatial memory skills facilitate this process by acting as a blackboard upon which the numbers may be represented (Heathcote, 1994). Nevertheless, general mathematical skills are a function of the ability to hold and manipulate numerical information in order to solve mathematical problems (Furst & Hitch, 2000). This emphasises the need for adequate development of working memory in young children. Therefore, short-term memory and working memory perform together to facilitate optimal learning in children.

Working memory functioning can be fractionated into verbal and visuospatial skills, which are each essential components of working memory. There are specific frontal cortical areas involved in memory for visual objects and visuospatial abilities, particularly the dorsolateral prefrontal cortex which has been implicated in short-term memory function (Banich, 2004). This differs from the neural correlates implicated in the verbal component of working memory. This constituent may be further separated into the phonological store, which correlates with the left supramarginal gyrus, and the subvocal rehearsal system, which is associated with Broca's area (Paulesu, Frith, & Frackowiak, 1993). In addition, the sensory areas of the posterior parietal and temporal cortices are associated with working memory (Banich, 2004).

Ericsson and Kintsch (1995) propose an alternate working memory model to that of Baddeley (2000). They postulate that working memory capacity may be expanded upon through the acquisition of domain specific knowledge, as well as memory strategies that are responsible for the rapid encoding of this knowledge into long-term memory and, subsequently, the rapid retrieval of this information. In this way, the process of working memory relies, to an extent, on the effective encoding of domain specific information into long-term memory and the consequent association of this information with retrieval cues. Ericsson and Kintsch (1995) refer to this relationship, between working memory and long-term memory, as skilled memory whereby long-term memory and working memory are mediated by reliable retrieval structures that allow for an expansion of short-term memory capacity. Essentially, should an individual experience proactive (the ability to inhibit old information in order to learn new information) or retroactive (difficulty recalling old information because of newly learned information) interference, the model proposes that this can be overcome through the mechanisms of recency and elaboration. Recency refers to the ability to use temporal information about the time around which information was encoded as a retrieval cue in and of itself. Thus, there is no need for additional elaboration in the process of retrieving the

targeted information. Elaborative encoding is somewhat more complex in that it relies on the associations of not only a retrieval cue, but also the formation of additional semantic links between the encoded information as well as retrieval structures for activities that require long-term retention. The principal assertion of this model allows for the mechanisms of long-term memory and working memory to dovetail together in such a way that allows for the expansion of the capacity of working memory through the development of effective methods of storing information in long-term memory in such a way that allows for rapid accessibility.

Long-term memory functions in parallel with working memory (Purser, et al., 2012), by encoding the information for later retrieval (Banich, 2004). Unlike working memory, long-term memory has an unlimited capacity that is able to store information for varying periods of time (Lezak, 1995). The hippocampus is implicated in the encoding, consolidation, and retrieval of learned information (Lopez et al., 2012). The hippocampal circuit is highly plastic and is the initial site for encoding new information (Carr, Jadhav & Frank, 2011). In addition, the hippocampus interacts with both cortical and subcortical neural regions in order to establish long-lasting representations in hippocampal-neocortical circuits.

Long-term memory is separated into implicit and explicit memory. Implicit memory, or non-declarative memory, is an unconscious memory system in which information is acquired without awareness (Moscovitch et al., 2005). Procedural memory is one form of implicit memory that is the means by which motor skills and language are attained (Winters, Saksida, & Bussey, 2008). Implicit information is not processed at higher cortical levels but is dependent on intact striatal structures and is stored independently of the temporal lobe (Moscovitch et al., 2005). Implicit memory was not assessed in this study. The focus of this study has an aspect of explicit or declarative memory, with its conscious and intentional recollection of experience (Hunsaker, Tran, & Kesner, 2008). Explicit memory includes the ability to learn about and to remember perceived information (Lezak, 1995). Conceptually driven processing allows for an individual to re-organise information in such a way that, when it is stored effectively, later recall of that information is accurate (Hunsaker, Tran, & Kesner, 2008). Thus, the efficacy of storage is fundamental.

Explicit memory is generally separated into episodic and semantic memory (Heaton, Marcotte, Rivera-Mindt, Sadek, & Moore, 2004). Episodic memory is autobiographical in nature as it is the memory that represents the past personal experiences of the individual that are founded in a subjective time and within a specific spatial context (Kolb & Whishaw, 2004). Prospective memory is a function of episodic memory, where a memory is needed in

order to remember to perform a task at an appropriate time. There are two types of prospective memory; the first is time-based prospective memory, where a particular point in time necessitates that an action be carried out. The second is event-based which involves the memory that a specific task needs to be completed in the presence of a specific condition. These memories are externally mediated. Event-based prospective memory has two components. Immediate-execute tasks require an immediate response to a stimulus while delayed-execute tasks there have a delay between the perceived instruction of the task and the action that the task requires to be carried out (Brandimonte, Einstein, & McDaniel, 1996).

Consolidation, or the progressive stabilisation of memories over time, in the neocortex largely depends on the reactivation of associations that have been previously encoded by the hippocampus and generally occurs during sleep (Carr, Jadhav & Frank, 2011). In order for encoded experiences to be consolidated into long-lasting memories, it is necessary that the consolidation process endures for a period following the individual's actual experience. As a result of this ongoing processing, memories are encoded in distributed networks in the brain. The Multiple Trace Theory of Consolidation (Nadel & Moscovitch, 1997; 2001) differentiates between the neural mechanisms responsible for the consolidation of episodic and semantic memories. According to this theory, all information that is attended to is encoded rapidly in the hippocampal complex. The neurons in the hippocampal complex connect with the neocortical neurons in the region of the brain that best represents that information. This hippocampal-neocortical connection comprises the episodic memory trace, thus each time the memory is retrieved that trace is activated and intensified with the creation of a new and overlapping trace.

Essentially, as a result of a trace multiplication process, an episodic memory is strengthened within the hippocampal-cortical connection, thus facilitating a continued dependency of episodic memories on the hippocampal complex. Each time related episodic information is consolidated in this manner the hippocampal complex creates a new, but integrated, trace which results in a network of interrelated memory traces. The creation of these networks of episodic memory traces allows semantic knowledge that has been encoded by the hippocampus, as part of the episodic memory consolidation process, to be stored independently of these memories in the neocortex. Thus, as semantic information is reactivated it will gain a higher degree of independence from the hippocampal complex. This process allows for learning to occur. As a result, through a better understanding of memory in this population their learning ability may also be explored.

Lesion studies have confirmed that the hippocampus has a fundamental role in the retrieval of stored memories (Fortin, Wright, & Eichenbaum, 2004; Squire, Clark & Knowlton, 2001; Tulving & Markowitsch, 1998). Once a memory is retrieved the internal representation of the initially encoded experience is reactivated. This occurs instantaneously, thus indicating that memory retrieval occurs within a compressed time frame (Carr, Jadhav & Frank, 2011). The retrieval of a memory may be facilitated by the sensory input that one experiences in their environment; therefore a memory may be cued by a sensory stimulus. According to Eichenbaum and Cohen (2001) the hippocampus is intrinsic to the retrieval of a memory that has been consolidated in distributed hippocampal-neocortical circuits as the structures responsible for the encoding and consolidation of a memory will be reactivated when that memory is retrieved. These processes utilise neural circuitry that is involved in facilitating integrative functioning for the effective storage and retrieval of memories (Carlson, 2007). HIV has a destructive effect on the myelination of these circuits, thus hindering the development of these circuits which are essential for the processes of storing and retrieving information.

Reviews of lesion studies have revealed results that suggest that retention and recovery of autobiographical memories consistently depend on the hippocampus, whereas the retrieval of semantic memories predominantly relies on extrapyramidal areas and merely benefit from the activation of the hippocampus (Maguire & Frith, 2003; Moscovitch, Rosenbaum, Gilboa, Addis, Westmacott, Grady et al., 2005). This suggests that the unified notion of the Multiple Trace Theory of Consolidation is favoured as developing a parsimonious account of the functioning of memory retention and related neural structures. Banich (2004) postulates that the amount of hippocampal activity that occurs during encoding predicts how well information is remembered. In addition, the degree to which the hippocampus is activated during information retrieval is related to how well that information was initially remembered. Thus, learning is a crucial function of long-term memory. Once this information has been encoded into long-term memory the learnt material is consolidated or strengthened in order for the retrieval process to be successful (Banich, 2004).

The Multiprocess Framework of Prospective Memory (McDaniel & Einstein, 2000), suggests that prospective remembering is supported by several processes, both automatic and controlled. These processes depend on several factors. The subjective importance placed on a task will facilitate the extent of attentional resources required for the strategic processing used for that task. The attentional processes utilised in prospective memory are not a function

of the initiation of the executive system, which is essentially involved in active planning and problem solving responses, but are rather associated with a developed external attentional system which is responsible for the production of involuntary orienting responses. Thus, targeted, subjectively important prospective memory events involuntarily acquire attention resulting in the retrieval of the task to be remembered using limited attentional resources. In addition, the more distinct the targeted prospective memory events are, the higher the likelihood of remembering the associated task. The extent to which a targeted prospective memory event is associated with the task that is to be remembered, increases the possibility that that task will be remembered. This is due to the nature of the prospective memory process whereby awareness for the targeted stimulus is distributed automatically when the stimulus is associated with the prospective memory event. Therefore, the more adequate the association, the more effortless the process of remembering will be.

In so much as parameters are necessary for the targeted stimulus, parameters for the ongoing task are essential in order for the memory not to be confounded by multiple activities or unrelated stimuli. Should an individual be involved in an ongoing processing task, the focus of the embedded features of the target associated with the intended action may be disorientated by the demands of the current task. In such instances, the individual would need to implement a self-initiated strategic process. Essentially, if the association of the targeted stimulus with the prospective memory event is high and the context is not demanding then the prospective memory process will utilise automatic attentional resources. In contrast, the weaker this association and the more complex the environment, the more likely the prospective memory process will assume a more strategic and controlled approach to the retrieval of the memory. Furthermore, the ongoing activity may vary according to how demanding it is, thus having an effect on how engaged the individual needs to be in order to effectively complete the task. The extent to which an individual is engaged with a task limits the resources that are available for utilising strategic approaches to remember the prospective task. However, the extent to which an individual may rely on automatic prospective memory processes depends on the effectiveness and degree of planning that is required for a given task. If one is engaged in a demanding ongoing task one would need to employ a reliable planning strategy in order to rely on automated awareness of targeted stimuli required for prospective remembering. Alternatively, the less complicated and demanding one's environment is, the less effort will need to be utilised in the planning process as the available resources for remembering will not be used in the completion of more engaging tasks.

Importantly, the prospective memory process is highly dependent on the individual's personality style and working memory capacity (McDaniels & Eistein, 2000).

While, autobiographical and prospective memories comprise one aspect of explicit memory, the second aspect of explicit memory is semantic memory, which is the memory for general knowledge that is not stored within a contextual framework (Banich, 2004). In addition to general facts about the world, semantic memory includes external information necessary to read, to do mathematics, and recognise people and places. Semantic memories were once episodic memories where the personal detail associated with the memories have faded. Collins and Quillian (1969) developed a model of semantic memory that was based on the assumption of the structure of semantic memory as well as the processing of retrieving information from this structure. The structure of semantic memory has been likened to a network of knowledge that represents a related set of concepts, with each concept characterised a node within this network. Each of these concepts is connected to one another by means of pathways that are correlated with one another in the network (Collins & Quillian, 1970). Reisburg (1997) used the analogy of the way in which two cities are essentially connected to one another by various means, such as direct highways or indirect roads. Each node is, in much the same way, associated with every other node. Each connection is representative of the proposed relationships between two concepts.

The model describes one principal process that is responsible for the functioning of this network. This process is known as spreading activation and it is the means by which information from this network is accessed and retrieved through mental activity. The process of retrieval occurs when a concept is activated. The activation extends directionally throughout the network consequently activating other nodes so that the meaning of a concept may be retrieved. Concepts that have close connections to the activated node are first to receive the spreading activation, therefore closely related concepts become accessible for retrieval. Most often more than one concept is activated simultaneously, thus there are multiple activation patterns within the network. Should two activation patterns intersect, there is a decision stage whereby the conceptual pathway that holds the most validity is selected over less valid concept relations (Collins & Quillian, 1970).

Effectively, semantic memory and episodic memory are linked. As mentioned earlier, episodic memory leads to semantic memory but the specific episodic information fades. Physiologically, explicit memory is dependent on the hippocampal system in the medial temporal lobe (Moscovitch et al., 2005). The neural circuitry for the processing of explicit

memories involves the thalamus, prefrontal cortex, amygdale, and the rhinal cortices in the temporal lobe (Kolb & Whishaw, 2004). However, there is some difficulty locating the neurophysiology of memory due to the involvement of multiple individualised senses and experiences. The frontal lobes have been implicated in the encoding and retrieval of long-term memories, damage to the frontal systems of the brain results in the impaired use of context for the storage and retrieval of information (Bosshardt, Schmidt, Jaermann, Degonda, Boesiger, Nitsch et al., 2005). More specifically, the ventrolateral regions of the prefrontal cortex are involved during the acquisition and encoding of information. In order to ensure the accurate formation of memories, these regions work together with the hippocampus (Banich, 2004). For the most part, it is difficult to locate the neurophysiology of memory due to the involvement of multiple senses and experiences.

HIV and Memory.

Memory deficits are common in children with vertically acquired HIV infection, particularly impairments in working memory, semantic memory, verbal memory, and visuospatial memory, since HIV preferentially affects the fronto-striato-thalamo-cortical circuits of the brain (Boivin, 2010; Petito, 2004). Markedly poor performance in terms of verbal learning and recall has been found in children with HIV CNS disease (Gendelman, 2005). These memory impairments stemming from HIV infection have an understandably significant impact on the academic performance of these children. Notably, HIV positive children who have been HAART naive have been found to be “slow progressors” at school (Hoare, Fouche, Spottiswoode, Donald, Phillips, Bezuidenhout, et al., 2012). In particular, working memory is preferentially affected by HIV due to the effect of the infection on the fronto-temporo-thalamo-cortical system, the location of the central executive in working memory (Bassel, Rourke, Halman, & Smith, 2002). As a result of this, the individual’s ability to manipulate and temporarily store verbal and visuospatial information declines dramatically (Goldman-Rakic, 1995; Petrides, 1995, 1998). Specifically, significant deficits have been found in verbal working memory in the HIV positive adult population (Schiller, Foley & Burns, 2009). Since working memory has a direct impact on attention, HIV positive individuals also experience difficulties with the modulation of attention.

Chang et al. (2001) suggest that the fronto-striatal 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). There is presently very little research on the

effects of HIV on visuospatial memory and, in what literature there is, the results are conflicting (Schiller, Foley, Burns, Seller, & Golden, 2009). Several studies have found visual reproduction deficits in an HIV positive sample and hypothesised that visual recall abilities were significantly more impaired than recognition ability (Delis et al., 1995; Peavy et al., 1994; Poutiainen, Haltia, Elovaara, Lahdevirta, & Iivanainen, 1991). In contrast, studies have shown that there are no visual memory deficits whatsoever in the HIV positive population (Becker et al., 1995; Reidel et al., 1992; White et al., 1997).

Research suggests that the impairment in memory processing in HIV positive populations is mostly evident in memory retrieval and recall, whereas the function of memory recognition remains somewhat spared, suggesting that memory storage is minimally affected (Delis, et al., 1995; Peavy, et al. 1994; White, et al. 1997). As such, despite having impairments in memory acquisition individuals who are HIV positive tend to perform better when they are provided with cues rather than on free recall tasks (Sadek, et al., 2004). Memory consolidation neural circuits in the hippocampal complex extend to the thalamic and orbital frontal areas as information is encoded and stored in the brain. Thus, damage to the entorhinal cortex or the pathways from the orbital frontal gyrus to the hippocampus, due to the effects of HIV, will have a direct effect on the individual's ability to encode and consolidate information (Blumenfield, 2002; Frey & Petrides, 2002; Laroche, Davis & Jay, 2000).

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.

In addition, HIV positive individuals experience difficulty in utilising the necessary complex cognitive strategies needed for the performance of actions facilitated by the future intentions of prospective memory (Carey et al., 2006). Deficits in prospective memory have been measured in the adult population and have been found to be due to the effect HIV has on the fronto-striatal circuits as a result of an inability to strategically encode and retrieve retrospective episodic memory. This, in turn, has a profound effect on an individual's potential for episodic learning. According to Murijs et al. (2003), difficulties with encoding information, and subsequently effectively organising it in order to engage in planning, adversely influences the efficiency of the retrieval of that information. Prospective memory

failures occur on tasks that are both event-based and time-based in nature, thus the cause is most likely in the phase of encoding the information, regardless of the specificity of the cue provided to aid retrieval (Henry et al., 2004).

The HIV infection targets neural systems found in the striatum and basal ganglia (Gendelman, 2005). Subcortical atrophy in these regions gives an indication of possible deficits in procedural memory. This may also have a pronounced effect on an individual's ability to perform psychomotor tasks necessary for everyday life, such as riding a bicycle (Boivin, 2010). However, studies have postulated that deterioration of the memory processing systems may not be targeted themselves by the HIV, but rather it is the decline in general cerebral deficiency that is responsible for memory processing impairment (Bassel et al., 2002). Sadek et al. (2004) found that the memory profile of an HIV positive population was qualitatively similar to that of Huntington's patients indicating that much of the neurological compromise is subcortical. However, these reported studies have been conducted on an adult population and significantly less is known about the memory profiles of children and adolescents affected by HIV.

External and Internal Factors that Influence Memory Functioning.

In addition to the biological properties of the brain, a multitude of social, medical, and psychiatric factors may influence the performance on neuropsychological tests. Grant et al. (1987), as well as Woods and Grant (2005), examined the relationships between the neuromedical, psychiatric, environmental and test characteristics that affect a child's neuropsychological test performance. Certain factors affect neuropsychological performance directly, namely demographic factors such as age, gender, language, race and socio-economic status (Woods & Grant, 2005). It is therefore essential that an attempt is made to match these factors as far as possible when comparing the neuropsychological performance of HIV positive and HIV negative individuals. The inclusion of an HIV negative contrast group is especially important in the South African context as few (if any) neuro-cognitive tests are normed for the South African adolescent population. Thus, an appropriate comparison group from the same language, education and socioeconomic background is necessary.

Language in the context of neurocognitive assessment is a challenging factor in South Africa as it is not only diverse in and of itself, but it is also representative of the plethora of heterogeneous cultures and ethnicities South Africans identify with. It was not possible to determine whether English was exclusively spoken at the schools these participants were attending due to the partial implementation of the Revised National Curriculum Statement's

(RNCS) language policy. This language policy uses an additive approach to bi- or multi-lingualism, where the first language is maintained and used as a basis for the learning of another language (The Advisory Panel on Language Policy, 2000; Chick & McKay, 2001). 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, pp. 37). However, since South Africa has eleven official languages, this creates logistical difficulties which, together with the widespread preference for education in English, results in the RNCS language policy only being partially implemented (Adler, 2001; Department of Education, 2002; Vesely, 2000).

Due to the partial implementation of the language policy, South African educators face the challenge of large numbers of English Speakers of Other Languages (ESOL) learners in their classes (PANSALB, 2000). In this respect it is important to draw the distinction 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" (Cummins, 2000, pp. 28). Although the participants in the current study may be able to use English competently with their peers and in social settings (BICS), they may not necessarily 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 between five and seven years to reach the same level as their first-language peers in terms of CALP (Cummins, 2000; Hall, 1996). Since the participants in this study were in Grade 8 to 10 they may just have reached that level, assuming that they had sufficient English teaching from Grade 1.

In addition to language factors, neuromedical factors other than HIV can also severely affect test performance. These factors include premorbid or co-morbid diseases which include central nervous system diseases, trauma, psychoactive medications, substance abuse, systemic illnesses, psychiatric conditions, developmental disorders and learning disabilities. Substance abuse has a notably high co-morbidity rate in HIV infected adults; this may be a result of risky lifestyle behaviours that include sexual promiscuity. The impact of various legal or illicit drugs on the brain and cognitive functioning may strongly confound the neuropsychological performance on tests (Woods & Grant, 2005). These factors need to be carefully considered when interpreting disparities in results. In an attempt to control for their potential confounds, these factors informed the exclusion criteria that were utilised in this study. Woods and Grant (2005) propose that the neuropsychological findings will also be

varied according to the disease characteristics such as the disease markers (viral load in the cerebrospinal fluid), effectiveness of treatment and opportunistic infections. This data was captured in the current study so that comparisons may be drawn.

Internal factors influencing neuropsychological performance include mood, fatigue and effort. As a result of the progression of HIV, the adolescent may suffer fatigue and a lack of motivation, specifically in the later stages of the disease. This plays a major role in affecting the child's ability to complete and excel on many of the tasks in the neuropsychological battery. Mood disturbances are another theoretical confound in neuropsychological assessment of HIV individuals, most specifically depression. The prevalence of major depression is elevated in HIV positive children as well as seronegative individuals that have a high risk for HIV infection (Woods & Grant, 2005). For these reasons children with any neurological or psychological compromise were excluded from the study.

Since both external and internal factors play such a vital role in performance, due consideration was taken to ensure that a fairly homogeneous neurocognitive test sample was obtained. Within group clinical variations, such as duration of ARV treatment, drug regimen, WHO stage at diagnosis and CD4⁺ count were considered in the final analysis.

Rationale for the Study

The literature reviewed in this study provides 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). Given that HIV attacks the white matter tracts in the fronto-striatal brain areas, it is highly likely that memory is affected. Given the importance of intact memory functioning for learning and academic success, it is crucial to know if and how various aspects of memory differ in HIV positive and negative adolescents.

From a practical perspective, anecdotal evidence from medical practitioners and educators alike suggests that learning difficulties are more prevalent in HIV positive children. Moreover, given the history of South Africa, ARV-naïve children are also suspected of having the added disadvantage of only being placed onto an anti-retroviral regimen on presentation of clinical symptoms such as encephalitis, tuberculosis or pneumonia. By this time, some CNS functionalities may have already been compromised.

Given that a proportion of the South African population were denied this initial treatment at birth, the aim of this research was to provide a neuro-cognitive profile of the memory function of HIV positive adolescents currently on a managed ART programme. Based on the

literature reviewed in this chapter, it is hypothesised that HIV positive adolescents on HAART will have significantly poorer memory functions than a comparable group of HIV negative typically developing adolescents.

It was envisaged that this research would provide initial insight into these aspects of memory function so that appropriate psycho-therapeutic or psycho-educational interventions can be explored so as to optimise the psychological functioning and potential of the HIV positive child.

Research Question

Is there a significant difference in the memory functions between HIV positive adolescents and a matched group of HIV negative typically developing adolescents?

Chapter 2: Methods

This research compared the memory functioning of HIV positive adolescents receiving HAART and a typically developing group, matched as far as possible in terms of age, level of education, gender, and demographics. The data was captured in the form of two data sets for each group, namely a demographic data set gained from a biographical questionnaire and the results of the performance on the neuropsychological assessment battery.

Research Design

This research examined the cognitive characteristics of these participants to determine whether there are differences in an HIV positive group receiving ARV treatment in comparison to healthy contrasts. The trends of the variables were examined and there was no attempt to manipulate them in any way. Therefore, the design is an ex post facto, non-experimental, cross-sectional design.

Participants

Participants comprised two groups, an HIV positive group and an HIV negative typically developing group. These groups are described separately below. All participants were between the ages of 13 and 15 years old. The reason that this age range was selected was predominantly because, at the time they were born, there was limited access to ARV treatment from birth as there was no government rollout of ARVs (Butler, 2005). Thus, the HIV positive participants in this study were only treated with ARVs once they presented with an opportunistic infection or compromised immunity which may have occurred at any age. In this way, this sample is representative of the population that were ARV naive for some period of time and were subsequently not treated until a later stage. As a result, this study may provide some insight into the neurocognitive sequelae that occur when HIV is left initially untreated. The contrast group was matched as far as possible for age in order to compare the neurocognitive functioning of the HIV positive group with that of their typically developing peers.

This study adhered to relatively stringent inclusion and exclusion criteria. The sample base consisted predominantly of Black and Coloured, low socioeconomic adolescents, who spoke 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. For ethical reasons, as well as research evidence that institutionalisation brings with it its own set of neurobiological sequelae, children without parents or guardians were excluded from the study (Woods & Grant, 2005). Based on similar

neurobiological reasoning, additional exclusion criteria included children with any form of neurological compromise such as Epilepsy, Meningitis, and Traumatic Brain Injury in order to reduce the confounding effects of other neurological impairments on test performance. Thus the two samples were as follows:

HIV Positive Sample.

Purposive sampling was used to obtain participants for the HIV positive group. This was conducted at a government clinic. The HIV positive participants were each diagnosed with vertically acquired HIV by a clinician independent of this study. Each participant was on a managed Highly Active Antiretroviral Therapy (HAART) treatment program and was attending regular checkups at the local clinic. Nurses at the clinic who had access to their clinical files were able to screen for any previous neurobiological complications. Each participant was accompanied by their guardian who confirmed that they had received at least four years of English medium schooling. In total, the experimental sample consisted of 30 HIV-positive adolescents who each met the inclusion criteria.

Contrast Sample.

Purposive and snowball sampling were used to obtain participants for the contrast group. English medium primary schools and high schools in Soweto were approached to invite students to participate in this research. The contrast group was recruited from Soweto in order for the demographics of the two groups to be as similar as possible. Parental consent included acknowledgement of the inclusion criteria, including a negative HIV status. The total number of participants in the HIV-negative contrast sample was 69. These groups were matched as far as possible for gender, educational level, and socioeconomic status, the latter was operationalised by the area in which they live.

Ethical Considerations

This study followed the ethical guidelines for research with human subjects outlined by the Health Professions Council of South Africa (HPCSA) and the University of the Witwatersrand Codes for Research. Permission for testing the HIV group was obtained from a Primary Health Care Clinic (refer to Appendix F) while permission for testing the contrast group was obtained from the Department of Education (Appendix G).

Several participants were above the age of assent, but not above the age of parental or guardian consent. Thus, the legal guardian of the participant was required to fill in a consent

form (Appendix A; Appendix B) and the participants themselves were required to complete an assent form (Appendix C; Appendix D). Participants were assured that the data would be kept confidential, and would only be used for research purposes. The children in the HIV-positive sample all attended 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 participants were informed that the research was investigating the effect of the medication the child was receiving and the effects of HIV itself were not elaborated on.

Confidentiality was maintained and where the participants required any further information, this was provided in collaboration with the medical officer consulting on the case. If any participant, for any reason, experienced distress, they were provided with the contact details of free counselling services. However, as the participants needed to be physically present for the testing, there was no anonymity. The data captured were assigned codes.

All of the tests that were performed are non-invasive, manual, pen-and-paper style tests and therefore there was no harm and minimal risk in the participation. If the participant felt fatigued or uncomfortable at any time they were given a break between the tasks. The participants and their guardians were informed from the outset that there would be no negative consequences should the participant wish to withdraw at any stage. As the testing process took a few hours, light refreshments were provided for the participants. Those participants who had to travel to the hospital for the purpose of testing, rather than routine check-ups, were reimbursed their travel expenses. In these instances, participants were asked to attend testing sessions that occurred during the school holidays at their local school to prevent absenteeism. Reports were written for each participant regarding their performance on the neuropsychological assessment battery and were added to their medical files.

Procedure

Data gathering occurred at a local government hospital, one of the University of the Witwatersrand Medical School's three teaching hospitals, in the first half of the year. The hospital holds clinical check-up days on Wednesdays. Nurses at the clinic screened the files of the patients attending the clinic that day following a meeting comprehensively outlining the study's exclusion criteria. Patients who met the inclusion criteria were approached to participate in the study. A neutral party, an employee at the clinic, invited the child and guardian to participate in the study while they were waiting for their visit with the doctor. This was implemented to ensure that the patients and their guardian felt that they may decline

without the fear of negative consequences. Consenting participants were tested directly after their regular clinical check-up.

Quiet venues for the testing process were organised within the psychiatry ward of the hospital. There were nine assessors overall and each had received the same training in the administration of the test battery. Testers included six Masters students in Clinical Neuropsychology and three psychometric interns. Four assessors were present at each session.

Participants and their guardians had the process of the research explained to them and were then asked to complete a written consent form (Appendix A) and assent form (Appendix C). In cases where the guardian was neither literate nor proficient in the English language a medical professional at the clinic assisted in translation. The assessment battery was divided into two sections; each of the assessors began their assessment using one of the two sections of the overall battery. The WISC-R made up the IQ component of the battery and the neuropsychological battery comprised the Finger Tapping Test, the Grooved Pegboard Test, the Rey Osterrieth Complex Figure copy and 3 minute delayed trial, the Rey Auditory Verbal Learning Test, Trail Making Part A and B, Rey Osterrieth Complex Figure delay and recognition trials, Rey Auditory Verbal Learning Test delay and recognition trials, the Control Oral Word Association Test, the Stroop Colour and Word Test, and the Wisconsin Card Sorting Test. Participants were given a break between the two assessment sessions and were given light refreshments. The total time taken for the administration of the battery was four hours.

A similar procedure was implemented for the data gathering of the contrast group at the school. The school that was approached for participation in the study was in Soweto, where there was a low socio-economic demographic. A supervisor of the larger study initially approached the headmaster of the school. Once permission was granted, the supervisor approached the classes and distributed letters explaining the research which the students were being invited to participate in. 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 be 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 were operationalised in the HIV-negative contrast group and confidentiality was maintained.

The consent forms were handed in directly to the school office in a sealed envelope and then collected by the researchers in order to manage the responses in as confidential a nature as possible with minimal involvement of teachers. This was done in order to avoid any stigmatization surrounding reasons for adolescents not participating. Once the responses were obtained, contrast group participants were contacted and times were set up for assessment during the June/July school holidays. They were reimbursed for costs incurred for transportation.

Instruments

This study is a part of a larger one using a comprehensive neuropsychological battery. Only the tests relevant to this study will be discussed. It should be noted that these tests were not developed or normed in South Africa. However, this should not affect the interpretation of the results, as the contrast group provided a reference with a typically developing child from a similar background and the raw scores from each group were compared so as to avoid the utilisation of the norms.

Rey Auditory Verbal Learning Test (A. Rey, 1964).

The Rey Auditory Verbal Learning Test (RAVLT) was administered as a measure of verbal learning ability and verbal memory. Learning words in lists is the most sensitive way in which one can test verbal memory (Lezak, Howieson & Loring 2004). The test consists of a group of 15 words read out to the participant at a prescribed rate. This procedure is performed a total of five times (trials I-V) with the participant instructed that they must include words recalled in the 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 (Lezak, Howieson & Loring 2004).

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 as well as retention of memory. The number of words correctly recalled on each trial is scored.

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). The test-retest reliability is high, ranging from 0.61 to 0.86 for trials I-V and reliability coefficients of 0.51 to 0.72 for delayed recall and recognition (Lezak, Howieson & Loring 2004).

Skuy, Schutte, Fridjhon, and O'Carroll (2001) found that a sample of Sowetan adolescents recalled 44.74 out of a possible 75 words on the RAVLT, which indicates 59.65% of the words learned, whereas a North American sample (ages range from 13 – 16 years old) recalled 53 words, indicating 70% of the possible words learned. This gives an indication of the level at which a low socio-economic sample of South African adolescents perform in comparison to those in North America before accounting for the effects of HIV.

Rey Osterrieth Complex Figure Test (A. Rey, 1941).

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). Specifically the test is a measure of perceptual organization and visual memory (Lezak, Howieson & Loring 2004).

The ROCFT is made up of three conditions. In the initial phase, the participant is given the Complex Figure to copy. Three 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 participant is given a different coloured pen to draw in at various stages of completion; the administrator numbers the order in which the colours are used so as to record the copying sequence (Lezak, Howieson & Loring, 2004). 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.

In the study conducted by Skuy et al. (2001) it was 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 would 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).

Trail Making Test.

The Trail Making Test (TMT) is a measure of scanning and visuomotor tracking, divided attention, and cognitive flexibility (Lezak, Howieson, Bigler, & Tranel, 2012). There are two parts to the TMT. The first part requires the participant to draw lines that connect consecutively numbered circles on a worksheet. The second part requires the participant to draw lines that connect consecutively numbered circles to alphabetically ordered lettered circles by alternating between the two sequences. The participant is given the instruction to refrain from lifting their pencil throughout each task. Performance on the second part of the TMT is dependent on working memory (Crowe, 1998).

Reliability scores for adolescents have been found to be 0.79 for Part A and 0.89 for Part B indicating high reliability (Spreeen & Strauss, 1991). In addition, inter-rater reliability has been found to be 0.94 for Part A and 0.90 for Part B (Fals-Stewart, 1991). The correlation coefficient found for Part A and Part B is 0.31-6, indicating a moderate correlation which is explained by the fact that each part measures similar yet differing functions (Spreeen & Strauss, 1991). According to Spreeen and Strauss (1991), the average time adolescents took to complete Part A was 23 seconds and 47 seconds to complete Part B. A Sowetan sample of adolescents took 38.51 seconds on Part A and 85.72 seconds on Part B of the TMT (Skuy, et al., 2001). The results of the Sowetan sample were in the 10th percentile for Part A and below the 10th percentile of Part B measured against the norm standard provided by Spreeen and Strauss (1991).

Selected Wechsler Intelligence Scale for Children Revised (Wechsler, 1987)

Subscales.

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). The verbal scale is comprised of the Information, Similarities, Arithmetic, Vocabulary and Comprehension subtests and Digit Span, which is an optional subtest. The performance scale is comprised of the Picture Completion, Coding, Picture Arrangement, Block Design and Object Assembly subtests with Mazes being a supplementary test. Of interest in this study are the Arithmetic, Vocabulary, and Digit Span subtests of the VIQ as well as the Coding subtest of the PIQ as these provide a measure of different memory constructs.

The Arithmetic subscale is a reliable measure of working memory. Immediate memory, concentration, conceptual manipulation, and tracking are essential for good performance on this test. The Vocabulary subscale is a measure of long term semantic memory. The Digit Span subscale measures the span of immediate verbal recall. Digits Forward is a measure of attention while Digits Backward measures working memory capacity where both memory and reversing operations occur simultaneously. In addition, the Coding subscale is a measure of working memory (Lezak, Howieson & Loring 2004).

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.

An informal test of prospective memory was included in the battery. At a certain point in the assessment process the participants were told to write their names at the bottom of the page once they had completed that specific test.

Data Analysis

In order to address the research question, a series of statistical analyses were carried out. All statistical analyses were completed using SAS Enterprise Guide 3 (SAS Institute, 2004). Data obtained from the assessments was interval in nature, while the demographic data was coded as nominal data.

Due to the difference in size between the two groups, a multivariate matching sampling method, Propensity Score Matching (PSM), was used to allow for the adjustment of variables

necessary to ensure comparability between groups (Newgard, Hedges, Arthur, & Mullins, 2004). In this way, the two groups were matched as far as possible when accounting for demographic variables.

Chi-Squared Tests of Association were conducted within the experimental group in order to establish the nature of the relationship between specific demographic variables utilised in the study. These included gender, age, the age at which HAART was initiated, CD4+ count at the time HAART was initiated, and viral load at the time HAART was initiated (Howell, 1997). These analyses aimed to determine whether the independent variables were independent of one another and the extent to which they would be likely to impact performance on the assessment.

In order to employ parametric analyses, several assumptions should be met. It is reasonable to assume an interval scale of measure for the dependent variables and additive means was assumed where other assumptions had been met. However histograms and equality of variance checks were carried out in order to determine whether these data sets were normally distributed (Howell, 1997).

Although much of the data could be assumed normal, there were some instances where normality could not be assumed. As a result, two independent sample t-tests were run for all of the data, as well as its non-parametric counterpart the Mann Whitney U Test. Where significant results occurred, effect sizes were calculated in order to determine if the result was practically significant. These statistical analyses were employed to answer the posited research question. The findings are presented in the following chapter where the results are considered, as well as their implications.

Chapter 3: Results

The research question was addressed through a series of statistical analyses. This began with pre-analyses where attempts were made to match the HIV positive and contrast groups as far as possible, to establish the extent of the association between predictor variables assessed in the experimental group in the study, and to determine the suitability of the data for parametric analysis. Following this, statistical techniques designed to address the research question were carried out. Raw scores were used in the analyses as an attempt to control for the bias effect that the use of international normative data may have had on the results of a South African population. The results attained for these analyses are discussed in the sections below.

Sample Characteristics

The final sample comprised 30 adolescents who were HIV positive and 69 adolescents who were HIV negative. The groups were matched as far as possible for age, gender, demographics, and educational level using Propensity Score Matching (PSM), which resulted in no exclusion of any individuals in the contrast group indicating that the groups were well matched. Socio-economic status distribution within the sample as a whole was determined from parental educational level, and number of household assets, such as owning a fridge, owning a car and having access to running water and electricity, as well as reported living circumstances (Myer, Stein, Grimsrud, Seedat, & Williams, 2008). Living circumstances consisted of number of rooms in the house, whether a participant had their own bedroom, and their own bed.

There were no significant differences in the distribution of home language between the groups. Within the HIV group there were 70% Zulu, 17% SeSotho, 10% Xhosa, and 3% other home language speakers with HIV. In the typically developing contrast group there were 71% Zulu, 15% SeSotho, 12% Xhosa, and 2% other home language speakers (Refer to Table 1). There were no significant differences between the groups in terms of the number of participants in each grade, with the majority of both the HIV and contrast groups being in Grade 9. Thus the effects of level of education were controlled for as far as possible. In addition, there were no significant differences in the distribution of ages or gender within each group. Finally, there was no significant difference found in the distribution of the Full Scale IQ scores between the groups with the majority of the Full Scale IQ scores falling within the Low Average to Borderline range. As a result, in terms of demographic variables,

the two groups were closely matched. A summary of the demographic characteristics for both groups is shown in Table 1.

Table 1.

Demographic Information for the Sample

	HIV Group	Percentage	Contrast Group	Percentage
N	30		69	
<i>Age</i>				
13	10	33%	17	25%
14	9	30%	24	35%
15	11	37%	28	40%
<i>Gender</i>				
Male	14	47%	33	48%
Female	16	53%	36	52%
<i>Home Language</i>				
Zulu	21	70%	49	71%
SeSotho	5	17%	10	15%
Xhosa	3	10%	8	12%
Other	1	3%	2	2%
<i>Current Grade</i>				
7	5	17%	9	13%
8	8	26%	16	24%
9	14	47%	36	52%
10	3	10%	7	11%
<i>FSIQ</i>				
Mean	65.69		65.51	
SD	11.09		11.65	
Range	40-87		43-92	

Note: FSIQ = Full Scale IQ on the WISC-R

Relationship between the Predictor Variables in the HIV Group

In order to assess the extent to which the predictor variables in the HIV group were related, a series of Chi-Squared Tests of Association were carried out (Howell, 1997; Skuy, 2003). The variables of particular interest in this group were the age at which HAART was initiated, CD4+ count at initiation of HAART, and the viral load at the initiation of HAART. The aim of conducting these tests was to establish whether, and if so, to what extent, the distribution of one categorical variable is associated with a second categorical variable (Howell, 1997).

The results shown in Table 2 indicate that there were no significant relationships in the proportions of each of the independent variables (all $p > .05$). Therefore, it may be assumed that these would not act as extraneous variables in the experimental group within the study (Rosnow & Rosenthal, 1996). Thus, there are no significant relationships within the HIV group in terms of age that HAART was initiated, CD4+ count at the initiation of HAART, and the viral load at the time HAART was initiated.

Table 2.

Chi-Square Tests of Association between Variables in the Study

Variable	Pearson's Chi-Square	<i>p</i>
Age HAART	8.8000	0.1173
CD4+ Count	1.7333	1.0000
Viral Load	4.6667	1.0000

Normality of the Data

The utilisation of parametric techniques for statistical analysis depends on the satisfaction of five assumptions (Howell, 1997). These include random independent sampling, additive means, an interval scale of measure for the dependent variables, homogeneity of variance between the groups, and that the data is distributed reasonably normally. Despite random independent sampling not being possible, an interval scale of measurement could be assumed for each of the tests used. The normality of their distributions was assessed using histograms and measures of central tendency while a Levene's Test of Homogeneity of Variance was carried out on the dependent variables.

Examination of the histograms (Appendix H) revealed that the majority of the data were significantly skewed, both positively and negatively. This indicates that the majority of respondents performed either extremely well or extremely poorly on the assessments. The

visual examinations of the histograms were confirmed by the relative distances between the mean and median of the measures of central tendency. Tables 3 and 4 indicate that the majority of the scores on the memory tests were not sufficiently normally distributed and thus it would not be feasible to conduct parametric analyses on all of the data.

Table 3.

Basic Descriptive Statistics for Tests for the HIV positive group

Variable	Mean	Std Dev	Minimum	Maximum	N	Median
WISC_R_VT_ARITH	7.90	3.14423	0	12	30	9
WISC_R_VT_VOC	18.03	9.91509	0	32	30	19
WISC_R_VT_DS	7.90	2.91665	0	14	30	7
WISC_R_VT_DS_F	4.83	1.85850	0	10	30	5
WISC_R_VT_DS_B	3.07	1.48401	0	6	30	3
WISC_R_PT_BD	18.37	12.84250	0	49	30	15.5
WISC_R_PT_C	38.13	12.41171	0	57	30	37.5
ROCFT_CS	22.77	8.85489	0	35	30	25.5
ROCFT_IRS	13.95	5.52790	0	22.5	30	14.75
ROCFT_DRS	13.80	5.92277	0	22.5	30	13.5
ROCFT_RT_CORRECT	8.17	2.97209	0	12	30	9
ROCFT_RT_FALSE_POSITIVE	2.83	1.94906	0	8	30	3
ROCFT_O_PG	1.63	0.88991	0	4	30	2
ROCFT_TP	3.67	1.29543	0	5	30	4
RAVLT_I	5.87	1.85199	2	10	30	6
RAVLT_I_REPEATS	0.17	0.46113	0	2	30	0
RAVLT_I_INTRUSIONS	0.43	0.77385	0	2	30	0
RAVLT_II	8.23	2.25424	4	13	30	9
RAVLT_II_REPEATS	0.70	1.05536	0	4	30	0
RAVLT_II_INTRUSIONS	0.23	0.43018	0	1	30	0
RAVLT_III	9.97	2.02541	4	14	30	10
RAVLT_III_REPEATS	1.33	1.58295	0	5	30	1
RAVLT_III_INTRUSIONS	0.23	0.43018	0	1	30	0
RAVLT_IV	10.70	1.84110	5	13	30	11
RAVLT_IV_REPEATS	1.90	1.86344	0	6	30	1.5
RAVLT_IV_INTRUSIONS	0.13	0.34574	0	1	30	0
RAVLT_V	11.30	1.98529	6	15	30	11.5
RAVLT_V_REPEATS	1.43	1.35655	0	4	30	1
RAVLT_V_INTRUSIONS	0.17	0.37904	0	1	30	0
RAVLT_BI	5.30	1.89645	2	9	30	5
RAVLT_BI_REPEATS	0.20	0.48423	0	2	30	0
RAVLT_BI_INTRUSIONS	0.47	0.73029	0	3	30	0
RAVLT_VI	8.97	2.23581	5	14	30	9
RAVLT_VI_REPEATS	0.67	1.06133	0	4	30	0
RAVLT_VI_INTRUSIONS	0.30	0.53498	0	2	30	0
RAVLT_VII	9.27	2.83978	0	13	30	10
RAVLT_VII_REPEATS	0.82	1.48970	0	6	29	0
RAVLT_VII_INTRUSIONS	0.59	0.94526	0	3	29	0
RAVLT_RT_CORRECT	14.10	1.09387	12	15	30	14.5
RAVLT_FALSEPOS	6.00	6.95821	0	31	30	2.5
TRAILS_A_T	65.53	22.43416	36	118	30	59.5
TRAILS_A_E	0.433	0.72793	0	3	30	0

TRAILS_A_PG	1.57	0.97143	0	5	30	1
TRAILS_A_LQ	2.83	0.64771	0	3	30	3
TRAILS_A_STRAT	1.93	0.63968	0	3	30	2
TRAILS_B_T	149.83	63.64940	65	335	30	129
TRAILS_B_E	2.53	3.58861	0	15	30	1
TRAILS_B_PG	1.70	1.05536	0	5	30	1.5
TRAILS_B_LQ	2.63	0.96435	0	3	30	3
TRAILS_B_STRAT	1.90	0.66176	0	3	30	2

Note: VT = Verbal Test, PT = Performance Test, INFO = Information subtest, SIM = Similarities subtest, ARITH = Arithmetic subtest, VOC = Vocabulary subtest, COMP = Comprehension subtest, PC = Picture Completion subtest, PA = Picture Arrangement subtest, DS = Digit Span subtest, BD = Block Design subtest, OA = Object Assembly subtest, C = Coding subtest; ROCFT CS = Copy Score, IRS = Immediate Recall Score, DRS = Delayed Recall Score, RT = Recognition Trial, O_PG = Observation Pencil Grip, O_T = Observation Tremor, O_DA = Observation Drawing Ability, TP = Type of Production; Trails T = Time in seconds, E = number of Errors, PG = Pencil Grip, LQ = Line Quality, STRAT = Strategy.

Differences between the HIV and Contrast Groups

In order to establish if there were significant differences in performance on the neuropsychological assessment battery between the experimental and contrast groups, two independent sample t-tests and non-parametric Mann Whitney U and Kruskal-Wallis tests were carried out. Both parametric and non-parametric analyses were employed due to mixed distributions. Where the data distribution was considered normal, the parametric statistical analyses were interpreted and where it was not feasible to assume normality, non-parametric analyses were interpreted. Due to the small size of the experimental group, effect sizes were calculated for significant results as a means of determining whether the result is truly significant, or a result of the size of the sample. Table 5 shows the differences between the performances of the HIV group and the contrast group on the WISC-R. Since these data were normally distributed t-tests were calculated.

Table 4.

Two Independent Sample t-tests for Subtests on the WISC-R

Test	Pr > F	t-value	Pr > t	Lower Confidence Limit	Mean	Upper Confidence Limit
Information	0.7301	0.54	0.591	-0.76	0.29	1.98
Similarities	0.5575	-0.51	0.6141	-1.49	-0.39	2.86
Arithmetic	0.0835	-3.58	0.0005	-3.24	-2.09	-0.93*
Vocabulary	0.7392	1.28	0.2052	-0.36	0.65	1.93
Comprehension	0.6982	-1.12	0.2653	-1.77	-0.64	2.14
Picture Completion	0.0598	-0.08	0.9397	-1.26	-0.05	2.29
Picture Arrangement	0.6019	0.61	0.5452	-0.86	0.38	2.33
Digit Span	0.6228	-2.95	0.0039	-3.02	-1.80	-0.59*
Digits Forward	0.4362	-2.45	0.0162	-1.67	-0.92	-0.17*
Digits Backward	0.8757	-3.07	0.0027	-1.68	-1.02	-0.36*
Block Design	0.5824	-4.12	<.0001	-16.25	-10.97	-5.69*
Object Assembly	0.2783	-2.7	0.0082	-3.12	-1.80	-0.48*
Coding	0.2968	-0.25	0.7997	-1.56	-0.18	2.61
VIQ	0.4368	-0.54	0.5913	-7.10	-1.52	10.57
PIQ	0.6811	0.40	0.6870	-4.64	1.12	10.37
FSIQ	0.8100	0.07	0.945	-5.12	0.19	10.03

Note: VIQ = Verbal IQ, PIQ = Performance IQ, FSIQ = Full Scale IQ.

*p < .05.

There were significant differences between the groups on the Arithmetic ($t = -3.58$; $p = 0.0005$), the complete Digit Span ($t = -2.95$; $p = 0.0039$), as well as Digit Span Forward ($t = -2.45$; $p = 0.0162$) and Digit Span Backward ($t = -3.07$; $p = 0.0027$), Block Design ($t = -4.12$; $p < .0001$), and Object Assembly ($t = -2.7$; $p = 0.0082$) subtests of the WISC-R. In all instances, the typically developing group performed significantly better than their HIV positive peers. Interestingly, there were no significant differences in the Verbal IQ ($t = -0.54$; $p = 0.5913$), Performance IQ ($t = 0.40$; $p = 0.6870$), and Full Scale IQ ($t = 0.07$; $p = 0.945$) scores. Table 5 provides the effect sizes for each of the subtests that yielded a significant difference.

Table 5.

Effect Sizes for Significant Results on the WISC-R

Significant Tests	<i>d</i>	Interpretation
Arithmetic	0.78	Strong
Digit Span	0.65	Strong
Digits Forward	0.54	Moderate to Strong
Digits Backward	0.67	Strong
Block Design	0.90	Strong
Object Assembly	0.63	Strong

As shown in Table 5, despite the small sample size, the significant results yielded moderate to strong effect sizes as determined by Cohen's *d* (Thalheimer & Cook, 2002).

In order to determine if there were significant differences between the groups in terms of performance on the Rey Osterrieth Complex Figure Test both Mann Whitney U tests and Kruskal-Wallis tests were conducted. Non-parametric tests were conducted as the data was skewed. Table 6 shows the results of these analyses.

Table 6.

Mann Whitney U tests and Kruskal-Wallis tests for each trial of the Rey Osterrieth Complex Figure Test.

Trial	<i>U</i>	<i>Pr > Z </i>	<i>K-W</i>	<i>Pr > Chi-Square</i>
Copy	983.5	0.0002	15.54	<.0001*
Immediate Recall	1112	0.0039	8.74	0.0031*
Delayed Recall	1072	0.0015	10.63	0.0011*
RT Correct	1117	0.0049	8.30	0.0040*
RT False Positives	1684.5	0.1583	2.03	0.1540

Note: RT = Recognition Trial.

**p* < .05

These results indicate that there are significant differences between the groups on the copy trial (*p* < .0001), the immediate recall trial (*p* = 0.0031), the delayed recall trial (*p* = 0.0011), and the number of correct items on the recognition trial (*p* = 0.0040) on ROCFT, a test of visuospatial memory. Comparison of the mean scores for each group (experimental group = 32.78; contrast group = 57.49) demonstrates that the HIV positive group performed significantly below their typically developing counterparts on both visual constructional ability and visual memory. In order to determine the practical significance of the differences between the groups, effect sizes were calculated and the results are shown in Table 7.

Table 7.

Effect Sizes for Significant Results on the ROCFT

Trial	<i>d</i>	Interpretation
Copy	1.06	Strong
Immediate Recall	0.73	Strong
Delayed Recall	0.79	Strong
RT Correct	0.55	Strong

Note: RT = Recognition Trial

The strong effect sizes in all instances allow for the assumption to be made that, despite the small sample size, the significant results as determined through statistical analyses are, in fact, practically significant (Thalheimer & Cook, 2002).

In order to determine whether or not there were differences between the groups in terms of verbal learning and memory, Mann-Whitney U tests and Kruskal-Wallis tests were calculated for each trial of the Rey Auditory Verbal Learning Test (RAVLT). Non-parametric analyses were utilised as the data was significantly skewed. The results are shown for each trial in Table 8.

Table 8.

Mann Whitney U tests and Kruskal-Wallis tests for each trial of the Rey Auditory Verbal Learning Test

Trial	U	Pr > Z 	K-W	Pr > Chi-Square
I	1611.5	0.3929	0.74	0.3887
I Repeats	1316.5	0.0698	3.38	0.0661
I Intrusions	1505	0.9655	0.02	0.9616
II	1478.5	0.8716	0.03	0.8683
II Repeats	1353	0.2269	1.49	0.2224
II Intrusions	1457.5	0.6736	0.18	0.6690
III	1716	0.0990	2.69	0.0950
III Repeats	1433	0.5995	0.28	0.5956
III Intrusions	1472	0.7835	0.08	0.7791
IV	1578	0.5504	0.36	0.5465
IV Repeats	1587.5	0.4974	0.47	0.4933
IV Intrusions	1411	0.3262	0.99	0.3211
V	1503.5	0.9816	0.01	0.9785
V Repeats	1443	0.6593	0.19	0.6555
V Intrusions	1387.5	0.2498	1.35	0.2449
BI	1457.5	0.7465	0.10	0.7429
BI Repeats	1395.5	0.2853	1.17	0.2804
BI Intrusions	1454.5	0.6920	0.16	0.6878
VI	1398	0.4352	0.62	0.4330
VI Repeats	1449.5	0.6705	0.19	0.6665
VI Intrusions	1450.5	0.6404	0.22	0.6360
VII	1611	0.3799	0.73	0.3935
VII Repeats	1326.5	0.3529	0.88	0.3484
VII Intrusions	1516.5	0.8822	0.02	0.8782
RT Correct	1533	0.7904	0.07	0.7866
RT False Positives	1668	0.1995	1.68	0.1951

Note: RT = Recognition Trial. No significant differences between the experimental and contrast groups.

Table 8 illustrates that there were no significant differences between the two groups in terms of verbal memory and verbal learning ability as assessed by the RAVLT. Intrusions and repetitions were included in the analyses as each provides supplementary information regarding cognitive processes involved in verbal memory. Repetitions are most likely a reflection of a deficit in self monitoring and tracking, while intrusion errors indicate some difficulty in sustaining the distinction between information from an outside source and their own associations (Lezak, Howieson, & Loring, 2004). These results show no indication of significant differences between the groups in either repetitions or intrusions; thus the supplementary cognitive processes involved in verbal memory seem to be performing in much the same way across the groups.

In order to determine whether there were differences between the groups on the Trail Making Test (TMT), Mann Whitney U tests and Kruskal-Wallis tests were carried out. Non-parametric analyses were used as the data were significantly skewed. Table 9 shows the results of these analyses.

Table 9.

Mann Whitney U tests and Kruskal-Wallis tests for each trial of the Trail Making Test

Trial	U	Pr > Z 	K-W	Pr > Chi-Square
A_Time Taken	2100	<.0001	20.88	<.0001*
A_No Errors	1644	0.1412	2.216	0.1366
A_Strategy	1505.5	0.9466	0.01	0.9411
B_Time Taken	2043	<.0001	17.09	<.0001*
B_No Errors	1801	0.0145	6.21	0.0127*
B_Strategy	1469	0.7102	0.14	0.7049

*p < .05

The results presented in Table 9 indicate that there were significant differences between the experimental and contrast groups in the time taken to complete Trial A ($p < .0001$), the time taken to complete Trial B ($p < .0001$), and the number of errors that were made on Trial B ($p = 0.0127$). The HIV positive group took a significantly longer period of time to complete both Trial A and Trial B of the Trail Making Test; in addition, the HIV positive group made more errors than their typically developing peers on Trial B of the Trail Making Test. In order to determine the practical significance of the results, effect sizes were calculated using Cohen's d. Table 10 shows the results of these analyses.

Table 10.

Effect Sizes for Significant Results on the Trail Making Test

Trial	d	Interpretation
A_Time Taken	1.1109	Strong
B_Time Taken	0.8126	Strong
B_No Errors	0.7109	Strong

In all instances the effect sizes were strong indicating that the results are significant (Thalheimer & Cook, 2002).

The statistical analyses that were employed to answer the research question were presented in this chapter. In order to determine the extent to which the two groups were matched a Propensity Score Matching analysis was conducted. Results indicated that no exclusion of any participants in the contrast group was necessary; thus the two groups were closely matched in terms of demographic variables. No significant differences in the distribution of home language, grade, age, or gender were found between the groups. In addition, the differences in Full Scale IQ, Performance IQ, and Verbal IQ were found to be insignificant. As a result, the groups were matched as closely as possible.

In order to determine whether there were possible within group differences in the HIV positive group in terms of the viral progression and effects of treatment, a Chi-Square Test of Association was carried out. The results suggest that there were no significant relationships in the proportions of the age that HAART was initiated, the CD4+ count at the initiation of HAART, and the viral load at the initiation of HAART. As a result, the potential extraneous variables within the HIV positive group were controlled for as far as possible.

The visual examinations of the histograms and an analysis of the relative distances between the mean and median of the measures of central tendency indicated that the majority of the data were significantly skewed in both directions. Consequently, both parametric and non-parametric analyses were carried out where appropriate. In order to determine whether there were significant differences in the performance between the HIV positive group and the contrast group on the neuropsychological assessment battery Two Independent Sample t-tests as well as Mann Whitney U tests and Kruskal-Wallis tests were performed.

The Two Independent Sample t-tests of the individual subtests on the WISC-R indicated significant differences on the Arithmetic, the complete Digit Span, Digit Span Forward, Digit Span Backward, Block Design, and Object Assembly subtests. These differences were confirmed by moderate to strong effect sizes. The differences indicated that the HIV positive group's performance was significantly poorer on the aforementioned subtests than their typically developing peers.

Both the Mann Whitney U tests and the Kruskal-Wallis tests indicated significant differences on the Copy trial, the Immediate Recall trial, the Delayed Recall trial, and the number of correct items on the Recognition trial of the ROCFT. These significant differences were

confirmed by strong effect sizes and show that the performance of the HIV positive group on this task was significantly poorer than the contrast group. In addition, the utilisation of the same non-parametric analyses revealed no significant differences on each of the trials of the RAVLT. Furthermore, no significant differences were ascertained on the number or repeats or intrusions made by the participants in each group.

Finally, the Mann Whitney U tests and Kruskal-Wallis tests indicated significant differences in the time taken to complete both Trial A and Trial B of the Trail Making Test as well as the number of errors made on Trial B of the Trail Making Test. The significant differences found in the performance of each group on these tasks were confirmed by strong effect sizes. The results suggest that the performance of the contrast group was significantly better than that of the HIV positive group. Further discussion of these findings, and their consequent implications, will be presented in the following chapter within the context of the literature.

Chapter 4: Discussion

Introduction

This research aimed at determining whether, and if so how, the memory profiles of seropositive adolescents on a managed antiretroviral programme differ from an uninfected, typically developing group in the South African context. Given the importance of intact memory functioning for learning and academic success, it is crucial to know if and how various aspects of memory differ in HIV positive and negative adolescents. With this aim in mind, the exceptional circumstances of HIV in South Africa, including its environmental and demographic context, will briefly be discussed. The demographic variables of each sample will need to be taken into account, as well as potential extraneous variables that may have an effect on neurocognitive functioning. In addition, global cognitive functioning will need to be considered as deficits in processes that supplement the memory system have an impact on memory performance (Davidson, Troyer, & Moscovitch, 2006). Following this, differences between the groups in both verbal and visual memory functioning will be elaborated upon. Finally, psychosocial implications and recommendations will be suggested with regard to future research in South Africa in HIV child and adolescent populations.

There are several variables in this study that are unique to the South African context. These include relative living circumstances, socio-economic status, and multilingualism as well as the multicultural environment in which many South African children develop. Especially unique to the sample utilised in this study is the strain of HIV infection that has been transmitted to these adolescents. As mentioned at the outset of this report, the HIV-1 infection most commonly found in South Africa is clade C (Shisana et al., 2009). The current literature on HIV and developing children and adolescents generally reports on European and American populations where the most prolific viral strain of HIV is clade B (Ellis et al. 2009). Thus, it should be noted that the cognitive sequelae of infected adolescents in South Africa may be different to what would be expected based on the existing literature. Importantly, the clade C strain of the HIV infection is highly virulent and it may therefore be assumed that this subtype, as well as its associated opportunistic infections, has a more severe progression (Kanki, 1999). This claim may be substantiated by Brouwers et al. (1995) who found that there were significantly more adolescents diagnosed annually with neurological impairments in South Africa when compared to adolescents in Europe, which is a function of greater infection rates in Africa. This indicates the progressive effect a more virulent strain of HIV may have on the CNS. Both the clade of HIV and the contextual factors that are unique

to South Africa need to be taken into consideration when interpreting the neuropsychological profile of the adolescents in this study.

As a result of the direct effect many demographic factors, such as age, gender, language, race and socio-economic status, may have on neuropsychological performance it was essential to match the experimental and contrast groups as closely as possible (Woods & Grant, 2005). The efficacy of the inclusion and exclusion criteria utilised in the matching process in this study was confirmed through the use of the statistical technique of generating Propensity Matching Scores (Newgard, Hedges, Arthur, & Mullins, 2004). In this way it was established that there were no significant differences in the demographic variables that may have had an effect on each individual's performance on the neuropsychological assessment battery. In addition, the majority of the tests used in the assessment battery were not standardised in South Africa and, as a result, the application of the provided norms would render the results of the assessment invalid as the norms represent generally European or American samples. Thus, the contrast group allowed for a better understanding of the neuropsychological functioning of the HIV positive adolescents relative to a group of typically developing South African adolescents, where contextual and demographic variables were controlled for.

Other factors that may affect neurocognitive functioning in HIV positive adolescents include the age at which HAART is initiated (Laughton, Springer, Grove, Seedat, Cornell, Kidd et al., 2010). ARV-naïve children who were placed onto HAART after presenting symptomatically showed greater neurocognitive deficits in comparison to children placed on ARV's from birth. This is most likely due to the restrictive impact the treatment has on the progression of the disease. There was some concern that the age at which each of the adolescents in the HIV positive group commenced with the managed HAART programme may have had an effect on their neurocognitive functioning which would be reflected in their performance on the assessment battery. Consequently, a Chi-Square Test of Association was carried out in order to assess whether the age at which HAART was initiated, and the individual's CD4+ count and viral load at the time of the initiation of HAART, would have acted as extraneous variables. Since there were no significant relationships in the proportions of each of the variables, in the case of this particular group of HIV positive adolescents, their performance on the neuropsychological assessment battery was not likely to have been influenced by the age in which their ARV programme was initiated.

The pre-analyses indicated that the demographic factors that may have had an impact on each individual's performance on the neuropsychological assessment battery were matched as far

as possible and were thus controlled for. In addition, there was no association between the age that HAART was initiated, or CD4+ count at the initiation of HAART, or the viral load at the time HAART was initiated; as a result, none of these independent variables could act as extraneous variables when contemplating test results. Important factors that should be noted in the consideration of the results of the assessment is the clade of HIV to which the majority of South African HIV positive adolescents have been exposed and the specific environmental context within which these adolescents developed and currently live.

Global Functioning

Due to the fact that memory is in no way a unitary function and is closely inter-related with all other cognitive processes including attention and concentration, information processing speed¹, organisation, strategy, effort, and self monitoring (Davidson et al., 2006), it stands to reason that memory processes will be influenced in some way by various cognitive processes. Deficits in the processes external to the memory system can, therefore, affect memory performance (Lezak et al., 2012). An example of this is that if an individual performs poorly on a simple attentional task, such as Digit Span Forward, it may not be possible to establish a valid measure of working memory, which would be determined on Digit Span Backward, as it would be unclear whether the poor performance on Digit Span Backward may be attributed to the deficit in simple attention rather than the secondary process of the manipulation of information. As a means of exploring the relationship these processes have with distinct memory functions, the WISC-R was carried out in order to establish whether there were differences in the general intellectual performance of each group and, if so, which particular cognitive processes were involved.

There were no significant differences in the Full Scale IQ, Verbal, and Performance IQs between the groups. Therefore, examination of performance at this level only may be misleading as the significant differences of the various subtests are hidden. These overall IQ scores indicated that the intellectual performance of both groups were from the Cognitively Impaired range to the Below Average range when compared to the foreign norms. Significant differences were found on the Arithmetic ($t = -3.58$; $p = 0.0005$), the complete Digit Span ($t = -2.95$; $p = 0.0039$), Digit Span Forward ($t = -2.45$; $p = 0.0162$), Digit Span Backward ($t = -3.07$; $p = 0.0027$), Block Design ($t = -4.12$; $p < .0001$), and Object Assembly ($t = -2.7$; $p = 0.0082$) subtests. The average of the results on the Arithmetic, Digit Span, and Object Assembly subtests indicated that the HIV positive group were performing within the

¹ Processing speed is implicated in all visual and verbal memory functions and is therefore considered a process that permeates all of these functions as opposed to a distinct process meriting its own consideration.

Borderline range while the contrast group were generally performing within the Low Average range. Performance on the Block Design subtest suggested that the HIV positive group were generally in the Low Average range while the contrast group were within the Average range. In all instances the HIV positive group performed significantly poorer than the contrast group. The Arithmetic², Block Design, and Object Assembly subtests are timed tests and therefore rely on an efficient speed of information processing. The significant difference on these three subtests between the two groups may indicate a slower speed of mental processing in the HIV positive group. The Block Design and Object Assembly subtests require several shared cognitive processes that are necessary in order for them to be completed effectively (Kaufmann, 1994). These skills include simultaneous processing, spatial processing, synthesis of part-whole relationships, evaluation of figural stimuli, spatial visualisation and orientation, and visual motor coordination. Each of these skills relies, to some extent, on holistic processing, which is essentially a function of the right hemisphere and, by extension, the integrity of the white matter tracts involved in processing (Rourke, 1989). In addition, the ability to complete these subtests effectively depends on an individual's cognitive flexibility, which is a function of the frontal lobes, and general cognitive style (Kaufmann, 1994).

Regions of the brain preferentially affected by HIV include the basal ganglia, the thalamus, the rostral brainstem nuclei, and projections to the cortex and frontal lobes (Schiller et al., 2009). As a result of the specific impact the virus has on the frontostriatal circuits, a prototypical pattern of deficits emerge, which include slowed information processing efficiency, executive dysfunction, as well as deficient episodic memory encoding and retrieval (Reger, Welsh, & Rizani, 2002). Memory processing will be affected by deficits in supplementary cognitive functions. Slowed information processing will most likely impact an individual's ability to perceive and retain information, thereby affecting their ability to learn. In the school environment many assessments and exams are completed under time constraints; consequently, slowed information processing may result in the HIV positive adolescent performing poorly on such tasks. In addition, understanding of the synthesis of part-whole relationships and spatial visualisation allows for the conceptualisation of objects which, according to the model Collins and Quillian (1969) postulate, is essential for processing, such as encoding and storing, and retrieving knowledge from long term memory.

Memory cannot be separated from general functioning as it is both affected by and affects other cognitive functions. Of significance are processing speed, holistic processing, and

² A discussion of the results on the Arithmetic and Digit Span subtests will be further elaborated on in the Verbal Memory subsection.

spatial processing which are each right hemispheric functions. The significant differences between the contrast and experimental groups in this study suggest that the HIV positive sample is performing well below their typically developing peers on tasks that utilise and depend on efficient right hemispheric processing.

Verbal Memory

Verbal memory as a construct was assessed by several measures, namely the Arithmetic and Digit Span subtests of the WISC-R and the Rey Auditory Verbal Learning Test (RAVLT). What is of particular interest is that there were only significant differences between the groups on the verbal subtests of the WISC-R that required numerical processing and working memory, namely the Arithmetic and Digit Span subtests. Alloway (2006) postulates that mathematical deficits may be a result of poor working memory skills. Although verbal short-term memory is responsible for the temporary storage of numbers, while the individual is attempting the manipulation of those numbers in order to complete a sum or the rearrangement of the digits so that their order is reversed, there is a large visual working memory component involved in both of these tasks. As a result, children with working memory deficits have been found to battle with maths at school (Alloway, 2006). According to Heathcote (1994), visual memory skills are imperative in the facilitation of the numerical reasoning process by acting as a kind of blackboard upon which the numbers may be represented. This being the case, a deficit in visual spatial memory or working memory will significantly affect the individual's ability to engage effectively in sequential processing.

Reflecting on Eriksson and Kintsch's (1995) model, the process of working memory relies, to some extent, on the effective encoding of domain specific information, which in this case would be verbal information, into long-term memory. Results from the groups' relative performance on the WISC-R, as well as the RAVLT, indicate that there were no significant differences on tasks that involved verbal long-term memory; thus, it may be assumed that the verbal long-term memory processes are functioning at much the same level in the HIV positive group as in the unaffected typically developing group. There seems to be some deficit in the verbal working memory profiles of the HIV positive group; however it is not possible to determine whether this is at the level of the phonological loop, passive storage, or the central executive, as the tests utilised were unable to discriminate these functions. This is supported by empirical evidence that the HIV infection has a preferential effect on the frontostriatal circuits, most specifically on the fronto-striato-thalamo-cortical circuit, thereby affecting working memory specifically (Petito, 2004). In addition, decreased working

memory capacity may be attributed to an HIV related change that occurs over time with disease progression in the white matter, basal ganglia, and prefrontal cortex, which may have instigated the disruption of the frontostriatal circuitry that is imperative for working memory processing (York et al., 2001). This is an important consideration as it has been established that the HIV-1 clade C infection is a highly virulent strain implying that the disease progression is relatively rapid and severe. Thus, not only is working memory likely to be affected by HIV, but some cognitive fallout in working memory domains may present earlier in the clade C population when compared to other strains of the virus.

The fact that there were no significant differences between the groups on any of the trials of the Rey Auditory Verbal Learning Test (RAVLT) is interesting as it is contradictory to the current literature (Becker et al., 1995; Delis et al., 1995; Peavy et al., 1994). Each of these studies, however, used adult samples and were conducted in the US indicating that the strain of HIV was most likely clade B. Grant et al. (1987) and Grant and Heaton (1990) reported a decreased learning ability for verbal information in an adult HIV positive sample when compared to an HIV negative sample while York, Franks, Henry, and Hamilton (2001) found that HIV positive children performed significantly poorer than a group of typically developing children on tasks of verbal memory in the US. Performance on the RAVLT requires the engagement of both short-term retention and long-term learning capacities (Lezak et al., 2012). The overall scores represent the organisational functioning of different neurobehavioural mechanisms, some of which include arousal, motivation, attention, concentration, auditory perception, verbal comprehension, immediate verbal memory span, short-term verbal memory storage and retrieval, and progressive learning abilities. Markedly poorer performance of these functions, specifically verbal learning and recall, has been found in HIV positive populations when compared to their unaffected counterparts (Gendelman, 2005). However, the majority of this research has been conducted on adult populations in Europe and the United States of America; thus, crucially, the results reflect the effect of a different strain of HIV altogether. Results from this study suggest that the clade C strain of HIV has a somewhat different presentation in terms of cognitive ability where verbal memory functions and verbal learning capacities seem relatively spared.

The contradictory results established on the verbal memory tasks, when compared to the literature, indicate some conflicting outcomes. No significant differences were found in tasks of verbal memory and verbal learning ability between the two groups, which is inconsistent with the results from previous international research where it was found that HIV positive

individuals performed significantly poorer than their unaffected counterparts. It is suggested that these results may be attributed to differences in the severity, progression, and general presentation of the various clades of HIV as well as the differing ages of the samples used, however further research would need to be conducted in order to explore this. In addition, the fact that there were no significant differences in long-term memory functioning between the two groups suggests that the poorer performance of the HIV positive group on verbal memory tasks is most likely due to limited working memory capacity or deficits in working memory processes; this is substantiated somewhat by evidence from previous research of the distinct effect that HIV has on the neural correlates of working memory.

Visuospatial Memory

The construct of visuospatial memory was measured by the Coding subtest of the WISC-R, the Rey Osterrieth Complex Figure Test (ROCFT), and the Trail Making Test (TMT). There were no significant differences between the performances of each group on Coding suggesting that visual perceptual tracking and visual short term memory are similar in the two groups (Kaufmann, 1994). In contrast, significant differences were found between the groups on each trial of the ROCFT [Copy trial ($p < .0001$), Immediate Recall trial ($p = 0.0031$), Delayed Recall trial ($p = 0.0011$), and the number of items correctly chosen on the Recognition trial ($p = 0.0040$)]. There were no significant differences in the number of false positive items selected in the Recognition trial of the ROCFT.

Organisational strategy on the Copy trial of the ROCFT is a predictor of performance on the subsequent recall trials (Ferraro, Grossman, Bren, & Hoverson, 2002). An individual who approaches the task conceptually and is able to consider the image as a whole, rather than copying the details one by one, is able to process the image as conceptually meaningful units rather than as discrete entities. Such an organised strategy allows for effective encoding. Where an individual experiences difficulties effectively organising information in order to engage in planning and reasoning the efficiency of encoding and subsequent retrieval of that information are adversely affected (Muriqi et al., 2003). The significant difference on this trial of the ROCFT indicates that the HIV positive group may have some difficulty with strategically organising information in such a way that encoding the required information will be ineffective. Consequently, this could adversely affect their performance on subsequent recall trials as the information has not been encoded effectively and can, therefore, not be retrieved. A qualitative interpretation of the initial copying of the complex figure indicated that the HIV positive group utilised a more piecemeal strategy, whereby components of the

figure were copied separately, while the participants in the contrast group employed a more holistic approach making the encoding of that information more effective. The low performances reflected by the results demonstrate that the HIV positive group have reduced visual perceptual skills and reduced visual motor integration relative to the contrast group (Meyers & Meyers, 1995). In comparison normatively, the average performance of the HIV positive group on this trial was within the Borderline range while the general performance of the contrast group was within the Low Average range. These visuospatial skills are associated with frontal cortical regions, specifically the dorsolateral prefrontal cortex, which are areas implicated in HIV-induced impairment (Banich, 2004).

In light of the aforementioned, interpretation of the results of both the Immediate Recall and Delayed Recall trials indicated that the HIV positive group may have experienced disruptions in the processes of both storage and retrieval. This further reflects the difficulties the HIV positive group has with systematically organising information in such a way that it allows for effective encoding and retrieval. Previous research has suggested that the impairment in memory processing in HIV is mostly evident in memory retrieval and recall, which is consistent with the results in this study (Delis et al., 1995; Peavy et al., 1994; White et al., 1997). However, contrary to this literature, which suggests that the function of memory recognition remains somewhat spared indicating that memory storage is minimally affected; the results of the current study demonstrate that there is a deficit in the process of memory consolidation and storage in the HIV positive group as they also performed poorly on the Recognition trial, although they did not make more false positive errors than their typically developing counterparts. These results make sense when contemplating the neural substrates involved in these processes. Memory consolidation relies on neural circuits that extend from the hippocampal complex to the thalamic and orbital frontal areas (Laroche, Davis, & Jay, 2000). It has been established that these circuits are preferentially affected by HIV and, as a result, encoding and storage deficits may demonstrate the limited use of higher order planning and organisational strategies (Muriji et al., 2003). Thus, there appears to be some dysfunction in the strategic, executive aspects of encoding, storage, and retrieval of visuospatial information in the HIV positive group.

Furthermore, previous research found that HIV positive populations tend to perform better on memory tasks when they are provided with cues (Sadek et al., 2004). Such a claim is supported in this study by the absence of significant differences between the two groups on the Coding subtest of the WISC-R. The key (cues) provided in the Coding subtest are

concrete external reminders that assist the individual in completing the task. The provision of these cues suggests that the individual does not need to hold the symbols mentally, which potentially may result in cognitive overload of the central executive in working memory (Kaufmann, 1994). Thus, the presence of the cues allows for the option of completing the task using concrete peripheral functioning rather than actively holding the symbols in working memory.

The number of correct items selected on the Recognition trial of the ROCFT provides an indication of the ability to retrieve visuospatial information when provided with cues (Meyers & Meyers, 1995). It would be expected that, due to the non-significant difference between the two groups on the Coding subtest, there would be no significant differences between the two groups on the Recognition trial as the two tasks are essentially a reflection of similar processes. The fundamental difference between these two tests is that Coding, despite being a subtest in the IQ battery, is an independent test where effective performance simply relies on the internalisation of the provided cues or efficient operationalisation of the symbols; whereas the Recognition trial of the ROCFT depends, to a large extent, on the effective encoding of the visual information from the diagram as a whole. The cues provided on the Recognition trial allow for a prompting of the memories associated with the initial figure, however if the image was not conceptualised and organised in an efficient manner the memory will not have been encoded and stored effectively and will thus impede the recognition of the discrete parts of the whole image.

In addition, significant differences were found on both trials A ($p < .0001$) and B ($p < .0001$) of the Trail Making Test (TMT) in terms of the time taken to complete each trial. This indicates that the HIV positive group took longer to complete each of the trials providing further evidence for a slower processing speed than their unaffected typically developing counterparts. Perceptual tracking is a core process involved in the effective performance on the TMT. The results on the Coding subtest demonstrated no significant differences in the process of visual perceptual tracking suggesting that this process is relatively intact in the HIV positive group when compared to the typically developing group. Alloway (2006) describes simple memory tasks as those that are relatively rote and depend on moderate levels of attention, such as the counting that is required in Trial A of the TMT. On the other hand, complex memory tasks necessitate the manipulation of information that is fundamental in the process of working memory, such as switching between numbers and letters in Trial B of the TMT. Thus, Trial A of the TMT may be said to be a simple memory task, whereas Trial B is

a complex memory task, as it is more demanding on cognitive processes and resources. Trial B of the TMT adds a further dimension that requires the components of divided attention and working memory in order to be performed competently. The significant differences in performance between the groups on trial B indicate some difficulty with visual working memory.

As mentioned earlier, working memory is specifically affected by HIV due to the preferential effect the virus has on the fronto-striato-thalamo-cortical circuit (Petito, 2004). Bassel, Rourke, Halman and Smith (2002) suggested that the central executive of working memory is preferentially affected by HIV. If this is the case, the functioning of both the phonological loop and visuospatial sketchpad will be adversely affected by HIV as the central executive is responsible for the monitoring and regulation of the general activity in each of these domains and controls the resources that are available to them (Alloway, Pickering, & Gathercole, 2006). As a result of this, the individual's ability to manipulate and temporarily store verbal and visuospatial information declines dramatically (Goldman-Rakic, 1995; Petrides, 1995, 1998). Therefore, the results from the current study suggest that working memory is affected by HIV-1 clade C irrespective of domain.

Finally, a significant difference was found between the experimental and contrast groups on the number of errors made on Trial B of the TMT. The HIV positive group made significantly more errors than the typically developing group which suggests that the former group found the visual perceptual processes in the task to be more demanding, which may have resulted in cognitive overload that adversely affects their performance on this task (Meyers & Meyers, 1995). Thus, the scores on the TMT not only suggest deficits in visual working memory, but possibly also some difficulty in visual perceptual processing.

The findings on tests of visual memory utilised in this study are contradictory to the literature which suggests that visual memory is largely intact in HIV positive adult populations (Riedel et al., 1992). This may, once again, be principally attributed to the difference in the effects of the clade of HIV that were measured in this study. The visual memory profile of this particular group indicates that the HIV positive adolescents present with deficits in visual constructional skills, reduced visual perceptual skills, reduced visual recall ability, disruptions in both storage and retrieval of visuospatial information, and visuospatial working memory. In addition, the results of these tests indicate that the HIV positive group have a significantly slower mental processing speed than their typically developing peers, while

simple visual perceptual tracking seems essentially unaffected, but other aspects of visual perceptual processes may be affected.

Prospective Memory

Prospective memory was measured in this study by instructing each participant to write their name at the bottom of the page only once they had finished the Mazes subtest of the WISC-R. This prospective memory task was not completed, or even attempted, by any individual in either group. Taking into consideration the Multiprocess Framework of Prospective Memory put forward by McDaniels and Einstein (2000), several factors may account for this. The efficacy of prospective memory depends, to a large degree, on the subjective importance that is placed on the task. This informs the amount and quality of attentional resources that are allocated to the task. Prospective memory may easily be confounded if an individual is engaged in multiple activities that may be novel or exciting (McDaniels & Einstein, 2000). The assessment battery that was administered on the two groups was mentally taxing and required ongoing processing. As a possible result, the focus of the embedded features of the prospective memory task may have been disorientated, and consequently forgotten, by the demands of the tests in the assessment battery that would have required sustained and focussed attention. The fact that both groups forgot suggests that it is a feature of the task rather than any inherent factor in the groups.

It is interesting to note that deficits in prospective memory have been found to be due to the effect HIV has on the frontostriatal circuits (Carey et al., 2006). According to McDaniels and Einstein (2000), the prospective memory process is highly dependent on the individual's working memory, which, it has been ascertained, is especially affected due to the preferential impact HIV has on the fronto-striato-thalamo-cortical circuits. Thus, poorer performance on tasks of prospective memory would be expected in the HIV positive group due to the cognitive deficits that have been established, with the frontostriatal circuits being the common underpinning. These deficits in prospective memory are most likely a result of difficulties with strategic encoding and retrieval of retrospective episodic memory, which may arise due to the differential effect HIV has on the ventrolateral regions of the prefrontal cortex and the hippocampal system that function simultaneously in order for effective acquisition and encoding of information to occur (Banich, 2004).

Despite the commonality of the structural correlates involved in different aspects of memory, no conclusions may be drawn with regard to prospective memory as there was no performance to be measured. It may be speculated that due to deficits resulting from the

effect of HIV on the frontostriatal circuits, as well as frontal and hippocampal systems involved in episodic and working memory that HIV positive adolescents may experience a higher degree of difficulty with prospective memory tasks than typically developing unaffected adolescents.

Summary of Results and Psychosocial Implications

The aim of this research was to determine whether, and if so how, the memory profiles of seropositive adolescents on a managed antiretroviral programme differ from those of an uninfected, typically developing group. With the plethora of heterogeneous demographic profiles in the South African population, it was imperative to match the groups as far as possible in order to control for the demographic variables that may have had an extraneous impact on the results. The matching process that was employed through Propensity Matching Scores was effective and extraneous variables that may affect the results of the performance of each group on the neuropsychological assessment battery were limited as far as possible.

The results indicate that the HIV positive group present with some general cognitive deficits which are likely to have an effect on efficient memory functions. These include deficits in terms of speed of information processing, holistic processing, and visuospatial processing; all are predominantly right hemispheric processes. In addition, while verbal memory appears to be largely unaffected in the HIV positive group, there were significant differences evidenced in many visuospatial memory processes. These included visual constructional skills, reduced visual perceptual skills, reduced visual recall ability, disruptions in both storage and retrieval of visual information, and visual working memory. Both the verbal and visuospatial working memory domains were significantly weaker in the memory profile of the HIV positive group. It is possible that the central executive component of the working memory system may be preferentially affected by HIV, directly impacting on the functioning of both the phonological loop and visuospatial sketchpad.

The overall memory profile of the HIV positive adolescents reveals significantly poorer functioning on visuospatial tasks in comparison to their unaffected peers. It has been established that HIV preferentially affects the frontostriatal circuits which extend throughout the brain. These circuits are myelinated fibres connecting various regions of the brain facilitating integrated functioning (Carlson, 2007). It is well established that the white to grey matter ratio in the right hemisphere is greater than in the left hemisphere (Butler et al., 1994; Goldberg & Costa, 1981; Rourke, 1989). It may then be deduced that the preferential effect HIV has on these circuits will be that much more prominent in the right hemisphere. This is

consistent with the findings in this study, as the results suggest predominantly right hemispheric functioning deficits. This is not to imply that the impact HIV has on neural functioning is in any way simplistic, rather the results provide an indication of the profile of cognitive deficits that pertain to memory in an HIV population. This profile is, in some ways, similar to that of an individual with a non-verbal learning disability. Future research may be needed in order to determine the extent to which scholars with the progressive HIV infection could benefit from remediation in much the same way as those with non-verbal learning disabilities.

Deficits in the functioning of the right hemisphere during neurodevelopment may have adverse consequences for the individual in terms of both cognitive and emotional adjustment (Rourke, 1989). Golberg and Costa (1981) propose that right hemispheric functioning activates the cortex to a larger degree than left hemispheric functioning so that the individual is able to process novel information, develop innovative descriptive systems, and process complex information. Thus, deficits in right hemispheric functioning, particularly tasks that utilise visual information, result in difficulties learning new information by associating it with previously learned ideas (Logie, 1995). In addition, it has been found that children who have difficulties understanding novel events, rapidly processing information, and combining elements of a situation in order to understand it as a whole, have difficulty understanding the gestalt of a social exchange, this is likely to interfere with social interactions and responses (Schnoebelen, Semrud-Clikeman, Guli, & Corlett, 2002). The literature also suggests that interpreting the emotions of others depends, to a certain degree, on the individual's ability to understand and make sense of the process of emotional functioning (Borod, Angleman, Obler, Tweedy, & Welkowitz, 1992). In order to manage this effectively, an individual uses spatial organisation to make sense of others' emotions, while working memory processes allow the individual to apply appropriate inferences to their own and others' emotions. Deficits in spatial organisation and working memory, as found in this study, may limit the adolescent's ability to process the details that are involved in emotional exchanges.

In addition to scholastic and emotional difficulties, individuals with neuropsychological impairment in a fundamental area, such as memory, may be limited in terms of functional outcomes (Schiller et al., 2009). Remediation strategies should be employed as early as possible in order to address neuropsychological fallout. Interventions employed for children and adolescents with non-verbal learning disabilities include increasing social awareness, teaching problem solving strategies, encouraging generalisation of problem solving

strategies, strengthening and improving verbal skills, interpreting competing stimuli, providing structure for exploration, utilising concrete aids, and teaching self evaluation and monitoring (Rourke, 1989). Thus, future research on the efficacy of applying these intervention strategies to HIV positive children and adolescents in South Africa may provide a way in which right hemispheric functions may be strengthened and enhanced as much as possible.

Depression in the HIV population will also need to be considered as depressive symptomatology may inhibit the improvement of the neurocognitive sequelae of HIV (Gibbie et al., 2006). This is particularly relevant in South Africa where there are high levels of orphans and child headed households due to the HIV pandemic. Clinicians will need to be aware of this when treating or assessing HIV positive adolescents. Waldrop-Valverde, Ownby, and Kumar (2005) found that moderate to severe depression in HIV positive individuals was associated with lower neurocognitive performance. These findings suggested that depression has a reductive effect on attention, memory, constructional skills, motor functioning, processing speed, and executive functioning, indicating that the outcome is diffuse. In addition, Vázquez-Justo, Rodríguez Álvarez, and Ferraces Otero (2003) found significantly poorer neurocognitive performance in an HIV positive sample with depression than in an HIV negative sample with depression. This further indicates that depression exacerbates the independent effect HIV has on neurocognitive performance.

The results indicated general deficits in the neuropsychological profile of HIV positive adolescents receiving antiretroviral treatment. This included speed of information processing, holistic processing, and visuospatial processing, each of which are predominantly right hemispheric functions. In addition, although verbal memory seemed to have remained intact when compared to their typically developing peers, the comparison of the performance on tasks of visuospatial memory in the HIV sample was significantly poorer. These results create a similar profile to that of a non-verbal learning disorder and efforts may be made to establish whether HIV positive children and adolescents may respond to similar remediation strategies as those used for non-verbal learning disorders. Comorbid depression has been shown to exacerbate neurocognitive deficits associated with HIV and will need to be treated both psychiatrically and psychologically in order for the deficits in functioning attributed independently to HIV to be remediated.

Limitations

There were a number of limitations in this study related to the sample, procedure, and tests used that may limit the generalisability of the results. These limitations are discussed below with particular reference to the South African context.

Sample.

Due to time constraints for this particular research a larger sample size was not possible. The unequal numbers between groups were great and a larger experimental group sample size would have been an advantage. In addition, a third group of HIV positive adolescents who had initiated HAART treatment from birth would have supplemented the study to a degree, and would have allowed for the investigation of the effect of HIV treatment on cognition prior to symptomatology of immuno-compromise.

Language.

Language difficulties may, to some degree, have had an effect on the adolescents' performance on the assessment battery. None of the participants in this study spoke English as a first language. An attempt was made to control for this by the inclusion criterion that each participant had to have completed at least four years of education in an English medium school. However, it was not possible to determine whether English was exclusively spoken at the schools which the participants attended due to the partial implementation of the Revised National Curriculum Statement's (RNCS) language policy (Adler, 2001; Department of Education, 2002; Vesley, 2000). The assessment battery was administered in English by English speaking assessors. Consequently, the results from the assessment battery may not be a true reflection of each individual's ability as their level of English proficiency may not have been at the standard at which the assessments required. The general qualitative sense of their English language ability was that they were largely proficient, however the fact that English is not their first language requires some consideration. The use of a control group who were also second language speakers attempted to deal with this situation.

Assessment Battery.

Some of the content of, and the language used in, the assessment battery was not culturally relevant to a South African sample. An example of this is the Vocabulary subtest on the WISC-R which requires the adolescent to define words such as "Nuisance", "Stanza", "Belfry" and "Espionage". For second language English speakers, these words are complex and not generally used in everyday conversational English, which is what this sample is generally exposed to at school. In addition, the Comprehension subtest of the WISC-R necessitates that the adolescent answer questions posed to them in such a way that is

practically and morally appropriate. One such question is “What are you supposed to do if you find someone’s wallet or [bag] in a [shop]?”. The accepted answer is that one would return the wallet or bag to the owner or, alternatively, give the wallet or bag to the shop owner. However, the adolescents in this particular sample were from low socio-economic brackets where the majority of them struggled financially to the extent that their parents were concerned at the prospect of providing three meals a day. In the postulated situation, it may be credible for the adolescent to answer that they would use the money in the wallet to buy food for their families. Thus, contextual factors are instrumental in the interpretation of the results.

Foreign elements that would not be understood by the adolescent, such as “pocket book” or “pounds”, and questions, such as “Who discovered America?” or “From what country did America become independent in 1776?” were adapted to the South African context in order to make them more accessible to the South African population. Nevertheless, ongoing attempts to create assessments standardised for the South African context are vital in order for assessment in South Africa to be as fair and as unbiased as possible.

Choice of Assessment Battery.

As this study was part of a larger study the assessment battery used was predetermined and did not allow for flexibility. Replication of this study, or future research on the effect of HIV on the memory profiles of seropositive adolescents, would possibly need to adapt the assessment battery and employ the use of purer memory assessments such as the Child Memory Scale, as an example. Nevertheless, the intelligence assessment that was administered supplemented the interpretation of the memory processes and allowed for a richer analysis of memory as a construct subject to various cognitive processes.

Conclusion and Suggestions for Future Research

With the prevalence of HIV in Sub-Saharan Africa being the most affected area worldwide, it is apparent that further research in the field is necessary. In the 2011 statistics on HIV/AIDS internationally, South Africa has been reported to be home to the largest population of infected people in the world with an estimated 5.6 million individuals living with HIV (UNAIDS, 2011). It has been found that the primary mode of infection in South Africa is vertical mother to child transmission and despite efforts to institute Preventative Mother to Child Transmission (PTMCT), it remains the most prominent mode of infection (Newell, Coovadia, Cortina-Borja, & Rollins, 2004; UNAIDS, 2012). In addition, it has been estimated that 90% of children orphaned by AIDS worldwide live in Sub-Saharan Africa

(UNAIDS, 2010). This being the case, it is likely that these orphans are infected with the virus and may remain ARV naïve until they begin presenting symptomatically. These statistics reveal the urgency with which research needs to be conducted in these populations in order for the country, as well as the continent, to best deal with the pandemic. Importantly, future research will need to focus specifically on HIV in the child population as the effect of the virus on the development of a Southern African population is largely unknown.

Much of the current research that has been conducted in HIV populations, where ages and demographics vary considerably, has been done in Western countries where the prevalent strain of HIV is clade B (Ellis et al., 2009). However, in South Africa specifically the population is predominantly infected by clade C HIV (Shisana et al., 2009). As a result, the conclusions that are drawn from the current literature may not apply to Southern Africa due to the differences in the clinical symptomatology of each clade. This was most notably seen in the current study which found that there were no significant differences in verbal learning ability and verbal memory between the HIV positive group and their typically developing peers. These findings are in contrast to previous literature whereby significant differences in verbal memory were found between HIV positive and HIV negative samples (Becker et al., 1995; Delis et al., 1995; Peavy et al., 1994). This provides an example of the way in which neurocognitive profiles between clades that have different rates of progression and different levels of severity may differ. In this regard, further research may also focus on a comparison of the effects of the clades, not only on child development, but also on differing neurocognitive profiles in both pediatric and adult populations. In addition, longitudinal studies would be useful in order to track change in memory functioning over time. It is possible, for example, that the effects of HIV on verbal learning may only emerge at a later stage which may be found as a result of conducting longitudinal research.

In addition, literature from the US showed that ARV-naïve children who were placed onto HAART after presenting symptomatically present with greater neurocognitive deficits when compared to children who are placed on ARVs from birth due to the restrictive impact the treatment has on the progression of the disease (Laughton et al., 2010). South Africa has faced, and is currently facing, much the same difficulty whereby children who are ARV naïve are only administered HAART once they present symptomatically. The sample in the current study comprised such individuals. Thus, replication of these studies that have been conducted in the US would be useful in South Africa whereby the neurocognitive profiles of children who have received ARVs from birth may be compared to those whose treatment began later.

In this way, the differential effect of the progression of HIV on child development may be better understood.

The results of the current study indicate significantly poorer functioning in processing speed, holistic processing, and spatial processing as well as specific visual functions such as visual constructional skills, visual recall ability, disruptions in both storage and retrieval of visuospatial information, and visual spatial working memory. The common neural underpinnings of these functions may be attributed to right hemispheric processes (Butler et al., 1994). The findings in this study suggest that the preferential effect HIV has on frontostriatal circuits may be responsible for the proposed neurocognitive memory profile, whereby the right hemisphere is more significantly affected than the left hemisphere due to the increased degree of white matter tracts. Should this be the case, the neurocognitive profile of HIV positive children and adolescents may be similar to those with non-verbal learning disorders. Future research may establish the degree to which this is possible and, by extension, the implications of this finding for cognitive remediation as early as possible. Research may also investigate the efficacy of the use of interventions targeted at children with non-verbal learning disabilities in an HIV positive population and adapt them where necessary.

In addition, the assessment battery used in the current study was limited by the aims of a larger cohort. Thus, future research may be conducted further investigating the effects of HIV on developing memory functions and potentially understand the interacting memory processes in a more holistic manner through the use of an assessment battery more targeted to memory. This may facilitate a better appreciation for the manner in which the affected memory functions may be remediated. Alternatively, an understanding of the effect HIV has on general cognitive functioning, and how this relates to and affects memory, will allow for insight into which cognitive functions may be strengthened in order to compensate for deficits in functioning. An example of this is the way in which information is presented to children and adolescents in school. Should visual memory functioning be compromised by HIV, the school syllabus may place more emphasis on verbal learning strategies for HIV positive pupils and limit, as far as possible, dependence of information presented visually.

With the prevalence of HIV in Sub-Saharan Africa, especially South Africa, being so high it is imperative that further research is conducted in various aspects of the effects of HIV in order to gain insight and understanding into the pandemic this country faces. Due to the fact that the prevailing literature on HIV originates predominantly from the US, the

generalisability of the results of these studies is unreliable as a result of differences in clade, demographics, and country. The consequence of HIV on memory functioning directly effects learning ability and will therefore continue to impact the education and development of children and adolescents thereby a permitting a perpetuation of the social impact of HIV in South Africa unless further research is initiated and interventions are attempted.

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Appendix A: Parental Information Sheet (Empilweni 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

Appendix B: Parental Consent Form (Empilweni Group)



**UNIVERSITY
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

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 C: Participant Information Sheet (Empilweni 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 your 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

Appendix D: Participant Assent Form (Empilweni Group)



UNIVERSITY
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 your 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: _____

Appendix E: 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

☐

Female

☐

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

4. Home Language: Sotho

☐

Zulu

☐

Xhosa

☐

English

☐

Afrikaans

☐

Other

☐

5.	Age at which HAART initiated	
6.	WHO stage of HIV at diagnosis	
7.	CD4+ count at time of HAART initiation	
8.	Viral load at time of HAART initiation	
9.	Current CD4+ 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 books 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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Appendix F: Permission Letter from Primary Health Care Clinic



**Empilweni Services and Research Unit
Rahima Moosa Mother and Child Hospital, JHB**

South Africa (Private Bag X20 Newclare 2112) • Tel: +27(0)11 470 9290 / 9105
Fax: +27(0)11 673 4905 • E-mail: Ashraf.Coovadia@wits.ac.za



6 February 2012

To whom It May Concern:

Re: Neuropsychological research on HIV positive adolescents attending the Empilweni Clinic

Ms Urvashi Chiba, Mr Daniel Greenslade, Ms Shona Fraser, Ms Stephanie MacIlwaine, Ms Kelly Holland

This letter serves to confirm that, I, Professor Ashraf Coovadia, support the study conducted by the above-mentioned MA (Neuropsychology) students.

In my capacity as head of the Wits Empilweni Clinic; access to the database of patients attending the Empilweni Clinic is granted with permission to conduct the neuropsychological research assessments on willing participants.

Yours faithfully

Professor Ashraf Coovadia
Head of HIV services and Director of ESRU
Rahima Moosa Mother and Child Hospital

RAHIMA MOOSA MOTHER & CHILD HOSPITAL



Dr Edward Hank
Clinical Manager and Superintendant
Rahima Moosa Mother and Child Hospital
Tel: (011) 470 9031
Fax: (011) 477 4117
E-mail: Edward.Hank@gauteng.gov.za

Professor Cleaton-Jones
Chair of the Wits University
Human Ethics Research Committee

6 February 2012

Dear Professor Cleaton-Jones,

Re: Neuropsychological research on HIV positive adolescents attending the Empilweni Clinic

On behalf of the hospital management I would like to confirm our approval for the conduct of the above named study at our institution. This study will be conducted in the Empilweni Clinic who have through it's head, Professor Coovadia, provided permission to do so. The researcher will be able to access hospital records provided she has ethics approval and receives signed informed consent from the caregiver of the study participant.

Yours faithfully

Dr Edward Hank – BSc Hons B Pharm, MBCh

Cc – Mrs S Jordaan – CEO, Rahima Moosa Mother and Child Hospital
- Prof A Coovadia – Head HIV Services, Rahima Moosa Mother and Child Hospital,
Department of Paediatrics and Child Health

Appendix G: Permission Letter from the Department of Education



education
Department of 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/HQ	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.

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. Rates 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

Appendix H: Histograms for the Qualitative Assessment of the Statistic Analyses

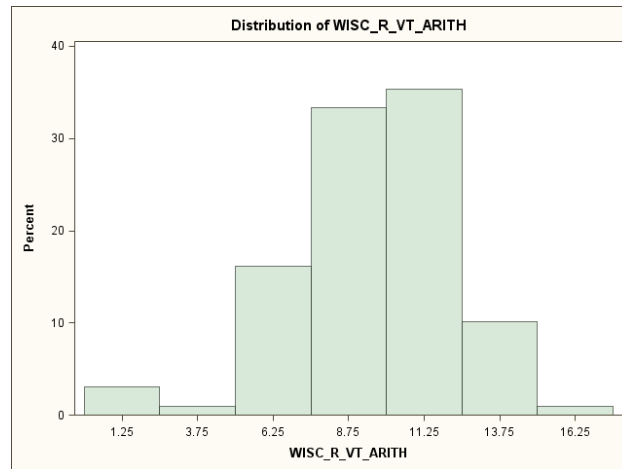


Figure 1. Histogram: Arithmetic Subtest of the WISC-R

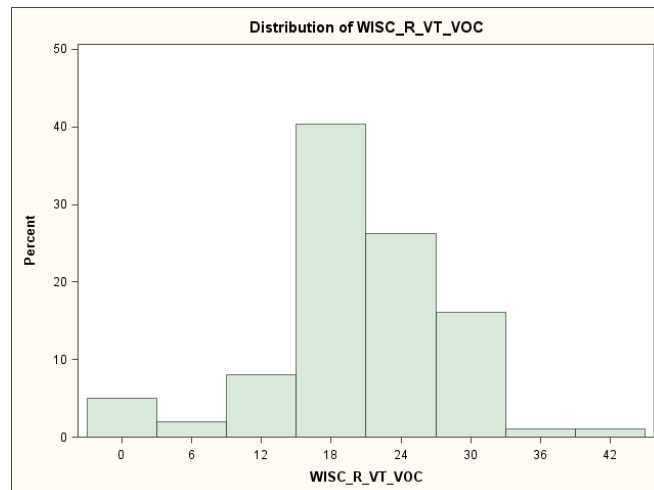


Figure 2. Histogram: Vocabulary Subtest of the WISC-R

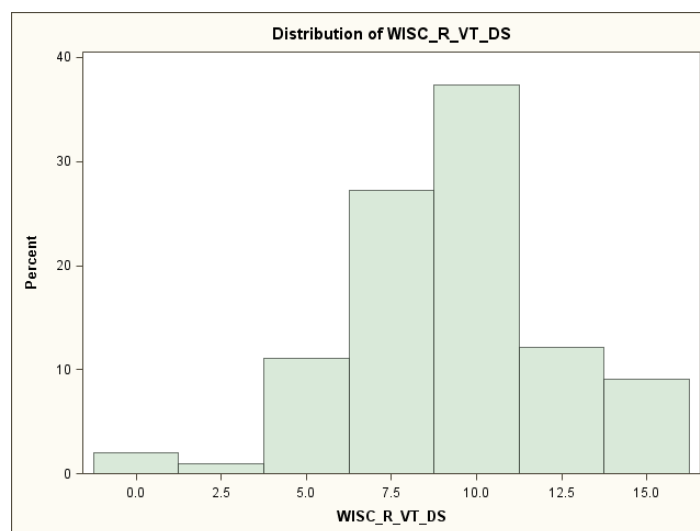


Figure 3. Histogram: Digit Span Subtest of the WISC-R

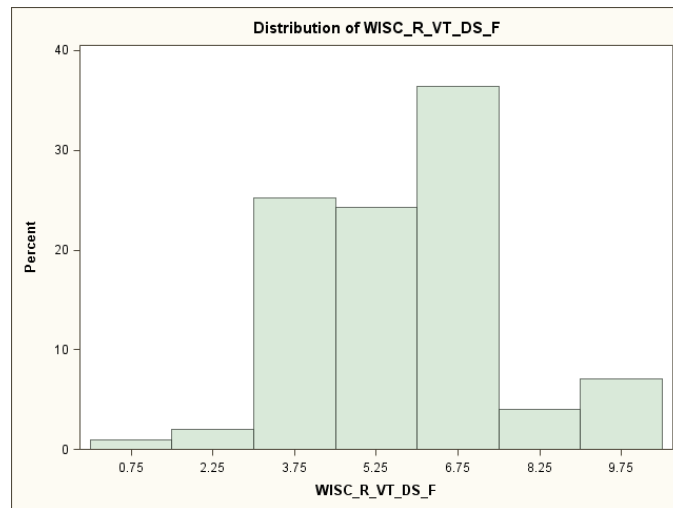


Figure 4. Histogram: Digit Span Forward in the WISC-R

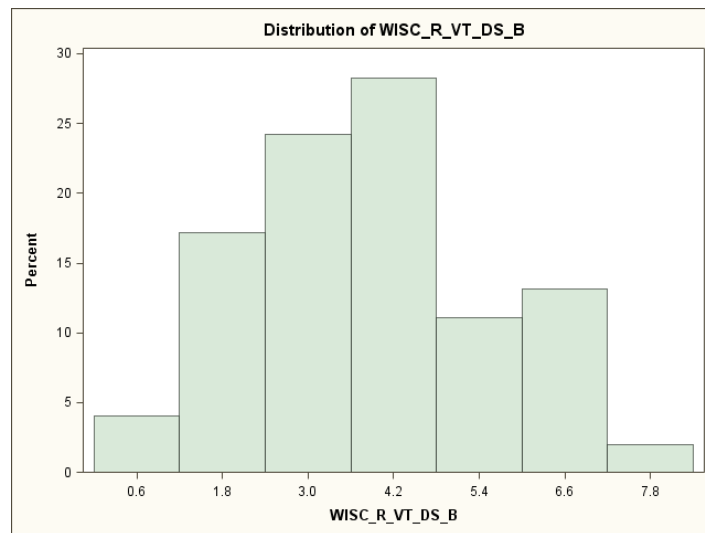


Figure 5. Histogram: Digit Span Backward in the WISC-R

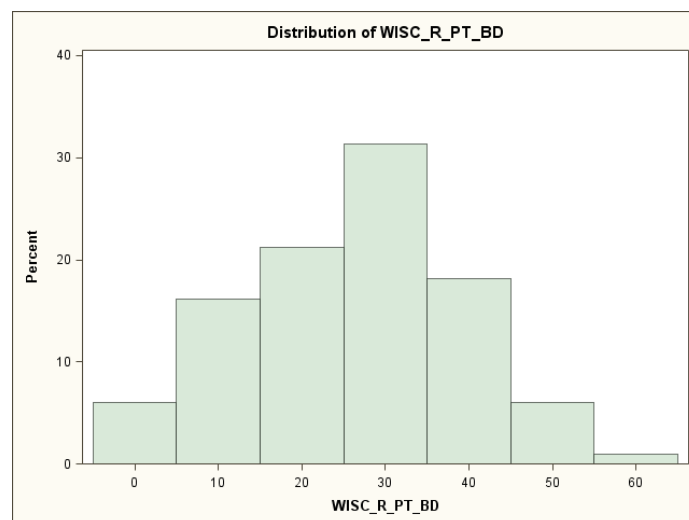


Figure 6. Histogram: Block Design Subtest of the WISC-R

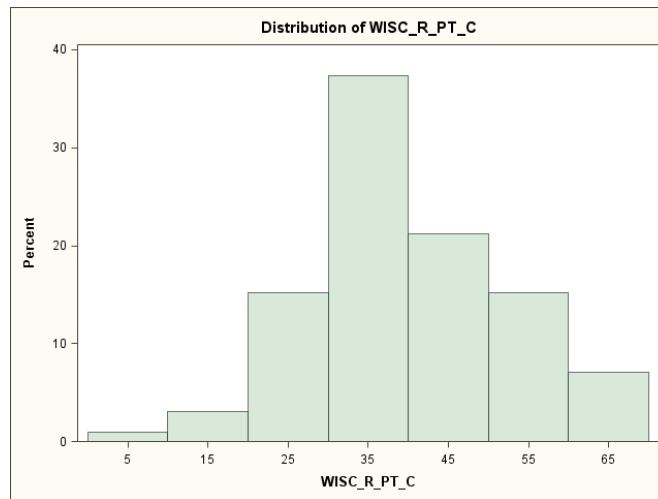


Figure 7. Histogram: Coding Subtest of the WISC-R

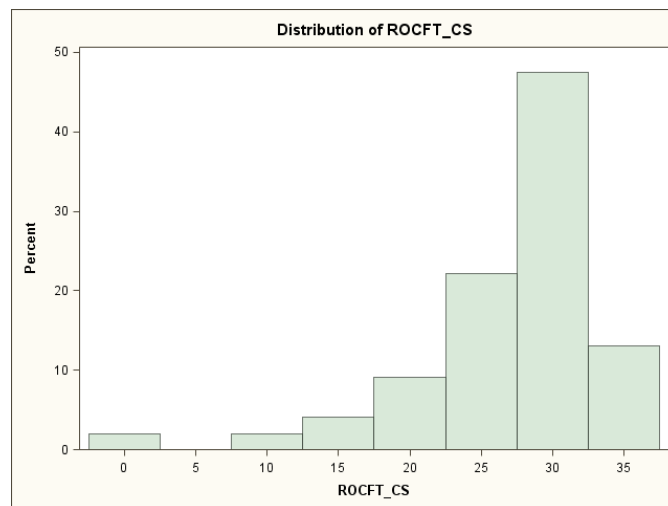


Figure 8. Histogram: Copy Trial of the ROCFT

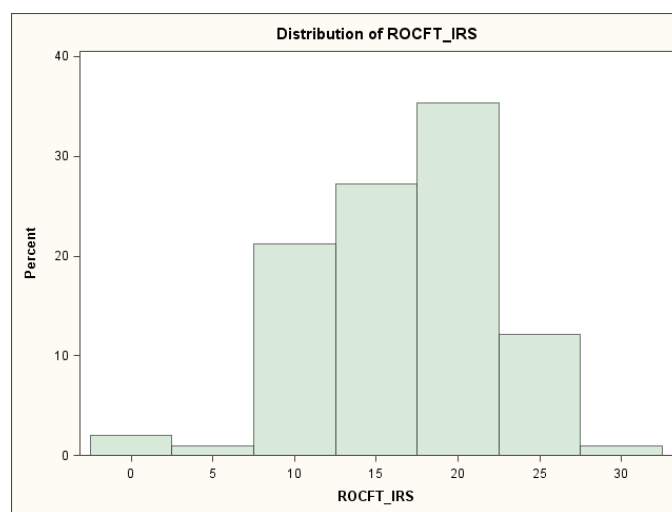


Figure 9. Histogram: Immediate Recall Trial of the ROCFT

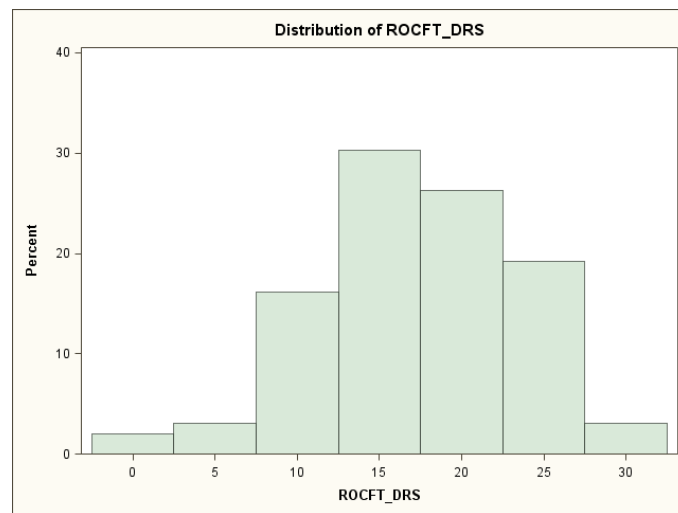


Figure 10. Histogram: Delayed Recall Trial of the ROCFT

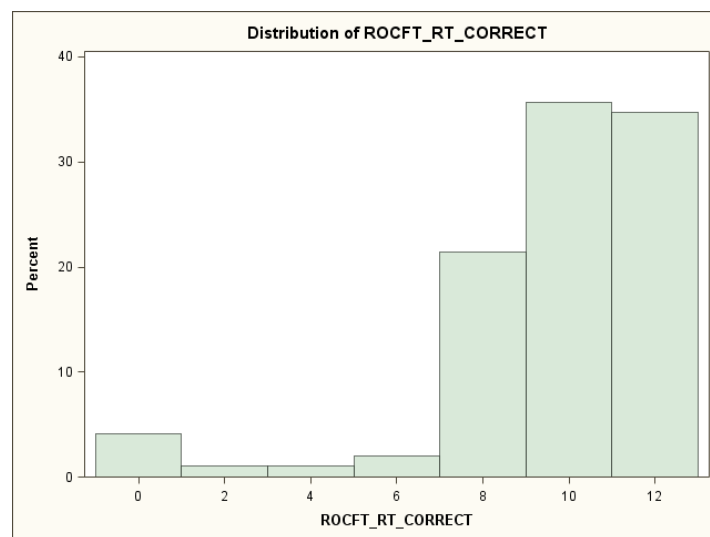


Figure 11. Histogram: Recognition Trial of the ROCFT: Number of Items Correct

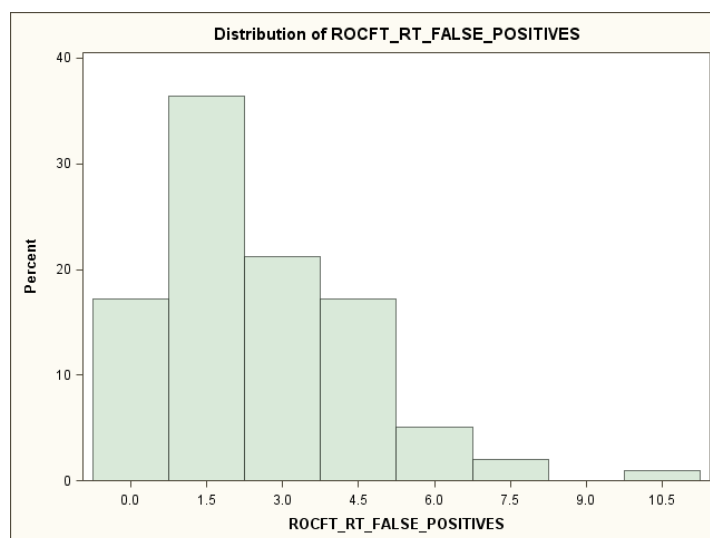


Figure 12. Histogram: Recognition Trial of the ROCFT: Number of False Positives

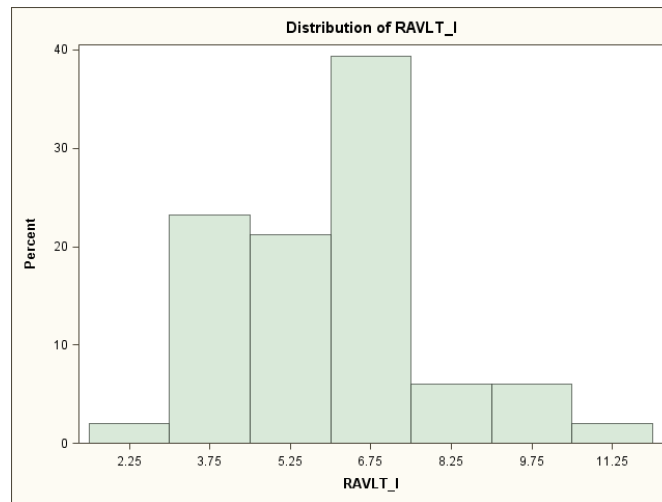


Figure 13. Histogram: Trial I of the RAVLT

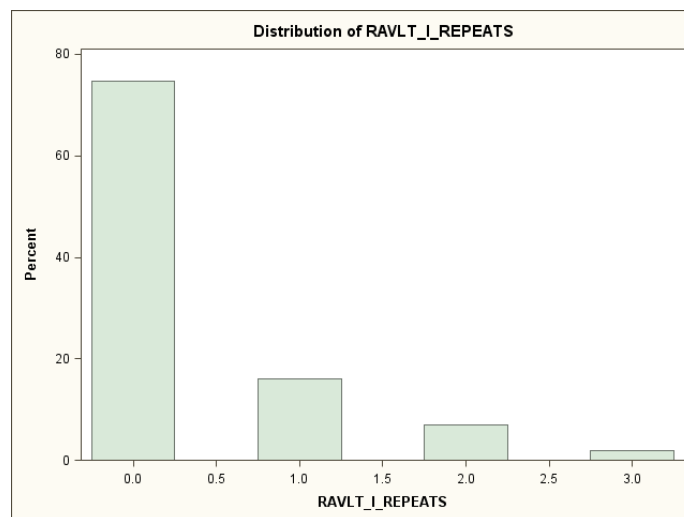


Figure 14. Histogram: Trial I of the RAVLT: Number of Repeats

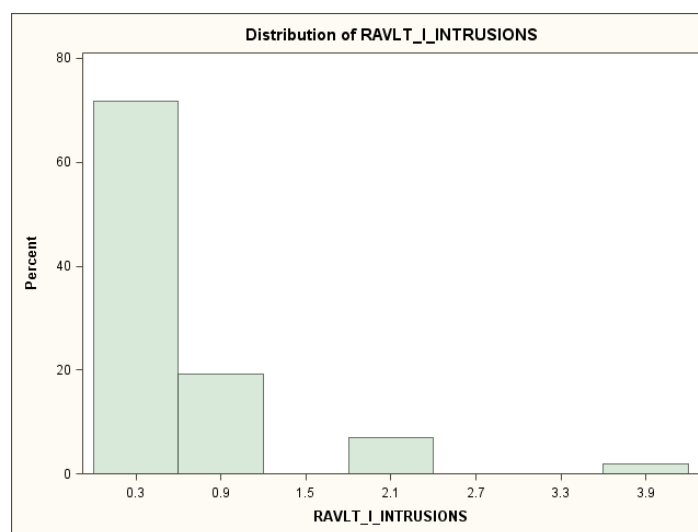


Figure 15. Histogram: Trial I of the RAVLT: Number of Intrusions

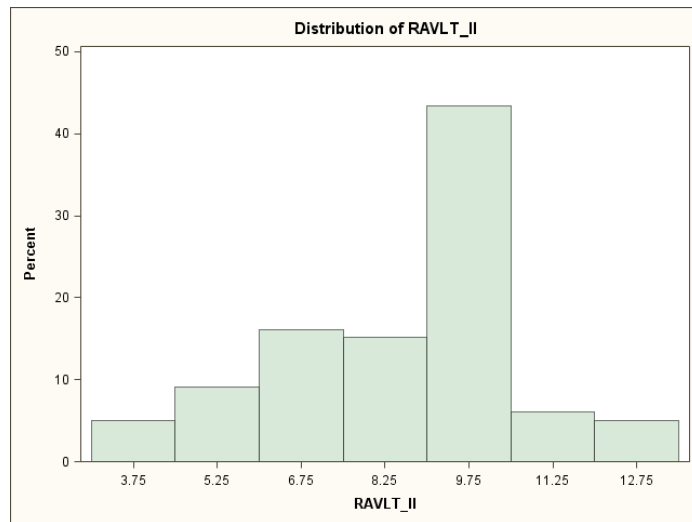


Figure 16. Histogram: Trial II of the RAVLT

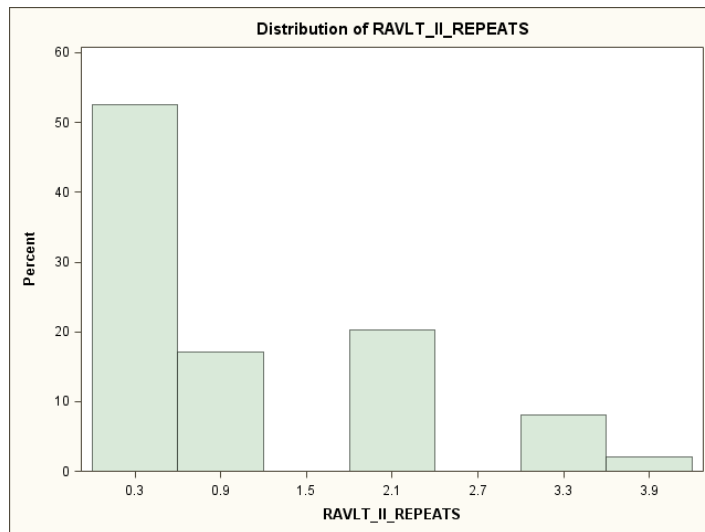


Figure 17. Histogram: Trial II of the RAVLT: Number of Repeats

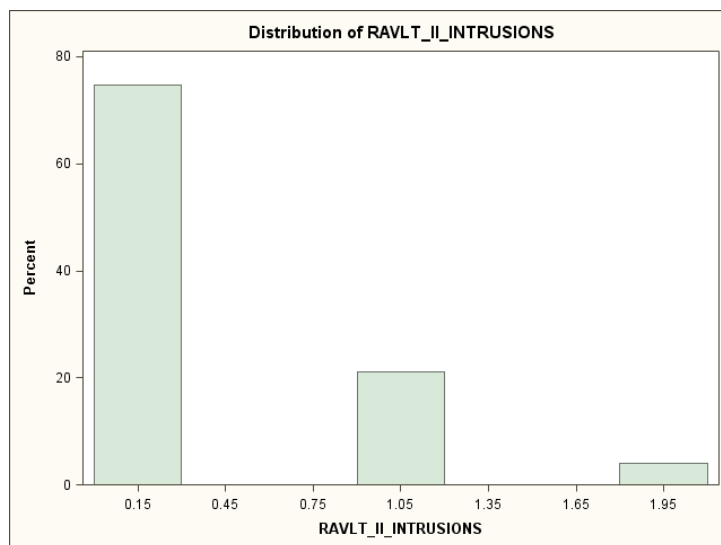


Figure 18. Histogram: Trial II of the RAVLT: Number of Intrusions

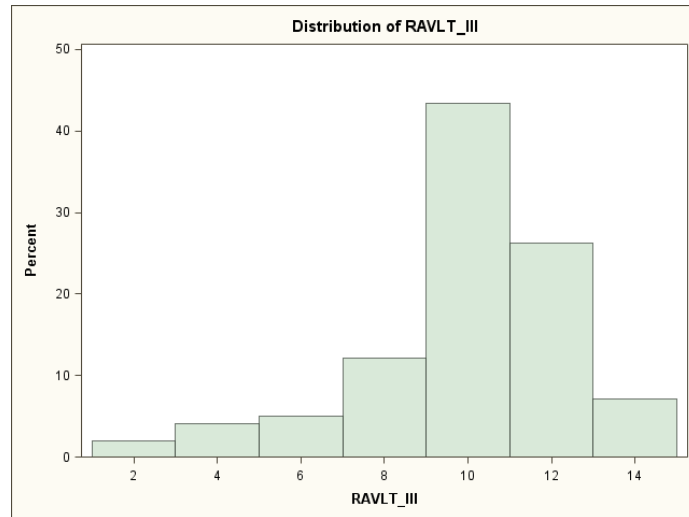


Figure 19. Histogram: Trial III of the RAVLT

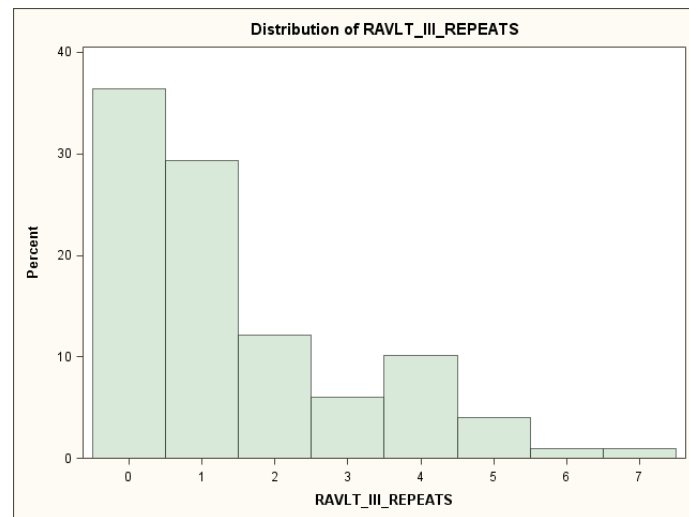


Figure 20. Histogram: Trial III of the RAVLT: Number of Repeats

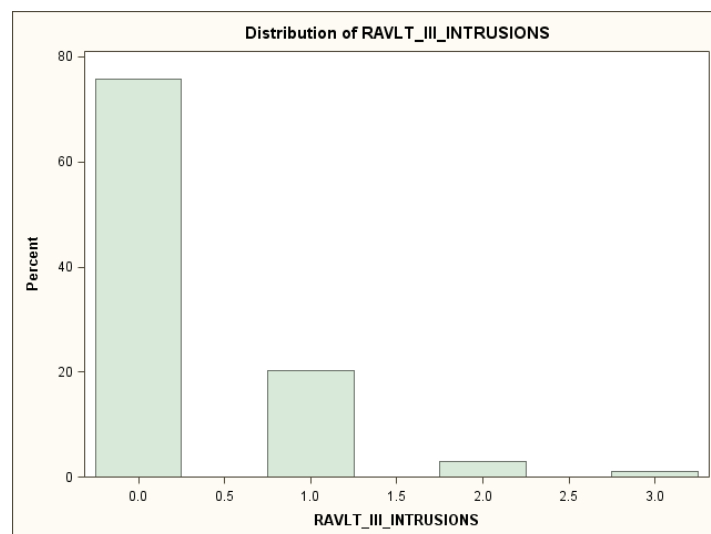


Figure 21. Histogram: Trial III of the RAVLT: Number or Intrusions

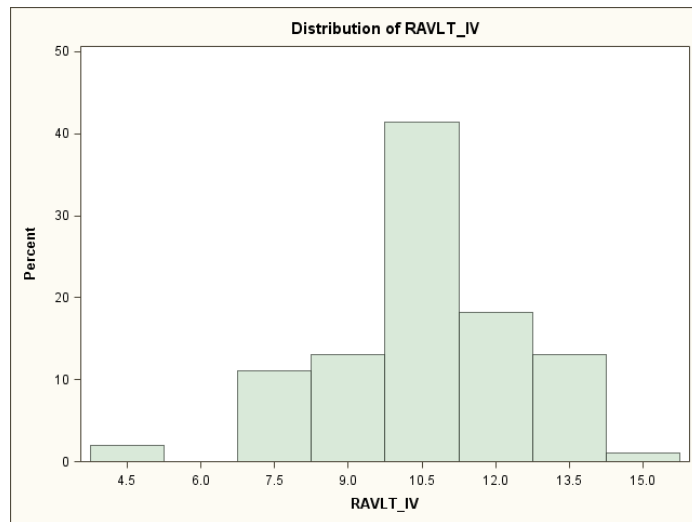


Figure 22. Histogram: Trial IV of the RAVLT

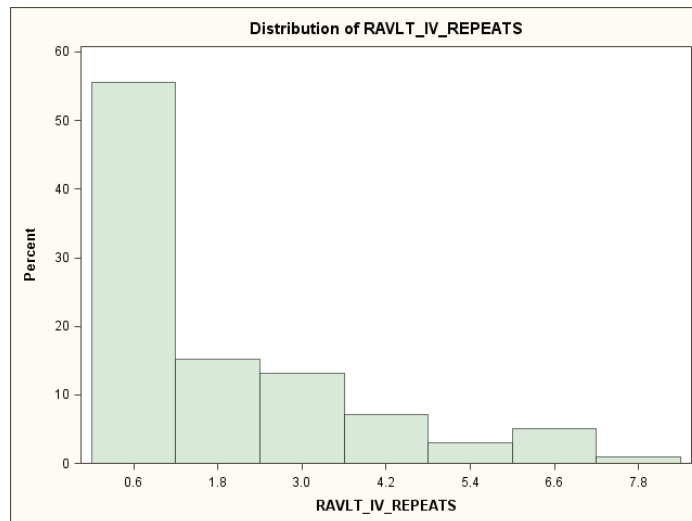


Figure 23. Histogram: Trial IV of the RAVLT: Number of Repeats

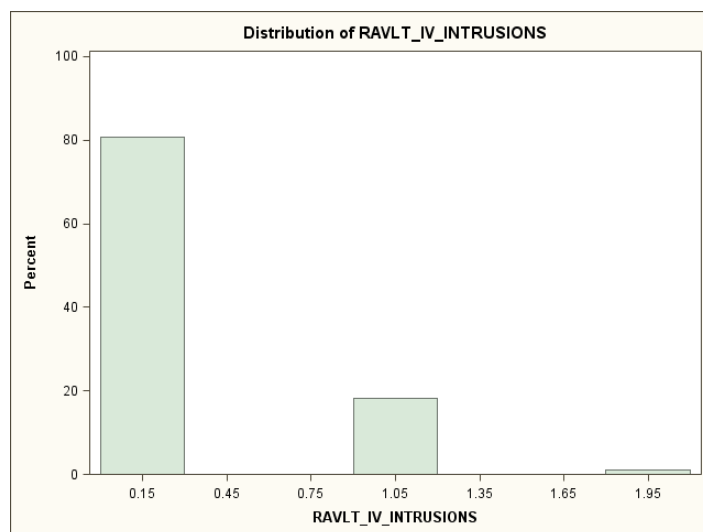


Figure 24. Histogram: Trial IV of the RAVLT: Number of Intrusions

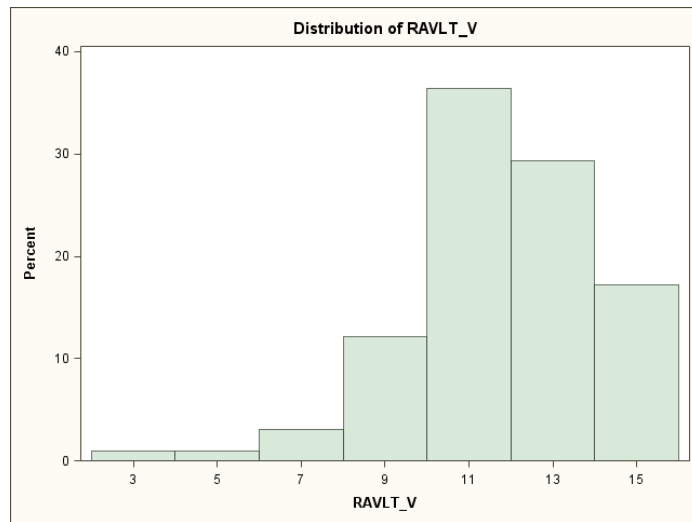


Figure 25. Histogram: Trial V of the RAVLT

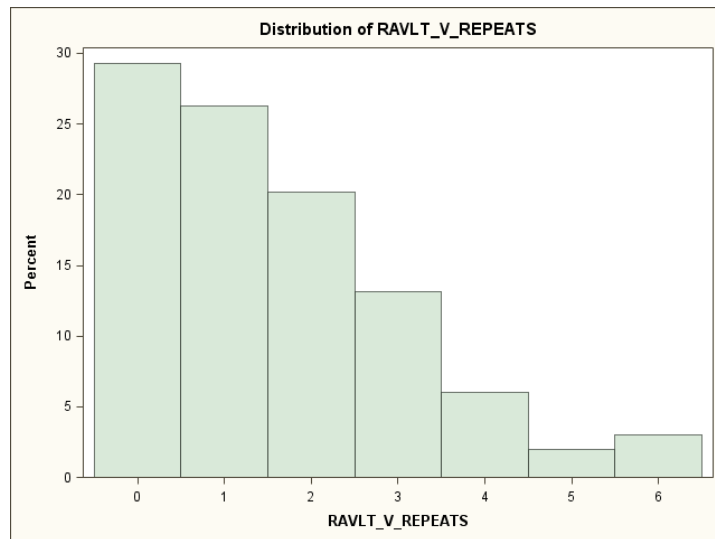


Figure 26. Histogram: Trial I of the RAVLT: Number of Repeats

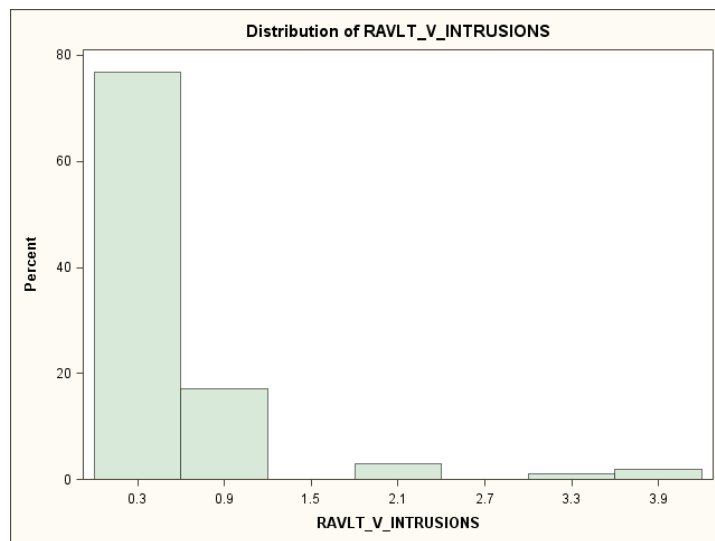


Figure 27. Histogram: Trial I of the RAVLT: Number of Intrusions

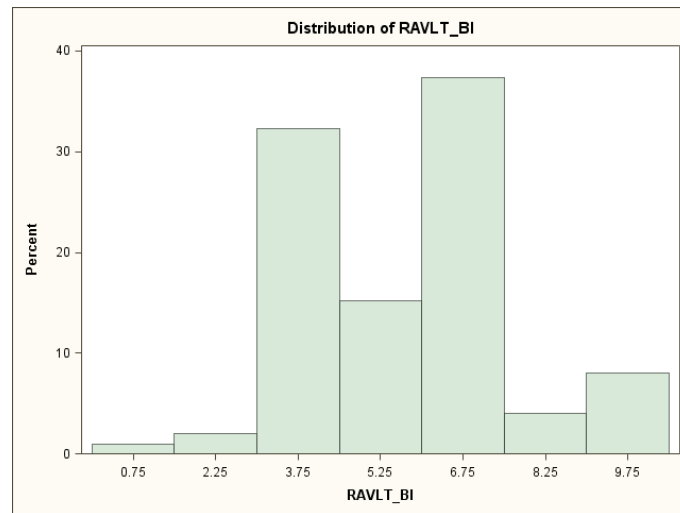


Figure 28. Histogram: Trial BI of the RAVLT

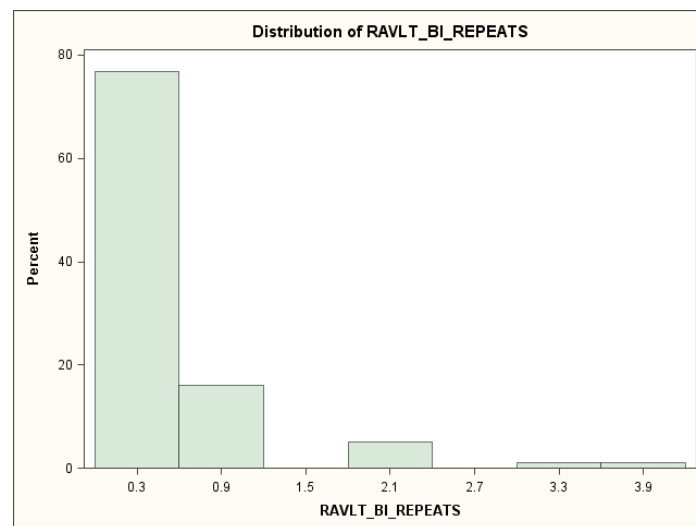


Figure 29. Histogram: Trial BI of the RAVLT: Number of Repeats

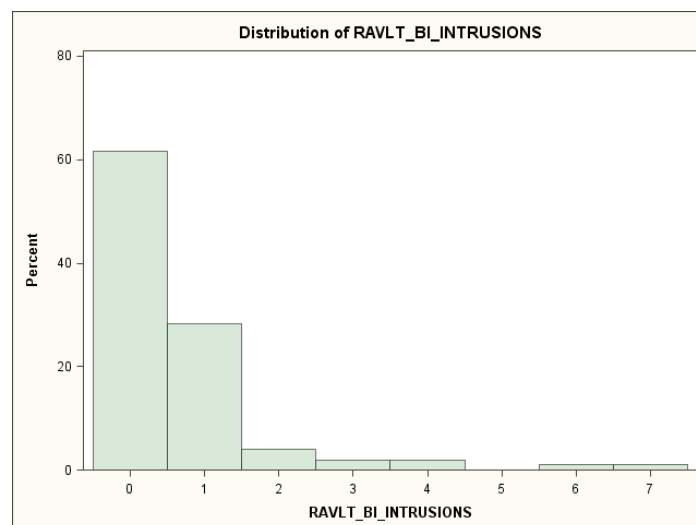


Figure 30. Histogram: Trial BI of the RAVLT: Number of Intrusions

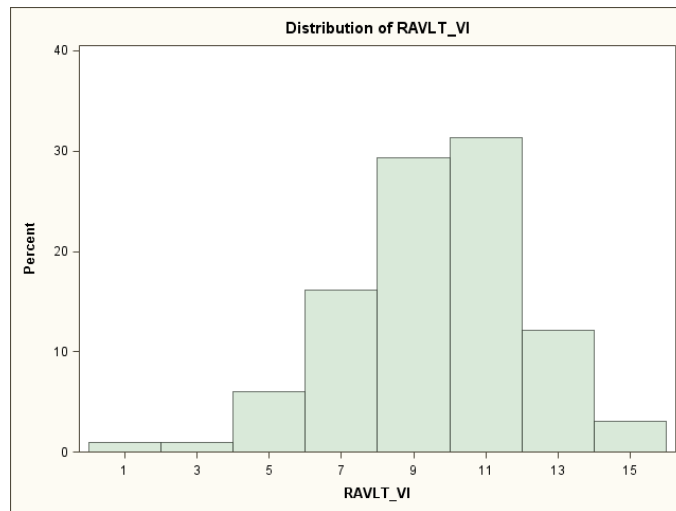


Figure 31. Histogram: Trial VI of the RAVLT

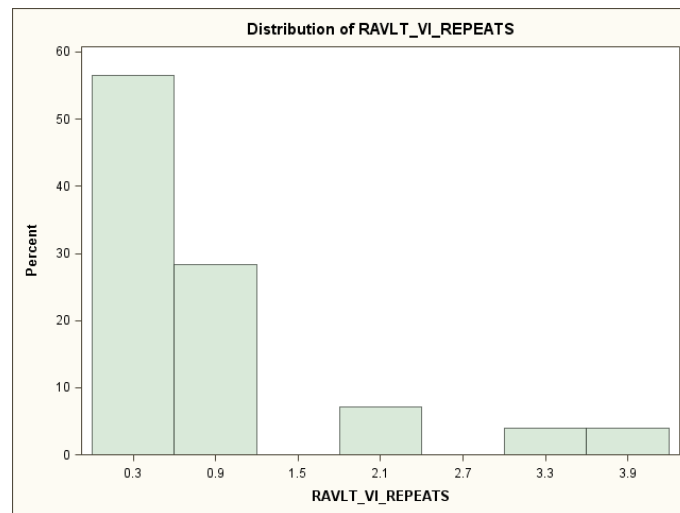


Figure 32. Histogram: Trial VI of the RAVLT: Number of Repeats

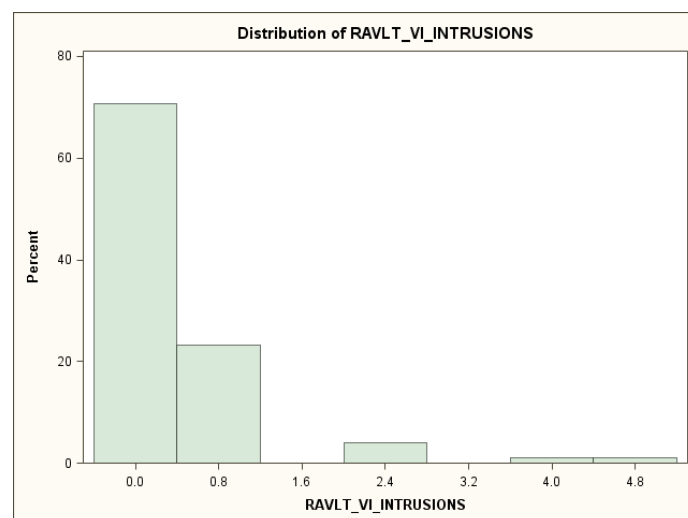


Figure 33. Histogram: Trial VI of the RAVLT: Number of Intrusions

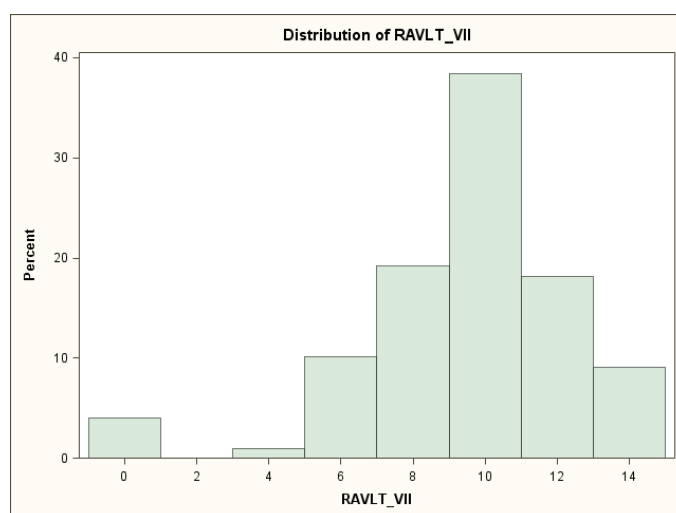


Figure 34. Histogram: Trial VII of the RAVLT

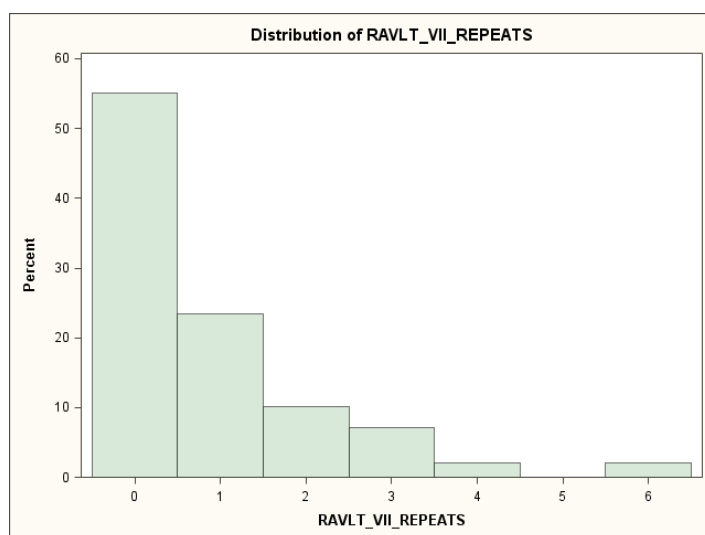


Figure 35. Histogram: Trial VII of the RAVLT: Number of Repeats

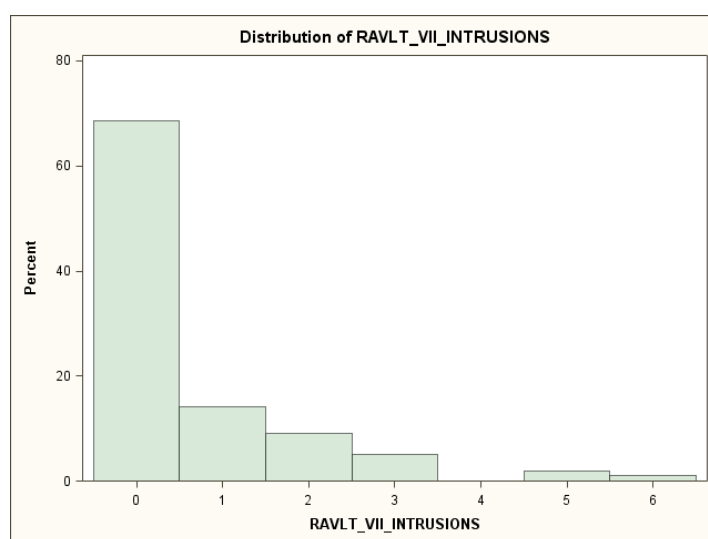


Figure 36. Histogram: Trial I of the RAVLT: Number of Intrusions

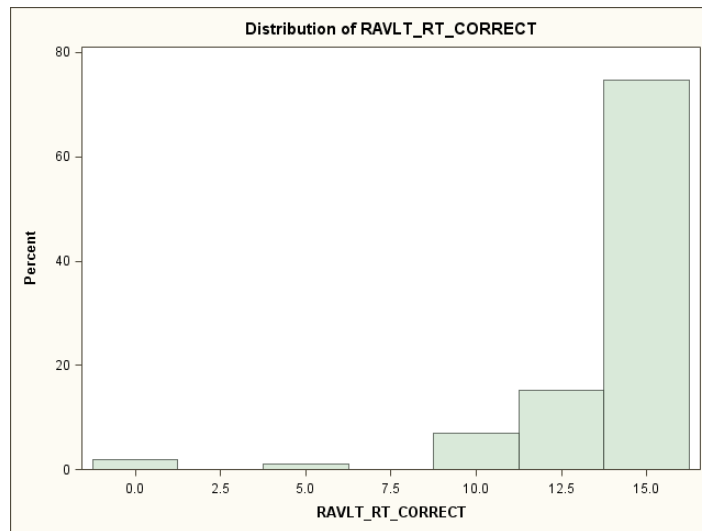


Figure 37. Histogram: Recognition Trial of the RAVLT: Number of Correct Items

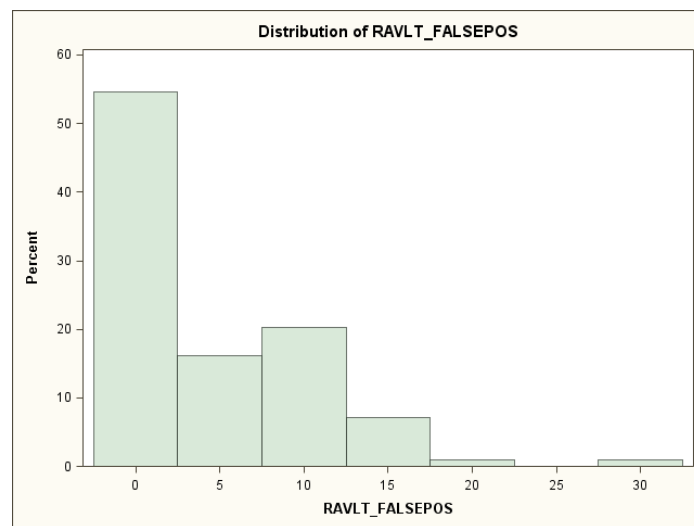


Figure 38. Histogram: Trial I of the RAVLT: Number of False Positives

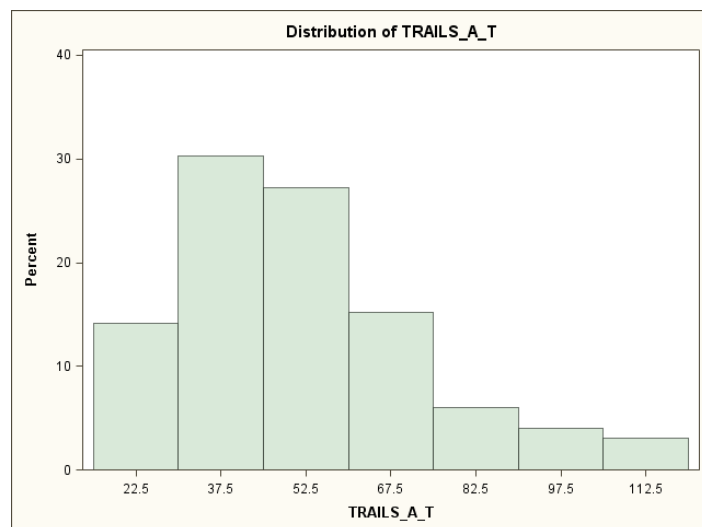


Figure 39. Histogram: Time Taken to Complete Trial Making A

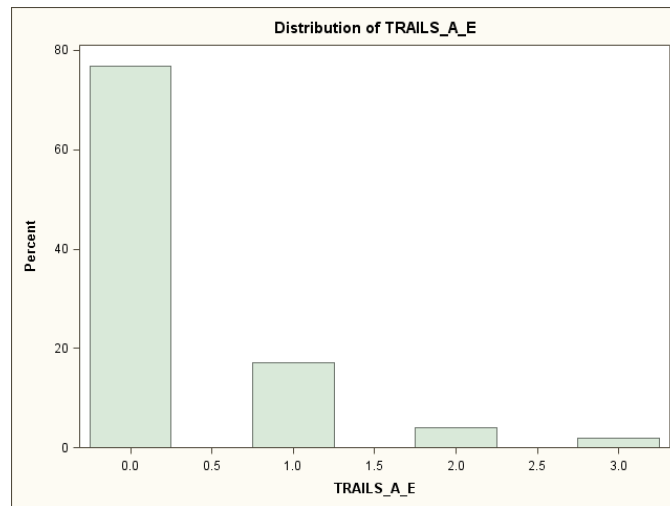


Figure 40. Histogram: Number of Errors Made on Trail Making A

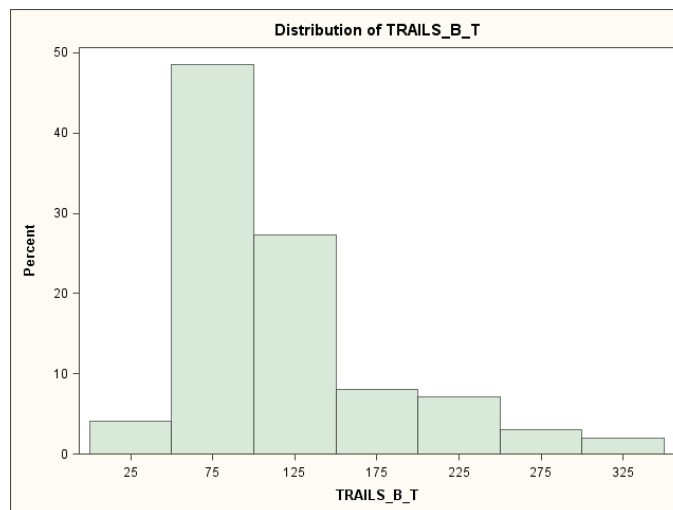


Figure 41. Histogram: Time Taken to Complete Trail Making B

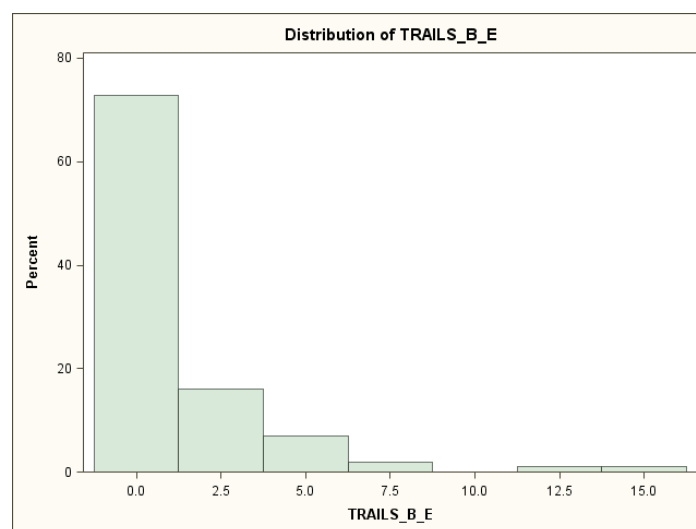


Figure 42. Histogram: Number of Errors Made on Trail Making B