Executive Function performance in HIV Positive Adolescents on Anti-Retroviral Treatment in Johannesburg, South Africa

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To Meera and Misha….

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Abstract

Executive Function is conceptualized in this study as the ability to form (the planning functionality obtained through initiation and working memory), maintain (response selection and the ability to self-regulate and inhibit) and switch (cognitive flexibility, mental tracking, organization and sequencing) mental processes in order to effect a positive outcome. The present research is a quasi-experimental study embedded in the Positivist tradition that sets out to empirically evaluate the Executive Function profile of seropositive adolescents (n = 29) emerging from a low socio-economic background and currently on a managed ART programme when compared to a healthy contrast group (based on age, socio-demographic and educational system). As a quantitative study, Executive Function was operationalized through the use of multiple tests of Executive Function such as the Delis-Kaplan Executive Function Colour Word Interference Test (D-KEFS CWIT), the Wisconsin Card Sorting Test (WCST) and the Trail Making Test Part B (TMT-B). As the study formed part of a larger study that included additional neurocognitive tests, including the WISC-R, selected subtests from the WISC-R were used to validate specific arguments relating to the study. The results showed that HIV positive adolescents were inclined to have poorer Executive Function performance especially under situations of higher cognitive load when compared to the unaffected group. The implications of these results are discussed in this research.

Introduction

Executive Function (EF) is an elusive term that is evidenced by at least a dozen (if not more) definitions. Researchers have consequently attempted to explore EF using different approaches. One such approach includes the evolutionary and embodied cognition approach that serves to understand EF in terms of its evolutionary purpose of maintaining fitness for survival. As such, EF studies are based on its 'adaptiveness' facility (Barkley, 2001; Buller, 2006; Koziol, Budding, & Chidekel, 2011). While this approach is indeed commendable, it may be considered atheoretical – with EF measurement tools of adaptitivity still emerging (Barkley, 2001). Other researchers have opted to explain EF from a clinical syndromatic approach (Scott & Schoenberg, 2011) and identify EF deficits according to its neural correlates. This definition has been based on clinical populations as well as animal lesion studies and the use of double dissociations to localise deficits. While advantageous, it can nevertheless be an expensive process with appropriate clinical subjects being few and far between. Furthermore clincial observations do not always correlate with imaging data.

An alternate approach to understanding EF emerges from cognitive neuroscience and the use of standardised neuropsychological tests as a means of eliciting and measuring behaviour. This approach first conceptualises EF in terms of its complex functions and the processes it is concerned with and then deconstructing it into its elemental parts. While this perspective is somewhat modular, it offers the advantage of being easily operationalised (especially in low resource settings) for research purposes. Elemental units can be studied

individually and then the 'puzzle' is reconstructed in order to visualise the picture in its entirety. This approach is gestalt-like with clear adoption of the adage that 'the whole is greater than the sum of its parts' to prevent against silo-like and reductionist opinions that can develop out of elemental analysis. Similar approaches have been discussed by researchers (see Lezak, Howieson, & Loring, 2004; Suchy, 2009)

While the exact definition of EF remains contentious, this study adopts the elemental view in order to gather empirical evidence of the functional deficits impacted upon by HIV on EF processes and what this might *suggest* about the underlying pathology. In this respect we considered how these sub-functionalities are related to different areas of the central nervous system (by incorporating evidence arising from the syndromatic and animal lesion studies approaches) and finally how all of this fits together (by considering some of the arguments posited by evolutionary neuroscience) - so as to arrive at a comprehensive understanding of the 'whole'.

With this in mind, this research begins with the definition that executive function involves those processes that allow people to shift their mind sets quickly and inhibit inappropriate actions so as to facilitate responses to an environment that is in constant flux (Jurado & Rosselli, 2007). Optimal EF performance therefore requires cognitive flexibility – a criterion believed to be necessary for cognitive, emotional and social skills. EF therefore incorporates the highest levels of human functioning viz. intellect, the ability to think and reason and apply it to decision-making; goal directed behaviour and social interaction (Anderson, 2008).

EF has been anatomically associated with the prefrontal cortices, the basal ganglia (and the limbic pathways), the posterior parietal cortex (Woods, Moore, Weber, & Grant, 2009) and cerebellum (Koziol, Budding, & Chidekel, 2011; Strick, Dum, & Fiez, 2009;). Neurodevelopmentally, a key area of executive function viz. the frontal lobes, are the last to achieve maturity. The stimulus-bound, reflexive nature of infants and younger children bears testimony to immature frontal lobe activity. As the child matures, so their ability to formulate a plan, hold it in mind as well as execute that plan becomes more apparent. During development, the child learns and uses feedback from previous failures and successes in order to achieve these goals (Zelazao, Craik & Booth, 2004). So saying, it would be expected that any insult to the cortical or subcortical areas or indeed any of the striatal tracts that connect the prefrontal cortices to the other parts of the brain will lead to compromised executive function.

The invasion of the human immunodeficiency virus on the developing brain suggests that mental processes *will* be affected. Because of the reciprocity between biological processes in the CNS and mental manifestations, it is thought that the way in which the HIV positive child understands and responds to their environment might be affected in some way. From a neuropsychological perspective, this is fundamentally related to an understanding of executive function as the cognitive process that predicts behaviour under novel situations (as discussed above). Against this background, this research has been designed to provide an indication of executive function as it relates to aspects of mental flexibility, response inhibition, generativity and self-monitoring in seropositive adolescents (currently on a managed anti-retroviral programme) and how it might differ from an ostensibly unaffected

group in South Africa (of comparable age, demographics and education). Factors such as the duration of ARV treatment; CD4 T-cell count, viral load drops and gender differences on executive functioning are also considered in the final analysis.

Chapter 1:

1.1 An Overview of HIV

The Human Immunodeficiency Virus (HIV) and the protagonist of the syndrome of Acquired Immunodeficiency Syndrome (AIDS) grew from obscurity in the mid-1970's and early 1980's achieving pandemic notoriety in the ensuing years leading up towards the new millennium. The dying years of the last century also saw the birth of antiretroviral treatment (ART) and along with it, renewed hope for HIV-infected individuals.

ART started with monotherapy and the use of Zidovudine (colloquially referred to as AZT) in 1987. The success of AZT was mixed, but it paved the way for further advances for pharmacotherapy intervention. Still, it was only after the introduction of combination antiretroviral treatment (cART) and highly active antiretroviral treatment (HAART) in 1996 that saw effective HIV-1 viral load suppression and with it improved quality of life (Dennis, Houff, Han & Schmitt, 2011). HAART drastically slowed down (if not stagnated) the rapid progression of the disease, reduced the incidence of HIV Associated Dementia (HAD), increased the lifespan of infected individuals and dropped the mortality rates of HIV infected people (Dennis et al., 2011; Rackstraw, 2011). In the wake of these successes, treatment programmes all over the world, shifted from palliative care to the active management of HIV as a chronic disease (Rackstraw, 2011). So, while morbidity levels have dropped with the advent of HAART, HIV infection is still viewed as a disease, affecting between 30 – 40 million people worldwide (Dennis et al., 2011), an alarming 20% of whom emerge from South Africa with a calculated prevalence of approximately 5.5 million people (Patel et al., 2012).

Having curbed mortality and increased lifespan in the post-HAART era, HIV research has increasingly focused on the effects of HIV on the Central Nervous System (CNS) and how this impacts on the functioning of the individual over the long term (Dennis et al., 2011; Moore, et al., 2011; Patel, et al., 2009; Rackstraw, 2011; Sherr, Mueller & Varrall, 2009). It is well established that physiological or organic changes in the CNS leads to psychological distress and neurocognitive deficits (Rackstraw, 2011). Such is the case with HIV-infection as a consequence of the high CNS penetration of the pathogen. Neurocognitive deficits and psychological changes inevitably do occur as a result of the organic changes induced by the virus.

In the pre-HAART era, one of the pathognomonic indicators for the advancement of the disease was severe neurocognitive decline referred to as either HIV Associated Dementia (HAD) (in the case of adults) or HIV-Encephalopathy (HIVE) (usually indicated in paediatric populations) and characterised clinically by the combination of cognitive, motor and behavioural changes (Singh, 2012). In the post-HAART era, the spectrum of cognitive disorders has been broadened to include HIV Associated Neurocognitive Disorders (HAND) which includes Minor Neurocognitive Disorders (MND) and Asymptomatic Neurocognitive Impairment (ANI) (Joska, Hoare, Stein & Flisher, 2010; Rackstraw, 2011; Singh, 2012). These definitions are based on the neurocognitive domains associated with HIV infection i.e. verbal/language, attention/working memory, abstraction/executive functioning, memory, information processing speed, sensory perception and motor skills (Singh, 2012). A diagnosis of HIV Associated Dementia (HAD) is based on acquired impairment in at least two domains (evaluated as being at least two standard deviations from age-appropriate norms) and is

accompanied with significant interference with activities of daily living. MND on the other hand is based on the acquired impairment occurring in at least two domains (evaluated as being one standard deviation from age-appropriate norms) and causing some interference with activities of daily living while ANI is defined at the same level of MND on neuropsychological evaluation but does not interfere with activities of daily living (Rackstraw, 2011; Singh, 2012).

Despite the accomplishment of pharmacotherapy used to stunt the disease and reduce morbidity, the pathogen's ability to penetrate the CNS leads to varying degrees of cognitive, behavioural and emotional changes that are more enduring. In the CNS HIV Antiretroviral Therapy Effects Research Project (CHARTER) spanning 2003 – 2007 and covering a sample of 1500 patients in the USA, only 2% of the cohort were found to meet the criteria for HAD with more than 50% meeting the criteria for HAND, half of whom satisfied the conditions for ANI and with the remaining participants falling within the MND group (Heaton, 2009 cited in Rackstraw, 2011).

1.2 The Neuropathology of HIV

Virus penetration into the CNS occurs within the first two weeks following HIV infection (Moore et al., 2010; Rackshaw, 2011). The virus typically enters the body through fluids infecting the CD4 lymphocytes (T-cells) thereby disrupting the genetic material of the lymphatic system of the host DNA (Ellis, Calero & Stockin, 2009). The virus then accesses the CNS via the cerebrospinal fluid (CSF) and in so doing is able to cross the blood-brain-barrier

(BBB). On entry an inflammatory response is triggered by the infection (Mirza & Rathore, 2012) ultimately leading to brain pathology (Civitello, 2003). According to the 2-compartment model, once the neuro-protective functionality has been breached, neurotoxicity becomes the primary cause of neural degeneration. It is generally thought that neural degeneration occurs as a result of the *reduced* neuro-protection functionality of the glial cells coupled with the increased neurotoxicity within the neural cells. In this model, the cytokine cascade is triggered via the metabolites of the neurotoxic gp120 and TAT protein in the plasma, which HIV binds to during infection. HIV acts as a carrier of these proteins and once it has crossed the BBB, the metabolites of the proteins (which include nitric oxide, quinolinic and arachidonic acids) elicit an inflammatory response. In so doing the metabolites affect the functioning of the Ca^{2+} channels of the neural cell walls leading to disruption of neurotransmission. Chronic and persistent toxicity eventually reduces neural integrity and culminates in neuronal death (Gonzalez-Scarano & Garcia, 2005). Over time, cognitive impairment is a fait accompli as a result of en-masse neuronal damage.

1.3 The Neuropsychological Sequela of HIV

HIV management for infected individuals in the post-HAART era has focussed upon post-exposure prophylactic treatment. These endeavours pertain to comprehensive general medical care (in children this includes the assessment of growth and development), HIV disease progression (including the physical examination, regular laboratory work-ups to ascertain levels of CD4 T-cell counts counts and viral loads) and psychosocial assessments (Abrams, Moon, Robinson & Van Dyk, 2006) to establish level of functionality.

Earlier studies have explored the neuropsychological sequela of HIV positive children (Tardieu et al., 1995). In the pre-HAART era, deficits included a broad range of disorders arising from HIVE induced pervasive CNS dysfunctions and neurodevelopmental delays (which has a slow onset) to CNS opportunistic infections. In older school-going children, the first signs were usually declining academic performances, behavioural changes, psychomotor impairment with eventual progressive cognitive impairment and the emergence of new pyramidal tract signs (Civitello, 2003). Given these findings, it is further understood that in vertically acquired HIV, the age at which HAART is initiated becomes a critical predictor for neuropsychological outcomes (Smith, Adnams & Eley, 2008).

Recently, emerging research reports the evidence of a *different* pattern of Neuropsychological deficits in the post-HAART era when compared with the pre-HAART era. Neuropsychological deficits in the pre-HAART era revealed *higher* levels of impairments in *motor skills, speed of processing* and *verbal fluency* (Mirza & Rathore, 2012). Based on the neuropathology of the virus on the CNS, it was also indicated that HIV infection followed a subcortical and white matter route (Heaton, Franklin, McCutchan, Letendre, LeBlanc, Corkran, S., . . . Grant, 2011). The evidence also points to more *impairment in memory and executive function in the post-HAART era* (Heaton et al., 2011). Evidence of this nature suggests that further investigation is needed to ascertain if the neuropsychological profiles of HIV infection in a post HAART era in South Africa reflect similar findings. However, based on this information one could predict that HIV-positive children who had been placed on HAART at a later age (for shorter period) may have more of the pre-HAART cognitive

pattern, while those who had been longer on HAART may present with the post-HAART pattern evidenced by Mirza and Rathore (2012).

1.4 HIV Epidemiology South Africa

It is estimated that the prevalence of HIV in South Africa is between 5.5 million and 5.8 million (340 000 of which are under 15 years of age) (Patel et al., 2012) and is as such is home to the largest prevalence worldwide. Within this group, Black South Africans account for 79%, of the prevalence (Shisana et al., 2009). While concerted efforts by governmental and non-governmental agencies through ARV education programmes and increased ART accessibility have been mobilised, HIV continues to leave its imprint on South African society (Shisana et al., 2009). Poor understanding of HIV infection, resistance to established treatment methods (including poor adherence) as well as conflicting public guidelines (in part as a legacy of past policy decisions), regrettably meant that new infections are still seen in South Africa. Women (especially Black females between the ages of 18 and 35 years old are reported to be the most at risk for infection (Shisana et al., 2009). Not surprisingly therefore, heterosexual transmission remains the primary mode of transmission.

Even though morbidity rates are slowly dropping in South Africa, interest in HIV-induced disabilities has increasingly come under spotlight due to the long term socio-economic burden induced by HIV management. In more affluent countries, ARV administration was initiated and controlled from birth for seropositive neonates, but in greater South Africa the scenario was different since many children were only placed onto ARV treatment based on the severity of clinical symptomology and/or CD 4 counts (Boulle et al., 2011). The limited

access to ARV's during the late 1990's and at least within the first five years of the new millennium - in South Africa - was due largely to the high cost of ARV treatment well as the limitations imposed by the health policies of the time (for both preventative mother to child treatment and post-partum treatment) (Coovadia, 2009). Epidemiological studies subsequently report that infant mortality was at its peak between 1997 and 2002 (Bourne, Thompson & Brody, 2009) in which only the Western Cape failed to mimic the National peak (attributed largely to the initiation of an effective preventative mother to child treatment (PMTCT) in that province from 1999) (Boulle et al., 2011). But for the Western Cape, the situation in greater South Africa was similar to the situation in countries such as Thailand where the lack of resources also prevented early initiation of ARV treatment (Puthanakit et al., 2010).

Studies from the United States of America show that early initiation of ARV results in better neurocognitive development and predicts better school adaptation and cognitive abilities (Tardieu, et al., 1995). This is especially true when affected children have the added advantage of enriched developmental environments. South Africa of course presents a unique scenario in that for the vast majority of children born prior to 2004, HAART was only initiated after children presented symptomatically – which may have been anything from birth to their current age. South Africa also presents with a population of HIV positive children who emerge primarily from environmentally impoverished areas or from areas where there HAART coverage was low or non-existent. Against this background, it is predicted that surviving HIV positive children born during the period (1997 – 2004/5) are

expected to be inclined to have residual neurocognitive deficits (Smith, Adnams & Eley, 2008).

1.5 The Effect of HAART on the CNS

HAART efficacy depends upon substantial and effective CNS-penetrating antiretroviral regimens in affecting survival after diagnosis of HIV encephalopathy. Patel and colleagues (2009) suggest that HAART inhibits or delays HIV dissemination in the CNS and in brains where infection has already been established, HAART reduces viral replication in this manner (Patel et al., 2009). Patel et al.'s (2009) study also revealed that without HAART, HIV-infected children often develop encephalopathy that have debilitating consequences, exacerbate their neurocognitive states and may even lead to death and that dramatic decreases in encephalopathy were observed following the introduction of HAART. While high CNS penetration for HAART efficacy is essential for the prevention of HIV-Encephalopathy (HIVE), it has also been shown to improve the prevalence of severe HIV-associated neurocognitive disorders (Joska, Hoare, Stein & Flisher, 2011). However, by its very nature, ARV's are in themselves neurotoxic as even low concentrations (10µg) of the ARV's have been shown to have adverse effects on the brain (Liner, Meeker & Robertson, 2010). The authors further stipulate that penetration of antiretrovirals into the brain at levels that are needed to effect viral suppression carries the risk of neuronal damage. Consequently increased titrations of HAART may lead to even greater adverse effects on the CNS (Liner, Meeker & Robertson, 2010). It is a note of caution to health care practitoners in the field and certainly warrants careful monitoring of HIV-positive populations on HAART.

While the neurocognitive profile is thought to mimic that of the post-HAART era, the implications of being placed onto HAART several years after vertical acquisition might suggest that a pre-HAART pattern could also emerge. Against the emerging research on different patterns of HIV-induced neurocognitive disorders (Abubakar, Van Baar, Van de Vijver, Holding & Newton, 2008), we envisage that those who have been longer on HAART might present with more executive function and memory disorders, while those who were placed onto HAART more recently may mimic the pre-HAART pattern of delayed processing and motor deficits. For the moment, this is speculative – without doing the research, we just don't know. Moreover, given that the pathogen affects the developing brain via the associated subcortical and striatal pathways as well as the development of the prefrontal cortices, it presents an opportunity to investigate whether executive function has been affected in some manner despite the delayed initiation of HAART (and by implication the lack of ART exposure soon after birth) . This research has therefore focussed on the construct of Executive Function in HIV positive adolescents.

Chapter 2:

2.1 Understanding Executive Function

Unpacking executive function as an indication of goal driven behaviour reveals a plethora of processes. Lezak et al's (2004) framework compartmentalises Executive Function into four processes viz. volition, planning, purposive action and effective performance.

1. Volition refers to intent and requires the desire to initiate an action as well as the awareness of the self in a particular context. *2. Planning* refers to the ability to use incoming stimuli of the problem at hand and to formulate an idea regarding its resolution. It requires the activation of existing knowledge and skills, followed by logical thought incorporating the organisation of the order of those facilities ie. hierarchically or sequentially, as well as the ability to predict the outcome.

As a component of executive function, planning takes into account the ability to develop alternatives based on the envisioning of likely outcomes and make adjustments as required. In this respect it differs from reflexive responses and automatisms (from overlearned behaviour) but pertains specifically to mental flexibility. In Norman and Shallice's Supervisory Attentional System (SAS) model, this refers to those processes that are automatic and those that require attentional effort. The latter responses require deliberate, attention – planning, decision making, troubleshooting, sequencing of actions, overcoming automaticity (habits) and problem solving (Anderson, 2008). In order to distinguish between automaticity and deliberation; Norman and Shallice (1986 cited in Anderson, 2008) proposed two supportive actions ie. contention scheduling and SAS. Schema control units

receive inputs from all over the brain. Contention scheduling is activated based on prior experience/learning but is inhibited if there is conflicting schemata. From this perspective planning is the effortful use and manipulation of existing schemata to a novel or problem solving situation. This means that the notion of generativity (the spontaneous ability to generate novel ideas and behaviours) (Turner, 1997 cited in Robinson, Goddard, Dritschel, Wisley & Howlin, 2009) is important.

3. Purposive action involves the execution of the plan and involves the use of internal or acquired (language, skills, knowledge) and external resources (tools) in accordance with the designated plan. *4. Effective performance* is based on cognitive control processes and includes monitoring and feedback mechanisms. The activation of attentional resources (SAS model) - sustaining, concentrating, sharing, suppressing, switching, preparing and setting (Stuss, 2011) are thus called into service. Certainly, response inhibition (the suppression of irrelevant or interfering information or impulses) (Robinson et al., 2009) and self-regulation (the ability to monitor thoughts and actions) (Hill, 2004 cited in Goddard et al., 2009) required to overcome the cognitive challenge falls within this domain.

Executive function relates to problem solving functionality and the ability to respond adaptively to novel or complex problems. As such, it includes the ability to inhibit, shift set, plan, organise, use working memory, problem solve and maintain set for future goals. Factor analysis has pointed to four EF factors: response inhibition and execution, working memory, set shifting, and interference control that are the key parameters of EF necessary for

optimal functioning (Miyake et al cited in Jurado & Rosselli, 2007). EF therefore involves those processes that allow people to shift their mind sets quickly and inhibit inappropriate actions so as to facilitate responses to an environment in constant flux.

The ability to shift mind sets, the ability to inhibit inappropriate responses and the ability to facilitate responses to an environment in constant flux all require three broad mental tasks i.e. to "(1) *form*, (2) *maintain* and (3) *shift mental sets*" (Suchy, 2009, p 112). Set *Formation* in this sense refers to volition as well as the ability to plan and reason. In order to do this, the neurocognitive processes of working memory (focused attention, memory retrieval and mental manipulation), sequencing as well as conflict resolution and response selection are called upon (Suchy, 2009).

The execution of the plan in response to the presenting complexity requires set *maintenance* functionality i.e. the ability to hold the plan in mind (working memory), the ability to self-regulate and inhibit initial responses (cognitive control), coupled with freedom from distraction (selective attention). Once the plan has been executed there are two outcomes for any action, either (1) successful solution or (2) increased complexity.

Finally, *Shifting Mental Sets* refers to the ability to alter behaviour in response to feedback from the environment. Once again, it demands problem-solving skills and taps into processes such as discrepancy detection, cognitive flexibility, switching attention, generativity and memory retrieval as well as working memory (Suchy, 2009). The thread of

constancy that passes through all these functions includes speed of processing (as opposed to impulsivity) and working memory.

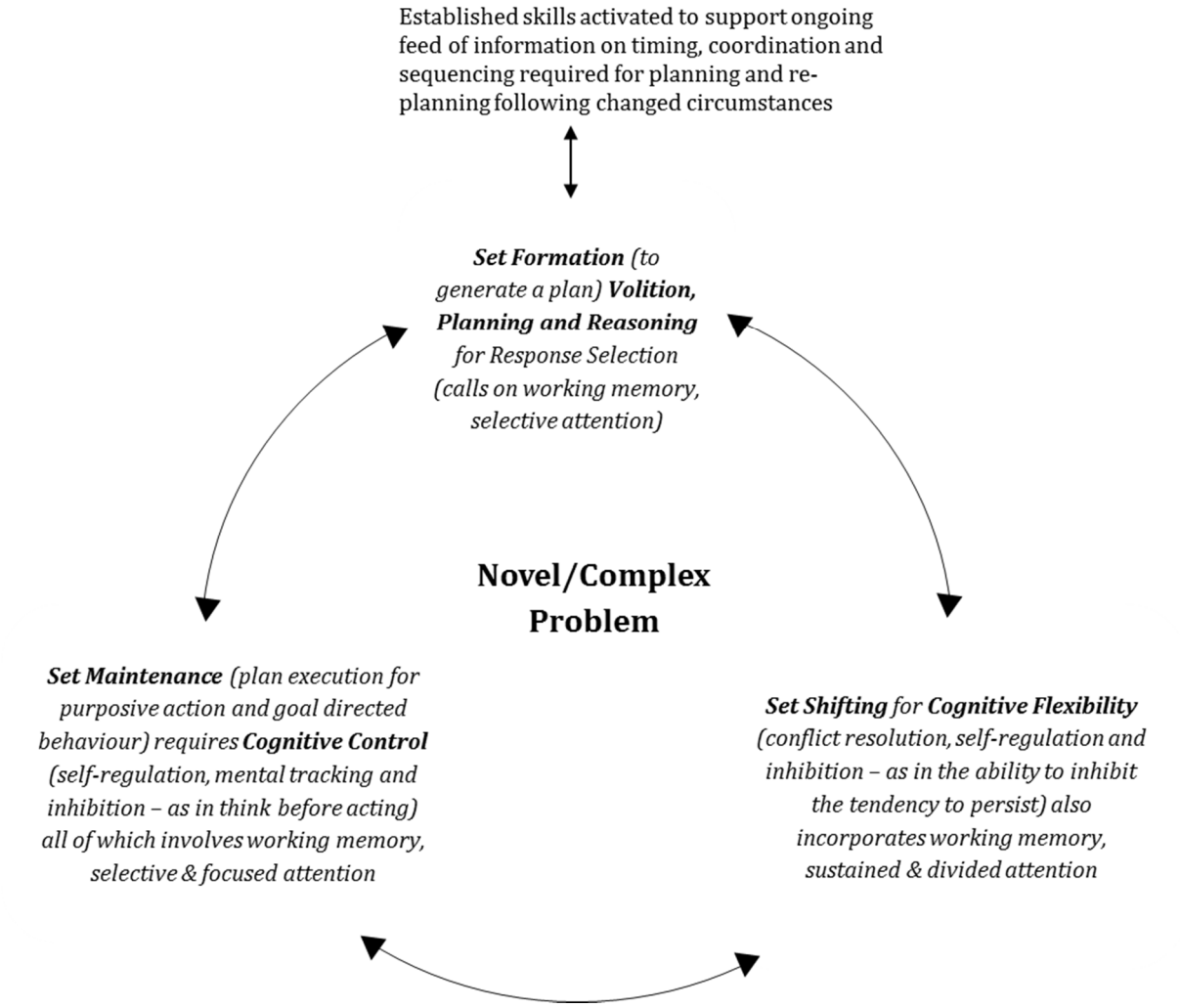


Figure 2.1: EF as dynamic, interrelated cognitive processes

Understanding EF in this manner is an elemental neurocognitive approach (Suchy, 2009) and offers the advantage of being easily operationalized for research purposes. However, it must once again be held in mind that each elemental unit in itself does not constitute EF – much

like the adage that 'the whole does not equal the sum of the parts', rather, it is useful to consider that a picture of EF emerges when the various criteria are considered collectively.

Executive functioning therefore imbibes people with the capacity for purposeful interaction with the environment (De Luca & Leventer, 2008). It can be thought of as the interaction of top-down processes activated both in response to external stimuli (via bottom up sensory cues) and internal stimuli (through motivation and memories). Impairments to any of the processes involved in executive function ultimately 'disrupts' these processes and leaves the person less capable of functioning effectively. Affected individuals therefore display higher degrees of distractibility, indecisiveness and a general lack of goal driven behaviour. Colloquially speaking, people so affected just 'cannot pull it together' – a statement which speaks to deficiencies in reasoning, decision making and judgement which ultimately manifest at a socio-cognitive level. Novel situations demand problem solving capability – when prior learning/experience cannot aid the current situation the brain becomes a learning organ and attentional resources, working memory, cognitive control and cognitive flexibility processes are activated.

2.2 The Neural Correlate of Executive Function

Unlike other domain dominant functionalities such as motor function, vision, language and emotion; executive function is not anatomically specific but an inter- and intra-cortically distributed function. While EF is closely associated with the Prefrontal Cortex (PFC) based on its involvement in the organisation of problem solving and achievement of goal directed behaviour (Crossman & Neary, 2010) The PFC is also believed to be a necessary part of the

executive function process rather than acting as the seat of executive function per se (Anderson, Anderson, Jacobs, & Smith, 2008).

The PFC is further broken down into the lateral prefrontal cortex (LPFC) and medial prefrontal cortex (MPFC also referred to as the anterior cingulate gyrus or ACC). The areas of the PFC are known to be intricately connected with the parietal, temporal and occipital cortex through a rich network of association fibres running in the subcortical white matter. In addition the PFC is connected sub-cortically through afferent fibres in the medio-dorsal and anterior nuclei of the thalamus (Crossman & Neary, 2010). These rich thalamic and cortical connections innervate the brain (Luria, 1982) implicating almost every cortical and subcortical structure of the brain in some way. Luria (1982), states that the PFC can therefore be regarded as 'the tertiary zones for the limbic and motor cortex' (p. 187).

Understanding the pathways highlights the importance of the PFC in executive functioning. Thus, while pathology or damage to the PFC does not directly result in primary disorders of perception and sensation (compared to the other lobes) its role in the guidance, direction, integration and monitoring of goal directed behaviour is clear. It follows that any disruption to the circuitry that connects to the PFC cortically or sub-cortically will lead to reduced executive function (Zillmer, Spiers & Culbertson, 2008).

Thus far, this review has focussed upon the presumed cortically specific domains of executive function processes. As discussed at the outset, in order to understand how these

processes come together requires an explanation of the circuitry that connects the various parts of the PFC and association cortices to the subcortical (or striatal) parts of the brain. In order to do this, the connecting role of the basal ganglia (BG) needs to be extrapolated upon.

It is generally accepted that there are five parallel segregated circuits (which the basal ganglia and thalamus participate in) which connect with different parts of the frontal cortex. Two circuits are associated with motor function viz. oculomotor and skeletomotor areas in the cortex, while the remaining three are to the dorsolateral prefrontal cortex, the lateral orbitofrontal cortex and the anterior cingulate (Bonelli & Cummings, 2007).

Common aspects of the BG circuitry involves the input and output nuclei. The input nuclei includes the caudate, putamen and ventral striatum and the output nuclei includes the globus pallidus interna (GPi) and the pars reticulate of the substantia nigra (SNr) (Middleton & Strick, 2001). All the circuits also have a common point of origination and destination. The circuits start from the frontal lobes and are projected to the striatum i.e. either the caudate, putamen or ventral striatum, the globulus pallidus (GP) and the substantia nigra (SN). From here on output connections to the respective thalamic nuclei are transmitted and the loop is closed with connections from the thalamus back to the frontal cortex (Bonelli & Cummings, 2007).

Each circuit communicates with the thalamus via two pathways, (a) the direct pathway and (b) an indirect pathway. The direct pathway from the caudate nucleus connects to the golbus pallidus interna (GPi) and the substantia nigra pars reticulata (SNr) complex before connecting to the thalamic nuclei. The indirect pathway which passes from the caudate nucleus to the globus pallidus externa (GPe) and deviates to the sub-thalamic nucleus (STN) first, before being redirected to the GPi-SNr complex and then connecting to the thalamic nuclei (Alexander & Crutcher, 1990).

Efferent projections from the direct pathway are GABA and Substance P heavy and result in a disinhibitive effect on the thalamic nuclei. GPe activation on the other hand release bursts of inhibitory GABA and encephalin to the subthalamic nucleus (STN) which in turn results in enhanced Glutamatine (Glu) activity to the GPi-SNr (Alexander & Crutcher, 1990). In this way, neurochemical activity from the direct-pathway interacts with neurochemical activity from the indirect pathway thereby modulating the communication output to the nuclei of the thalamus.

So while the five circuits operate through common structures, each circuit functions autonomously, maintaining its integrity even though further diversions may occur further along the pathway (Bonelli & Cummings, 2007). Each of the five circuits are therefore important for executive function capability in some way. The motor circuit begins in the supplementary motor area (SMA), premotor cortex (PMC), motor cortex (MC) and somatosensory cortex (SSC) and then projects somatotopically to the putamen before being directed to the GPi, GPe and caudolateral SN. Efferents from the GP then project to the

ventrolateral, ventral anterior and centromedianum nuclei of the thalamus and then loop back to the SMA, PMC and MC (Bonelli & Cummings, 2007). It is believed that these activations are not strictly sequential with *preparatory pre-movement activity* and serial processing of movements being activated in the cortex with 'concurrent parallel processing in the structures of the circuit' (Bonelli & Cummings, 2007, p. 143).

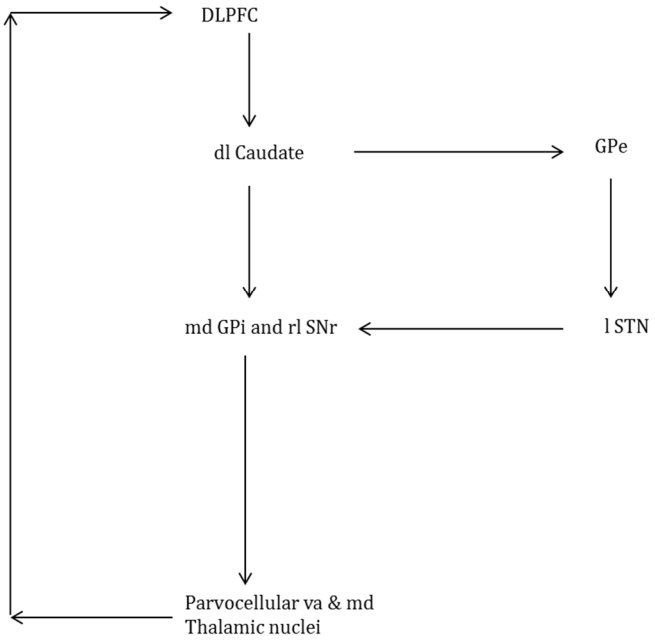
At this point it is worth noting that anticipatory effects and timing is thought to involve projections from the cerebellum (Strick, Dum & Fiez, 2009) – 'the cerebellum instructs the frontal systems on how to think ahead by providing anticipatory control mechanisms" (Koziol, Budding & Chidekel, 2011, p. 1). The timing component mediated by the cerebellum has also been linked with prefrontal cortex activity – where timing has been found to be important for sequencing and co-ordination required for planning. Since the cerebellum forms part of skill-based learning, it would be expected that many procedural and skill-based competencies that are cerebellar mediated become 'involuntarily' activated i.e. requires no effort but evoked nevertheless as an adjunctive support to the frontal lobes and its circuitry. Needless to say, compromised cerebellar activity would consequently be associated with problems in task shifting, switching as well as verbal working memory deficits (Strick, Dum & Fiez, 2009). In understanding EF, therefore, the 'silent' role of the cerebellum must be considered as part of the equation.

The oculomotor circuitry originates in the frontal eye-field area (BA 8) as well as the prefrontal and posterior parietal cortex which connects to the central body of the caudate nucleus followed by the dorsomedial GP and ventrolateral SN and then to the ventral

anterior and mediodorsal thalamic nuclei before finally linking back to the frontal eye-field area.

In terms of EF functionality, we mention the skeletomotor and oculomotor circuitry because of its importance in the actual execution of behaviour (which applies to purposeful action needed for goal directed behaviour). Since many actions are often reflexive or learned, it is as important to note that once learned or where the skill has become automated, committed EF functionality becomes redundant. So while the oculomotor and skeletomotor circuitry is an important aspect of EF, this paper focuses on the three remaining circuits that direct EF.

Consider the DLPC circuitry depicted in Fig 2.2.1:



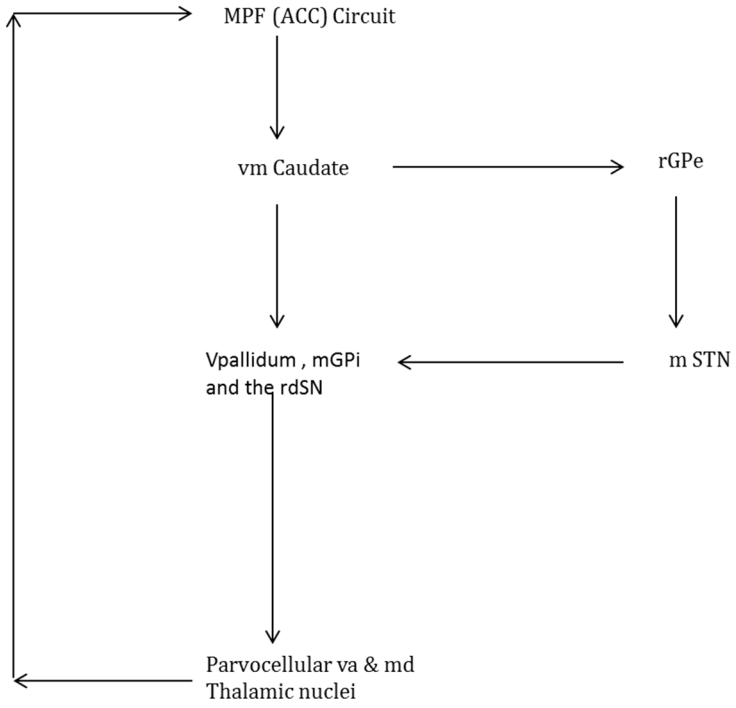
dl = dorsolateral , md= mediodorsal, l = lateral , rl = rostrolateral , va = ventro anterior , SNr = Substantia Nigra par reticularis , Gpe = Globus pallidus externa, Gpi = Globus Pallidus interna, STN = Subthalamic nuclei, DLPC = Dorsolateral Prefrontal Cortex

Fig 2.2.1: Dorsolateral Prefrontal Circuitry

(adapted from Grahn, Parkinson & Owen, 2008)

The DLPFC circuit originates in BA 9 and BA 10 (indicated in Fig 2.2.1 as the DLPFC) and projects to the dorsolateral head of the caudate nucleus before either directly projecting to the lateral aspect of the mediodorsal GPi and the rostrolateral SNr or indirectly passing to the GPe followed by the lateral STN which transmits activations to the GPi-SNr (Fig 2.2.1). The GPi-SNr complex then projects parvocellularly to the ventral anterior and mediodorsal thalamus respectively. The DLPFC circuit is believed to mediate executive function through the organisation of information needed to facilitate a response. Consequently disruption to the DLPFC circuit would be associated with executive dysfunction (Bonelli & Cummings, 2007).

The next circuit is the Medial Prefrontal Cortex Circuit or Anterior Cingulate Cortex Circuit represented by Fig 2.2.2:



dl = dorsolateral , md= mediodorsal, l = lateral , rl = rostrolateral , va = ventro anterior , r= rostral, m=medial, v= ventral, SN= Substantia Nigra , Gpe = Globus pallidus externa, Gpi = Globus Pallidus interna, STN = Subthalamic nuclei, MPF= Medial Prefrontal Cortex, ACC = Anterior Cingulate Cortex

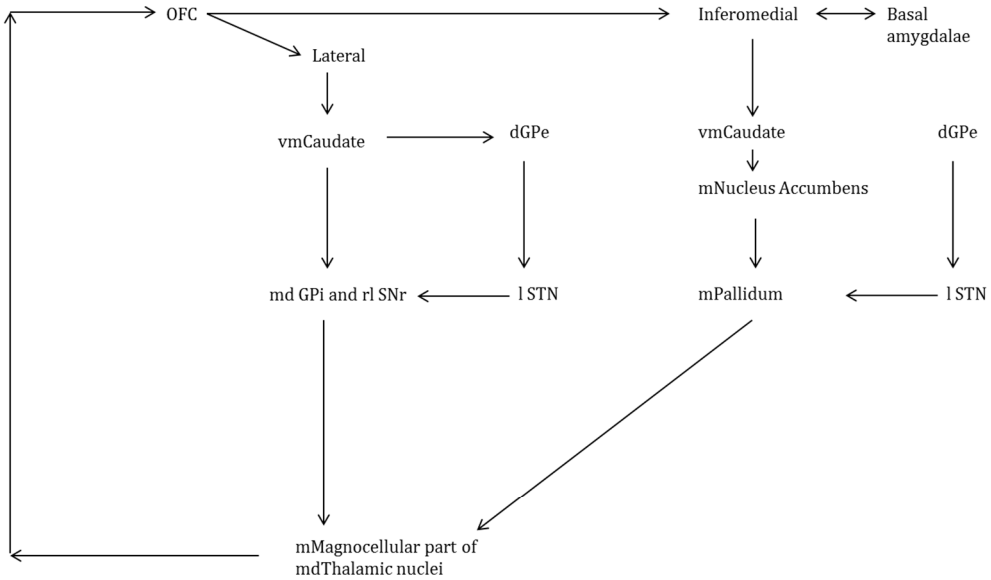
Fig 2.2.2: Medial Prefrontal Circuitry

(adapted from Grahn, Parkinson & Owen, 2008)

The MFC (or ACC) circuit (Fig 2.2.2) starts in BA 24 and then projects directly to the ventral striatum (Fig 2.2.2). Projections from here either move directly to the rostromedial GPi, the ventral pallidum and the rostrodorsal SN or indirectly to the rostral pole of the GPe followed by the medial STN before being redirecting back to the ventral pallidum. Once again the resultant transmission activates the magnocellular mediodorsal thalamus and the loop is

closed by returning back to the ACC. The ACC is concerned with volition and motivational aspects, thus lesions or dysruptions to the interconnecting pathways are associated with increased apathy (Bonelli & Cummings, 2007). In line with Norman & Shallice's model however, ACC activation and its importance for attentional mechanisms are important. While Bonelli and Cummings (2007) do not highlight attentional resources, it is nevertheless an important part of ACC functionality – motivational activity attracts attentional resources, so it follows that poorer motivational capability would correlate with reduced attentional mechanisms.

Finally, the OF circuitry (Fig 2.2.3) begins in the lateral orbital gyrus (BA 11) and the medial inferior frontal gyrus (BA 10 and BA 47).



dl = dorsolateral , md= mediodorsal, l = lateral , rl = rostrolateral , va = ventro anterior , SNr = Substantia Nigra par reticularis , Gpe = Globus pallidus externa, Gpi = Globus Pallidus interna, STN = Subthalamic nuclei, OFC = Orbitofrontal Cortex

Fig 2.2.3 : Orbitofrontal Circuitry

(adapted from Grahn, Parkinson & Owen, 2008)

From the OFC, efferent projections are directed to the ventromedial caudate which then send innervations to the mediodorsal GPi and the rostromedial SNr. Indirect projections are also sent to the dorsal GPe and the lateral STN which once again project back to the GPi-SNr complex. These neurons then move to the medial magnocellular aspect of the ventral anterior thalamus. Once again, the circuit is closed by projections from the ventral anterior thalamus to the OLPFC (Bonelli & Cummings, 2007). Bonelli and Cummings (2007), also highlight a medial portion on the OLPFC ie. the inferio-medial prefrontal cortex (in particular, the gyrus rectus and the medial orbital gyrus of BA 11) which sends sequential projections to the medial parts of the of the accumbens, the medial ventral aspects of the pallidum to the medial magnocellular part of the mediodorsal thalamic nuclei and then back to the medial orbitofrontal cortex. It is believed that the cortical connections reciprocate with the medial parts of the basal and magnocellular sectors of the accessory basal amygdale. Thus, cortical connections influence visceral functions through their shared amygdalar network (Bonelli & Cummings, 2007).

As an aside, this circuitry explains the involvement of physiological aspects in decision making. The somatic marker hypothesis (Damasio, 2006) for example, is a neurobiological account of how decisions are made under situations of uncertainty (Naqvi, Shiv & Bechara, 2006). Thus emotionally charged stimuli induce the release of neurotransmitters (such as serotonin, acetylcholine etc); actively modify somatosensory maps (such as those in the insular cortex) and adjust transmission signals towards identified somatosensory regions (Bechara & Damasio, 2005). The neurological structures believed to be involved in this process map onto the inferior medial prefrontal cortex. Damasio (2006) refers to this

cumulative body and brain enacted response as an emotion – or a somatic state. According to the hypothesis, somatic states can be induced by primary inducers or secondary inducers. Primary inducers are either innate or learned stimuli which cause pleasure or aversion (automatic and involuntarily). Secondary inducers, on the other hand, are generated from memories of the primary inducer (Bechara & Damasio, 2005). Damasio's empirical evidence came from a series of experiments which included people with ventro medial prefrontal cortex (vmPFC) lesions. These insights not only supported his theory but also localised the areas in the brain involved in this interaction. This area is particularly important as it serves to explain how affective components can either enhance or reduce EF.

Against this background, it is easier to see how OLPFC has connections with both the lateral and medial aspects where the medial parts are OLPFC facilitate integration with the amygdala (somatic activity) and the lateral areas are involved with the integration of limbic and emotional information required for appropriate judgement and decision making. Thus disruptions to the OLPFC circuitry would be associated with disinhibition, impulsivity and poor decision-making capabilities (Bonelli & Cummings, 2007). The OFC is also considered to be the neocortical representation of the limbic system (Lichter & Cummings, 2001 cited in Bonelli & Cummings, 2007) and would therefore would be vital for cognitive flexibility and strategy needed to respond to changed environmental factors.

In terms of the tripartite model adopted in this research, poor set formation has been associated with disorganisation (relating primarily to deficits in the dorsolateral prefrontal

cortex (DLPFC)). Failure to maintain set has been associated with apathy (relating to insufficiencies in the superio-medial prefrontal cortex or ACC) and disinhibition (relating to lesions in the ventromedial and orbitofrontal cortex). Set maintenance also requires cognitive control and attentional mechanisms. The MPFC has been associated with attention, monitoring and switching as well as motivational aspects which direct attentional resources while the OFC (inhibition) is thought to be necessary for cognitive control. It is a two way and integrative process in which inputs from the PFC feeds the MPFC and the outputs so generated from the MPFC feeds back to the PFC and the associated cortices thereby enabling problem solving and goal driven behaviour. An inability to set mental shift suggests cognitive inflexibility and is reported by the tendency to perseverate. These problems have been also associated with deficits in the DLPFC (Suchy, 2009). Certainly the cortical areas are important but it is as important not to overlook the implications of the Basal Ganglia mediated circuitry – especially the role of the caudate nuclei in terms of correcting action schemas and goal selection needed for goal directed behaviour (Grahn, Parkinson & Owen, 2008).

Based on this information, one can now superimpose the cognitive processes of EF according to its neural correlates (Fig 2.2.4).

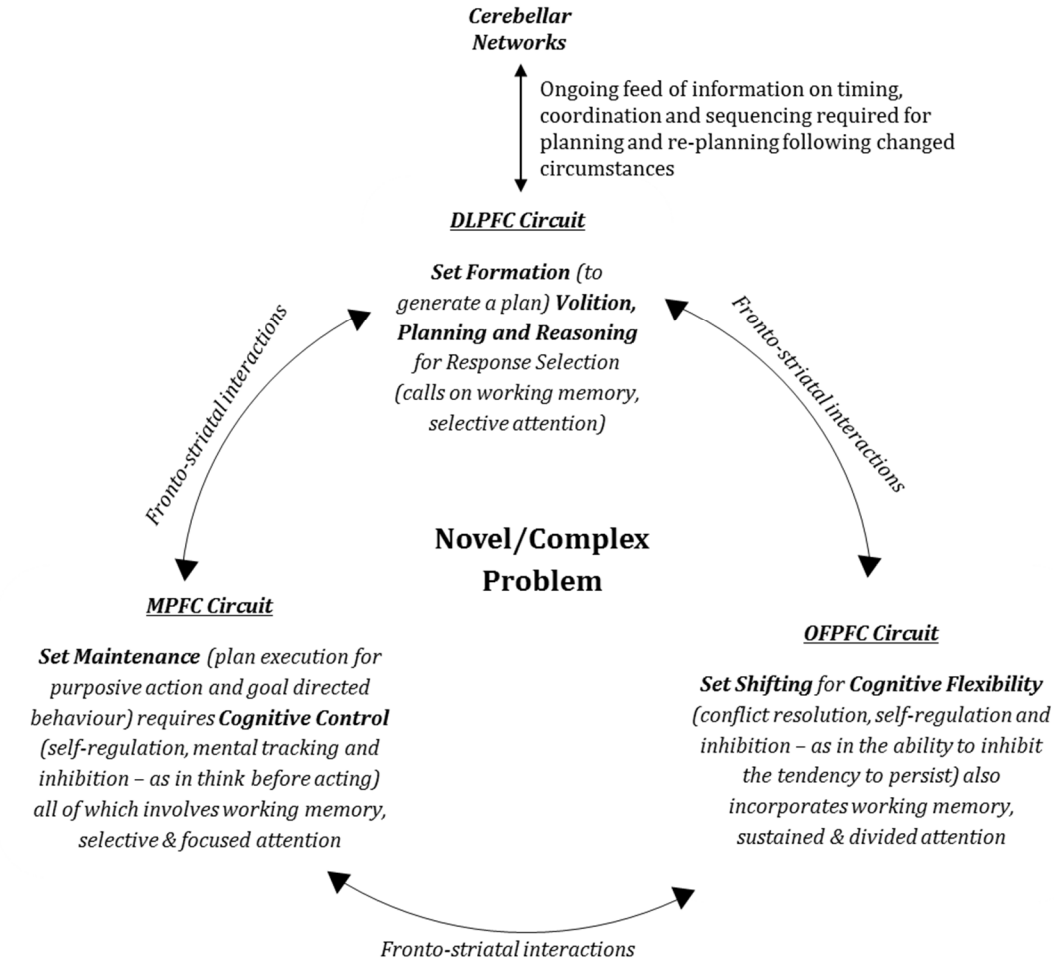


Figure 2.2.4: Conceptual Model of the Neural Correlates of EF

In order to conceptualise EF, one needs to view the processes involved in the circuitry as a dynamic operation and not a step-wise progression. An overview of Fig. 2.2.4 highlights the link between the fronto-striatal networks as well as reciprocal connections to the posterior parts of the brain that would be activated in response to complex or novel situations demanded by EF. In automated tasks, cerebellar activity bypasses the fronto-striatal tracts but in EF this communication is implicit and happens even if it is outside of the realms of conscious awareness. It would also imply that if the circuitry from the PFC to any of the areas highlighted in the schematic are in any way compromised, then EF will be affected.

Actions that are therefore automatic (or overlearned) and do not require attentional resources are expected not to be affected as much, while those that do require higher cognitive demand will manifest as defective EF with higher error-related responses and lower self-regulation abilities.

2.3 Development of the Prefrontal Cortex

The prefrontal cortex is developmentally the last to develop in the human brain. While the human nervous system begins to develop at around 18 days of gestation, the neurons that eventually become the prefrontal cortex emerge as neuroblasts from the anterior periventricular zone, radiating outward in sequential waves towards a developing cortical plate (De Luca & Leventer, 2008) and completing this migration by around 24 weeks of gestation. Development that follows hereon is primarily cortical organisation including axonal arborisation between structures to facilitate survival at birth. At this stage, the frontal lobes are still immature with synaptogenesis and myelination in the central nervous system continuing after birth. Over the next few years spanning infanthood, childhood and adolescence, the frontal lobes are moulded by both environmental stimuli and biological predispositions to arrive at a relative state of maturity. It is believed that the process of myelination follows a systematic developmental order from caudal to anterior; dorsal to ventral; sensory to motor and central to peripheral. Consequently, the dorsolateral and ventromedial areas of the prefrontal cortex (PFC) are the last to myelinate – often occurring well within the third decade after birth (De Luca & Leventer, 2008).

Based on these insights, earlier researchers postulated that executive function was an adult function – appearing just before puberty at around 12 years of age. The anatomical maturity of executive function further followed Piaget's developmental stages coinciding with childhood concrete thought and its progression into formal operational thinking with growth.

While executive function reaches maturity during adulthood, evidence of executive function development has become measureable over the last few decades. From the perspective of the affective and cognitive aspects of executive function, evidence has emerged from various studies revealing a development trajectory of executive function (and interestingly enough coinciding with frontal lobe development). Increased grey and white matter volume as well as metabolism during early childhood (till puberty), corresponds with improved inhibitory control, sustained attention improvements, advances in working memory and the emergence of planning and goal directed behaviour (cognitive aspects of executive functioning). In terms of the affective components of executive function, improvements in affective decision making, success at false-belief tasks as well as sophisticated adult-like theory of mind also emerges (De Luca & Leventer, 2008).

Adolescence is a marker for increased executive function maturation. Improved self-regulation is evident as the adolescent learns to control their thoughts and behaviours so as to achieve purposeful-driven actions (Crone, 2009). During adolescence, improvements in decision making develops with improved attentional control, processing speed, mature

inhibition and gains in working memory, strategic planning and problem solving (De Luca & Leventer, 2008). Evidence from several studies (Crone, Ridderinkhlof, Worm, Somsen & Van der Molen, 2004), show that young adolescents under the age of 16 years can be expected to achieve adult-level cognitive control.

If executive function was indeed simply the maturation of cognitive function then this review would have been completed by this stage. However the variable behaviour observed in adolescents specifically with regard to impulsivity, recklessness and increased risk taking behaviour is testimony to the importance of inhibition and self-regulation on executive function (Crone, 2009; Hazen, Schlozman & Beresin, 2008). Furthermore, the MPFC's (the anterior cingulate gyrus) is directly connected to the limbic system. Given its role as a regulating structure, the MPFC also contributes to the regulation of affect through the circuitry connecting the VMPFC. Should this circuitry be compromised, then one is likely to expect a reduction in volition and/or failure to inhibit and self-regulate leading to adynamia on the one hand or an inability to inhibit and switch resulting in disinhibited, reckless and impulsive behaviour on the other hand. Clearly, affect has a role in executive function performance (Bonelli & Cummings, 2007).

2.4 Executive Functioning and HIV

That HIV is associated with executive dysfunction has been supported by several multivariate and meta-analytic studies (Dawes, Suarez, Casey et al., 2008; Welsch, Razani, Martin, et al., 2008 cited in Dennis et al., 2011). Adult studies report deficits in tasks of reaction time, response inhibition, novel problem solving, abstract reasoning and set

shifting. These deficits have also been reported to further contribute to low EF performance (Dennis et al., 2011).

With HIV infection comes compromised fronto-striatal functioning (Melrose, Tinaz, Castelo, Courtney & Stern, 2008). To this end, studies have noted inhibition, set shifting and attention (working memory) as well as planning and cognitive sequencing impairments (Melrose et al., 2008) as indicators of executive function deficits (discussed in Section 2.1) Certainly, adult studies on HIV infection have shown that the degree of decline coincides with the severity of HIV stages (Melrose et al., 2008; Woods, Moore, Weber & Grant, 2009).

Because of its integrative role, executive functioning is impaired through multiple routes ie. cortically (by damage to the prefrontal cortex); sub-cortically via the tracts connecting the deeper subcortical parts of the brain to the frontal lobes or if indeed those subcortical and cortical areas are in themselves affected preventing any communication to the frontal lobes (Gazzaniga, Ivry & Mangun, 2009). Physiological/metabolic or structural insults to any of the structures or paths consequently culminate in executive function deficits (Anderson, 2008).

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

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

In South Africa, HIV-positive adolescent population who were exposed to environmentally poor conditions (with poor socio-economic and/or socio-educational systems), were ARV-naïve following birth may only have been placed on ART following symptomatic presentation. As a result, understanding the extent to which executive function has been compromised has been the focus of this study.

Since executive dysfunction emerges from impairments to any of the sub-components, it is anticipated that the executive function domains relating to planning, mental flexibility, response inhibition, generativity and self-monitoring profiles of the population under investigation would be affected and this impression may offer further information about the effect of HIV in the CNS.

Chapter 3: The Research

3.1 Rationale

As was evidenced in the literature, HIV is a deeply complex pandemic. Not only do the neuropathological pathways differ leading to very diffuse CNS disorders, but the additional effects of the medication and/or environmental variables cannot be ignored (Wachsler-Felder & Golden, 2002). Given the historical South African scenario, children that have been diagnosed as HIV positive may have the added disadvantage of being placed onto an anti-retroviral regimen only on presentation of clinical symptoms (encephalitis, tuberculosis or pneumonia). By this time, some CNS functionalities may have already been compromised (Allison, Wolters & Brouwers, 2009). Anecdotal evidence from medical practitioners and educators alike suggest that learning difficulties are indicated in HIV positive children but there is limited understanding of how this should be addressed.

The aim of this research is to understand the presentation of executive function of HIV positive adolescents currently on a managed ART programme. It is hypothesised that HIV positive adolescents on HAART will have poorer executive function (discussed in 2.1) profiles when compared to a contrast group of healthy children. This hypothesis is further based on the evidence of deficits of EF in populations who are currently on HAART (Cysque, 2004; Heaton et al., 2011). It is believed that aspects such as the duration of ARV treatment, age of initiation of treatment, the CD4 t-cell counts and viral load drops may also contribute to differential executive function presentations in the seropositive group.

In order to effectively test EF in the group identified, it was deemed necessary to adopt a Positivist (scientific) approach in this study. This framework posits that real events can be observed empirically and can therefore be explained with logical analysis (Krauss, 2005). The approach warrants that the researcher employ measures to control for extraneous factors that might affect the reproducibility and reliability of the result. Inevitably micro-level lab-like experimentation is usually implemented in order to improve internal validity but it can also do so at the expense of external validity. In the realm of psychology, pure scientific research is an arduous task but can nevertheless be achieved by using standardized tests and (where groups are concerned) through the use of non-probability sampling methods. Admittedly this has the disadvantage of eliminating random assignment and relies upon purposive sampling techniques however it does allow for the fairly meticulous selection of participants so as to arrive at a relatively homogeneous sample group. The study therefore cautions against the spurious generalizability of the results and advocates that the results be viewed in context.

3.2 The Research Question

Given the evidence presented on cognitive dysfunction in ARV-naïve populations (Laughton et al., 2010) and for the complexities raised by the South African scenario, this research is based on the following hypothesis:

HIV positive adolescents on a managed ART programme, exhibit executive deficiencies in mental flexibility, self-regulation and inhibition when compared with an unaffected contrast group

This research evaluated the executive function of seropositive HIV adolescents and compared them to an unaffected contrast group (of comparable age, socio-economic background and education). The research was operationalized by evaluating the performance scores based on standardised neuropsychological tests that measured '(1) form, (2) maintenance and (3) the shifting (of) mental sets' (Suchy, 2009, p 112) as dimensions of executive function. Since all three processes incorporate attentional mechanisms, speed of processing and working memory – these factors had to be considered in order to evaluate overall EF.

Data from the HIV-positive sample group also underwent an analysis to ascertain whether age of HAART initiation, viral load drops, duration of ARV treatment, current CD4 T-cell counts and gender differences contributed to EF performance.

3.3 Instruments

The study on EF study was designed as a limited scope study that formed part of a larger study consisting of a comprehensive neuropsychological battery. The larger study aimed to examine the neuropsychological profile of HIV positive adolescents by evaluating each of the specific cognitive domains. This study was further embedded in another study examining the Flynn effect in South African adolescents and which was positioned upon a predetermined battery of neuropsychological tests. Given the significance of finding appropriate normative data as well as the dynamic nature of South African society and the education system in particular, the advantage of using a single matched norm sample rather than having all the supplementary tests normed on different samples – much of which has been gathered at different points in time - was further motivation for linking the study to the one on the Flynn effect.

The extended study incorporated the Wechsler Intelligence Scale for Children – Revised (WISC-R) and supplementary tests as well as additional neuropsychological tests such as the Rey Auditory Verbal Learning Test (RAVLT), the Rey Osterreith Complex Figure Test (ROCFT), the Trail Making Test A and B (TMT-A and B) the Stroop, the Controlled Oral Word Association Test (COWAT) and the Wisconsin Card Sorting Test (WCST). Given that the motor domain was also being investigated, the Finger Tapping Test (FTT) and Grooved Pegboard Test (GPB) was also added to the battery. As a modification to the existing battery, the Delis-Kaplan Colour Word Interference Test (D-KEFS CWIT) replaced the more traditional Stroop due to the additional measure of Cognitive Flexibility in the task. It is also important to note that the WISC-R was administered rather than the more recent WISC-IV

battery) as it formed part of the original study as reported in Skuy et al. (2001) and was continued as part of the larger study on the Flynn effect and which is to be reported upon elsewhere. The tests selected were to some extent imposed upon the researcher(s) by virtue of being part of the larger study. The areas covered by the research included the Sensory Motor domain, the Verbal Domain, the Visuospatial Domain, Memory and Attention. These areas were examined independently by other researchers in the team.

Executive Function being the focus of this study chose to use the results of the WCST, the Delis-Kaplan Executive Function Colour Word Interference Test (D-KEFS CWIT) and the TMT-B while the WISC-R and the supplementary tests of Digit Span and Mazes were also included as additional tests. By including so many tests of EF, the various aspects of EF were covered i.e. planning, rule learning, and inhibition was covered by the WCST, the D-KEFS CWIT, TMT-B and the Mazes subtest. The D-KEFS CWIT also allowed for the evaluation of attention, working memory and processing speed needed for optimal EF function, while the Digit Span subtest further reinforced findings relating to working memory in the cohort. Other studies that examined EF in HIV-1 individuals applied similar test instruments. Minassian, Henry, Woods, Vaida, Grant, Geyer, Perry and the TMARC Group (2013) for instance used the WCST, TMT-B and Stroop as part of their battery to assess EF while Kahn, Riccio and Reynolds (2012) limited their findings to a version of the TMT (i.e. the Comprehensive Trail Making Test). What makes this study particularly interesting however were the different number of instruments used to evaluate EF and which allowed for the investigation of *which specific processes* were likely to impact upon EF. This is an important consideration since evaluating a multifaceted construct such as EF necessarily implies that one needs to look at

a variety of EF tests so as to effectively understand which of the underlying factors (described in Chapter 2) were involved in EF.

Understanding which tests to use to measure was critical in this study. The vast plethora of tests available allows for EF to be examined from different angles. While it is acknowledged that other tests of EF (eg. the Tower of London) has been proven to be an effective test of EF (i.e. evaluates planning, rule learning, and inhibition (Strauss, Sherman, & Spreen, 2006)), it was decided to limit the tests to the above mentioned tests given that the extended battery was already quite extensive and adequately allowed for the coverage of planning, rule learning and inhibition. As noted, selective subtests from the WISC-R further assisted in supporting the findings of the study. It was thus decided to report only on the results reflected by the WISC-R (FIQ, VIQ and PIQ), WISC-R (Digit Span), WISC-R (Mazes), the WCST, D-KEFS CWIT and TMT-B. Despite the fact that tests such as the COWAT, ROCFT and Picture Arrangement (WISC-R) also address issues of EF, the study *purposefully* and *judiciously* limited its findings to its relevance to EF to prevent infringing upon the outcomes of the other areas of research in the larger study.

In order to control for affective factors that may have also impacted upon the findings of the study, the Becks Youth Inventory-II (BYI-II) was also employed. The BYI-II evaluates depression, anxiety, anger, disruptive behaviour and self-concept. The following subsections provide a more detailed overview of the tools employed.

3.3.1 The Wechsler Intelligence Scale for Children (WISC-R)

The Wechsler Intelligence Scale for Children Revised (WISC-R) consists of ten scales and two additional supplementary scales, which have been designed to provide an indication of general intelligence (FIQ) consolidated out of a verbal dimension (VIQ) and non-verbal dimension (PIQ) (Weschler, 1974). Administration of the WISC-R as it applies to neuropsychological assessment has been widely accepted in clinical practice where large discrepancies between VIQ and PIQ as well as statistically significant scaled score scatters are usually suggestive of underlying cognitive deficits (Moffit & Silva, 1987). VIQ consists of the Information, Similarities, Arithmetic, Vocabulary, and Comprehension subtests while PIQ incorporates the Picture Completion, Coding, Picture Arrangement, Block Design, and Object Assembly subtests. Investigations on the WISC-R reveal that it is considered to be a reliable indicator of FIQ. The reliability coefficient for FIQ is reported as 0.96, with VIQ at 0.94 and PIQ at 0.90 (Weschler, 1974). The information pertaining to the FIQ, VIQ and PIQ was consequently used in order to evaluate if there were gross differences in intelligence between the HIV-cohort and the Contrast group. The WISC-R was administered with the testee seated across the tester and in accordance with the WISC-R manual (Weschler, 1974).

Due to its value in establishing working memory and attention mechanisms (an important part of EF), information from the Digit Span subtest of the WISC-R was used to determine if these factors may impinge upon EF. Administration of the Digit Span subtest involved 7 items from the Digits Forward series and 7 in the Digits Backward series with a maximum score for the task ceiling at 28 (One trial consists of 2 sequences). Participants were then

scored a 0, 1 or 2 for their efforts in each of the dual numerical trials. The Digit Span subtest is considered to be quite robust with a reliability coefficient of 0.78.

The Mazes subtest of WISC-R is also a supplementary test that offered additional information regarding problem solving and planning abilities. Given than the larger study incorporated the Mazes subtest it was decided to include these findings for additional insight pertaining to optimal EF functionality. In this task, participants were presented with nine mazes of increasing difficulty and scoring was based on the number of errors or failure to complete within a predetermined time for the completion of each maze. The Mazes subtest is reported to have a reliability coefficient of 0.72 (Weschler, 1974).

3.3.2 The Delis-Kaplan Executive Function System Colour-Word Interference Test (D-KEFS CWIT)

D-KEFS CWIT is a test originally based on the Stroop. The test consists of two baseline conditions ie. a Colour Naming Condition (Condition 1) and a Word Reading Condition (Condition 2) as well as two higher-level conditions viz Inhibition (Condition 3) and Inhibition/Switching (Condition 4). The various conditions administered provide an indication of attention, inhibition and set shifting abilities (Strauss, Sherman, & Spreen, 2006). In this test, inhibition involves the ability to focus on the task at hand without becoming distracted, (and specifically on this task) requiring 'the ability to override an over-learned response (reading), in favour of a more difficult one (colour naming)'. (Delis et al., 2001a, p.5) while the inhibition/switching condition has an additional mental tracking and flexibility component.

The version of the D-KEFS CWIT administered was originally standardised on a sample (stratified for age, sex, race/ethnicity, years of education and geographic location) of 1750 people between the ages of 8 – 89 years in the USA. Reliability on the D-KEFS CWIT was established via moderate to high internal consistency for all age groups ($0.62 \leq r \leq 0.86$). While good Test-Retest reliability ($r = 0.79$ for Condition 1, $r = 0.77$ for Condition 2, $r = 0.90$ for Condition 3 and $r = 0.80$ for Condition 4) was obtained the D-KEFS CWIT also revealed a slight practice effect. Standard Error of Measurement (SE_M) was also found to be good (Delis, Kaplan & Kramer, 2001).

3.3.3 Trail Making Test – Part B (TMT-B)

The TMT has been found to be one of the more commonly used tests to assess attention and executive functioning (Strauss et al., 2006). The Trail Making Test (TMT) consists of two parts ie. Part A (TMT-A) and Part B (TMT-B).

In TMT-A, participants are given a sheet with numbers surrounded by circles. The aim is to connect the numbers numerically and sequentially as quickly as possible. In TMT-B, the circled numbers are interspersed with circled letters. As in TMT-A, the participants are required to sequentially connect the numbers and letters (alternating between letters and numbers) in the shortest amount of time possible. Thus in the execution of TMT-B, in addition to the skills employed in TMT-A, the participant is required to employ dual mental tracking and cognitive flexibility. A practice run for each test is administered with careful explanation regarding error monitoring and pencil lifts.

TMT-A is primarily a test of attentional abilities and has been found to correlate with other tests of visual attention, scanning and speed of processing (Strauss, Sherman, & Spreen, 2006) while TMT-B has been found to be an effective test of executive function. Although TMT-A and TMT-B have been found to correlate moderately well with each other (r = 0.31 – 6), TMT-B demands more cognitive resources (based on switching demands, longer distances between digits and visual interferences), than TMT-A - and is therefore considered to be a dual-tracking test. Performance on the TMT-B is sensitive to problems with cognitive flexibility and sequencing. Raw scores reflect time to completion with greater scores indicative of poorer performance. The TMT is brief, easy to administer and has been used extensively in neuropsychological assessment by virtue of its sensitivity to neurological dysfunction (Kahn, Riccio & Reynolds, 2012).

3.3.4 Wisconsin Card Sorting Test (WCST)

The WCST is used to assess the 'ability to form abstract concepts, to shift and maintain set and to utilise feedback' (Spreen et al., 2006, p 526). The WCST requires "strategic planning, organized searching, utilizing environmental feedback to shift cognitive sets, directing behaviour toward achieving a goal, and modulating impulsive responding" (Heaton, Chelune, Talley, Kay & Curtiss, 1993, p 1).

The test consists of four stimulus cards placed in front of the participant. The cards are arranged in order from left to right beginning with a red triangle, two green stars, three yellow crosses and four blue circles. Participants are given two decks of cards, each

containing 64 response cards and advised to sort the cards in the pack according to the key cards placed before them and based on the instructor's feedback of 'Correct' or' Incorrect'. No further instructions are indicated and no warning is given in advance of change to the sorting rule (Spreen et al., 2006)

The instrument has been used to test individuals from 5years to 89 years. The test is thought to be a measure of executive function since it taps into planning, organised searching and the ability to use feedback from the environment in order to shift cognitive set, enable goal-oriented behaviour and modulate impulsive responding (Heaton, 1993 cited in Spreen et al., 2006). The test publishers also report excellent inter-scorer agreement for standard scoring instructions; however generalizability coefficients (the instrument measurement of the participants' true scores) for the WCST are somewhat lower with moderate to good levels achieved in a non-clinical sample of children and adolescents. In neurologically impaired populations, the test publishers maintain that there is sufficient evidence (from children, adolescents, and adults) which suggests that the WCST is a valid measure of executive function.

This research conceptualised EF as the ability to (1) form (2) maintain and (3) shift mental sets (Suchy, 2009). Formation (or set formation) is operationalized through initiation (*trials to complete the first category*), planning and reasoning (*categories completed*). Maintenance (or the failure thereof) is operationalized in the WCST as *Failure to Maintain Set* (which is also an indication of response selection, inhibition and attention) and

Conceptual Level Responses while Set Shifting is evaluated as *Perseverative Responses* on the WCST which demands inhibition and switching to enable cognitive flexibility. The test also allows for the evaluation of abstract reasoning (*categories completed*) much needed for optimal executive function performance.

3.3.5 Beck's Youth Inventory

Since this paper evaluates EF and the extent to which EF deficits impact the failure to inhibit understanding whether anger and disruptive behaviour played a role on EF performance needed to be factored into the study. These elements were ascertained using the Beck's Youth Inventory for Children and Adolescents (BYI-II). The BYI-II assesses symptoms of depression, anxiety, anger, disruptive behaviour and self-concept. For the purposes of the study only Anger and Disruptive Behaviour was considered as these were believed to best represent the failure to inhibit. The instrument was normed on adolescents from the US, showing good internal consistency (0.91 to 0.96) and good test-retest reliability (0.83 – 0.93) for adolescents from 11 – 18 years of age. The tool is also able to discriminate between groups with higher levels of distress when compared to those with lower levels of distress (Beck, Beck, Jolly & Steer, 2005) rendering this tool suitable for the population being assessed.

3.4 Procedure

3.4.1 Sample Selection

Sampling for the study followed a non-randomised purposive sampling style. Participants attending an HIV-management clinic in Johannesburg were initially invited to participate in

the study. An information letter as well as consent form (for the guardian) and assent form (for the participant) was given to the participant with the procedure explained as simply as possible. On agreement, participants were taken to the Psychiatry/Psychology Department at the Clinic where a demographics and medical screen was conducted by one of the researchers (usually with the caregiver and in collaboration with the available medical information). Where necessary or if psychological support was specifically requested, participants and/or caregivers were given the details of the Wits Psychology Clinic at the Emthonjeni Centre in Johannesburg.

All the participants involved in the study were demographically screened prior to the assessment to evaluate for bilingualism or multilingualism, grade and type of education, household details including access to running water, electricity as well as number of occupants per household were also captured. Participants were excluded based on their use of chronic medication (other than their ARVs), previous head injury or any other CNS associated injuries or illnesses. All the participants emerged from nuclear family-type homes.

A total of 30 participants were tested in the study, however an administrative oversight resulted in one participant being evaluated twice. The result of the second trial was subsequently removed bringing down the sample size to n = 29. The HIV positive adolescents were all sourced from an HIV Clinic in Johannesburg and formed the basis of the experimental group. All of the adolescents were aware of their HIV status and had received

the appropriate counselling by the hospital. Further information was extracted from the patient records regarding which HAART combination they were on, age of HIV initiation, CD4 T-cell counts and viral loads at time of HAART initiation as well as their latest CD4 T-cell counts and viral loads (permission was granted for this). Participants were also excluded if they were on second line treatment, if they had additional complications such as cerebral palsy or genetically derived intellectual development disorder such as Downs Syndrome. HIV associated Encephalitis (HIVE) was not ruled out but previous traumatic brain injury or psychiatric conditions were. A more detailed analysis of the sample demographics and details is provided in Chapter 5, Section 5.1.

A similar approach was followed with the contrast group (the subject of another study), however participants were excluded if they were found to be on chronic medication of any sort or had suffered traumatic brain injury, meningitis or other CNS associated childhood disorders (such as epilepsy).

3.4.2 Test Administration

Test administration began soon after consent forms (from the parents) and assent forms from the relevant care-givers had been received. Having met the selection criteria and demographic screen as stipulated in Section 3.4.1 (see also Appendix 9), participants then completed the Beck's Youth Inventory for Children and Adolescents (BYI-II). The order of administration of the larger neuropsychological test battery (incorporating the EF instruments) was randomised to control for fatigue effects beginning *either* with the WISC-R battery ***or*** the Neuropsychological battery (administered in the following order: the FTT,

GPB, ROCFT, RAVLT, TMT-A & B, D-KEFS CWIT, COWAT and WCST). Participants were given the option to break at any point during the assessment with light refreshments provided in between. The time taken for the administration of the complete battery varied between three and three and a half hours. All the assessors conducting the study were given uniform training on the battery by the supervising team to ensure that tests were conducted in a standardised manner.

3.5 Research Design

The study adopted a non IV-manipulated cross-sectional quasi-experimental post-test only with a contrast group, design. This design was selected as appropriate it was aimed at evaluating the executive function profile which occurred (in the adolescent age group) as a result of the HIV-infection. Since the study aimed to explore executive function only when compared to the unaffected group, no variable manipulations were conducted.

3.6 Analysis

Data obtained from all the tests was in the form of nominal data. Results were grouped according to HIV status, with the dependent variables evaluated via the various performance scores discussed. EF performance was operationalized through performance scores primarily on the WISC-R subtests (Digit Span and Mazes), WCST, D-KEFS CWIT and TMT-B tests.

As discussed, the performance of the HIV positive adolescents was compared to a contrast group of unaffected adolescents matched according to gender, socioeconomic and educational background. Given the uneven size of the contrast group as opposed to the experimental group as well as the specificity of the experimental participants (non-random sampling procedures), the assumption of normality could not be assumed. In addition the distributions were in many cases greatly skewed with high kurtosis, further deviating from normality. While the central limit theorem was met for some of the data, it was deemed more appropriate to keep with non-parametric measures. A cross check of parametric tests revealed similar significant differences, however effect sizes varied greatly which motivated us to retain the non-parametric measures. As a result, non-parametric Wilcoxon-test statistics were conducted (*Z*) to compare the performance of the HIV positive group with the unaffected contrast group. Effect sizes were calculated using the formula: $r = Z/\sqrt{N}$. Statistical computations were calculated using SAS® version 9.3 (SAS Institute Inc., Cary, NC).

Chapter 4:

4.1 Ethical Considerations

Participants were above the age of assent, but not above the age of consent. Each of the participants filled in an assent form (see Appendix 3) while their legal guardians completed a consent form (See Appendix 1). The children in the HIV-positive sample all attended an HIV clinic in Johannesburg and were on ARV's. Although each child's status had been disclosed (as indicated in the medical files) to them, due to the sensitivity surrounding HIV, further details regarding their status was not elaborated upon.

In capturing and collecting the data and once again due to the sensitive nature of the data, participants were allocated a code as per a master list. The master list was retained by the principle researcher in a secure environment who captured the data electronically before allocating to the respective researchers. Confidentiality was thus maintained by the coding system however as the participants needed to be physically present for the testing, anonymity was not possible. During the study, none of the participants, vocalised any distress and were cooperative during the assessment process. All of the tests performed were non-invasive, manual, pen-and-paper style tests. Since the testing process occurred over a few hours, refreshments were provided for the participants. To mitigate for the inconvenience caused due to the length of the assessment, participants were reimbursed for travelling costs.

Permission for testing the HIV group was obtained from the HIV-Clinic while permission for testing the contrast group was done with the consent from the school the

parents/Guardians and assents from the children themselves and the Department of Education. Ethics permission was obtained from the University of the Witwatersrand's Human Research Ethics Committee (Medical) under the approval number M120268.

Chapter 5: Results

5.1 Sample Statistics

Thirty HIV positive adolescents participated in the study. As noted, due to a duplication in testing, one participant from the HIV positive group was excluded bringing the sample size to *n=29*. Participants in the HIV positive experimental group were aged from 13 up to and including 16 years of age with a *50/50* age category split of 13-14yrs and 15 -16yrs. *45%* of the participants were Male and *55%* Female. The clinic from which the sample was drawn services predominantly Black South Africans of low socio economic background. Adolescents were also selected if they had at least four years of English medium education which served as an indicator of proficiency in the language of testing. Home language distribution was as follows English (*11%*), Afrikaans (*11%*), Zulu (*26%*), Sesotho (*19%*), Xhosa (*22%*), Venda (*4%*), Tswana (*7%*). Participants were also non-institutionalised (living in family settings) and had not been further neurologically compromised with conditions such as Epilepsy, Meningitis and/or Traumatic Brain Injury.

Table 5.1: Sample Distribution of HIV-positive adolescents:

	Mean	**SD**	**Var.**	**Min**	**Max**
Current Age	14.07	.923	.852	13	16
Grade	8	1.035	1.071	7	10
Age at HAART initiation	7.97	3.053	9.320	1	13
No of Years on HAART	6.10	3.098	9.596	1	14

Viral Load Change	-2.10E+05	5.38E+04	8.39E+10	-1.10E+06	94

Further analysis of the distribution of the independent variables depicted in Table 5.1 above allows for the following categorisation:

The age at which HAART was initiated was distributed as follows 5 - 6 yrs (*13.8%*), 7 - 8yrs (*31.0%*), 9 - 10 yrs, (*24.1%*), 11 - 12yrs (*13.8%*) and 13 - 14yrs (*17.2%*). At the time of HAART initiation the distribution of CD4 T-cell levels was *31%* with Severe Immunosuppression (< 200 cells/mm^3), *28%* had Advanced Immunosuppression (> 200 cells/mm^3 $\leq$ 349 cells/mm^3), *14%* had Mild Immunosuppression (> 349 cells/mm^3 $\leq$ 499 cells/mm^3) and *28%* had non-significant immunosuppression (> 500 cells/mm^3). At the time of the psychometric assessment CD4 T-cell distribution was as follows - *3.85%* of the sample were found to have Severe Immunosuppression, *19.2%* were found to have Mild Immunosuppression while *77%* were found to have non-significant immunosuppression. This corresponded with the higher percentage of viral load reductions i.e. *59%* of participants were found to have significant viral load reduction (ie. depicted by WHO regulations as a decrease of $\geq 10^2$). *31%* of participant's viral loads were either unchanged or non-significant changes (between 0 - 10^1) while *10%* had -significant increases in their viral loads (increase of 10^2). All the participants were on a managed ART programme with either Abacavir (ABC), Lamivudine (3TC), Efavirenz (EFV) (*50%*), Stavudine (D4T), 3TC, EFV (*25%*), D4T, 3TC, Multivitamins (MVT) (*10.71%*), ABC, 3TC, Aluvia (*3.57%*), ABC, EFV, Anuridine (*3.57%*), 3TC, Tenovofir (TDF) (*3.57%*) or 3TC, EFV (*3.57%*).

In terms of the ARV treatment, the mean age of HAART initiation was found to be ~ 8years (*SD 1.03*). It is again worth re-iterating that the children in this study were born in the pre-PMTCT era and therefore HAART initiation was implemented only after they had presented symptomatically. It is not surprising therefore that the range for age of HAART initiation (Range = 12) is a very wide. The mean duration of years on HAART also varied with a mean of 6.10 (*SD 3.10*). Again, with a range of 13 and a variance of 9.60 corresponds with the spread observed in the HAART initiation analysis. Thus although a significant viral log drop of 10^5 was observed the variance once again resulted in an extremely wide distribution. It should also be noted that the distribution was skewed with 59% achieving a significant viral load drop of 2 (10^2) while on the HAART programmes suggesting that ARV treatment was effective at reducing viral loads. Adherence and compliance factors were not explored which could in part have explained the remaining 41% with non-significant viral load drops.

5.2 HIV-positive vs Contrast Group: Data Analysis

As discussed, the performance of the HIV positive adolescents was compared to a contrast group of unaffected adolescents of comparable gender, socioeconomic and educational backgrounds. As alluded to before non-parametric measures were employed due to the smaller sample sizes and variable statistical computations (see Chapter 3, Section 3.6). Effect sizes were calculated using the formula: r = *Z*/√N. The following descriptors have been used to define the size of the differences (Huck, 2009):

Table 5.2.1: Definition of Effect Size based on group means:

Effect Size (r)	Definition
< 0 < 0.2	No Deviation
~ 0.2	Small
~ 0.5	Moderate
~ 0.8	Large

An alternate way of considering the data is by converting the data into z-scores. Here, the means of the affected group were converted to z-scores (*z*) using the mean and standard deviation of the contrast group. In this way, a unitary pattern could be obtained by which to establish trends in performance. By conducting this analysis, a visual representation of relative areas of performance deficits in the HIV sample could be determined. Z-score interpretations are thus established in terms of number of standard deviations from the

baseline and according to a normal distribution. The following descriptors have been used to define whether the difference is undeviated, mild, moderate or large.

Table 5.2.2: Definition of z-score deviations

Deviation from baseline (z-score)	Classification
< 0.66 – 0	No Deviation
0.66 – 1.0	Small
> 1.00 – 1.53	Moderate
> 1.53 – 2.0	Large
> 2.00	Very Large

The z-scores were mapped and accompanied by plots of the effect sizes associated with each of the subtests. This provided a graphical representation of the standardised means together with an indication of the effect sizes of these changes (up or down) – see Figure 5.1 on page 85.

5.3 Results for Overall Intelligence

Table 5.3.1: Composite Performance on the WISC-R (n= 29)

	Mean	Mdn	SD	Z-Score (Deviation from Contrast)
Verbal IQ	61.52	60.00	10.84	-0.10
Performance IQ	74.44	74.00	12.57	0.06
Full IQ	65.16	65.00	11.32	-0.05

VIQ, PIQ and FIQ performance scores of the experimental group was found to follow the normal distribution as evaluated in the original WISC-R normatization study (Skuy, Schutte, Fridjohn, & O'Carrol, 2001). A difference of approximately 13 points was also noted between the VIQ and PIQ performance. The PIQ of the group emerged as being slightly stronger than VIQ. This difference is in line with expectations as the study was conducted on participants where English is the second language and hence may explain the 13 point differential. FIQ of the group emerged as 65.16. Z-score comparisons to the contrast group (Table 5.3.1 and see also Fig 5.1 on p 84), reveals a relatively undeviated pattern. This performance suggests that the composite scores alone are insufficient to evaluate differences between the groups.

Table 5.3.2: T-tests - Composite Performance on the WISC-R (n = 88)

	Wilcoxon (*Z*)	**p-value (p)**	**effect size (r)**
Verbal IQ	-0.230	0.76	-0.02
Performance IQ	0.46	0.64	0.05
Full IQ	-0.032	0.97	0.003

Although the PIQ measured marginally higher and the VIQ and FIQ marginally lower, statistically speaking, the measured performances of the HIV positive and healthy samples were comparable. Non-parametric t-tests between the experimental group and the contrast group (Table 5.3.2) reveals that the HIV-positive adolescents had comparable global intelligence quotients (Z = - 0.032, p = 0.971, r = - 0.03), verbal intelligence quotients (Z = - 0.23, p = 0.76, r = - 0.02) and performance intelligence quotients (Z = 0.46, p = 0.64, r = 0.05) when compared to the contrast group. Although the PIQ measured marginally higher and the VIQ and FIQ marginally lower, statistically speaking, the measured performances of the HIV positive group and healthy samples were comparable.

5.4. Results for Digit Span Forward and Backward

Table 5.4.1 Digit Span Subtest on the WISC-R (n = 29)

	Mean	**Mdn**	**SD**	**Z-Score (Deviation from Contrast)**
Digits Forward	4.86	5.00	1.88	-0.52
Digits Backward	3.10	3.00	1.50	-0.63

The Digit Span subtest is a test of verbal auditory memory incorporating short term memory (digits forward) and working memory (digits backward) components. As can be seen in Table 5.4.1, the experimental group has a STM capacity of 5 digits. Digits Backward emerged 2 digits below the performance for Digits Forward at a mean of 3 digits. This is within the expected range and the deviation from the contrast group is small.

Table 5.4.2: Non-Parametric T-Test Digit Span Subtest (n= 95)

	Wilcoxon *(Z)*	**p-value**	**effect size (r)**
Digits Forward	-2.44	0.015	- 0.25
Digits Backward	-2.31	0.021	- 0.24

A t-test analysis (Table 5.4.2) on the Digit Span Forward subtest revealed a statistically significant difference between the HIV-positive group and the unaffected group. The effect of this difference was weak (Z = -2.44, p = 0.015, r = -0.25). Since digit span forward is a

measure of short term memory, this result suggests that the experimental group have a shorter auditory memory span than the contrast group but that the effect of this difference is small. Consequently it is not unexpected that performance on digit span backwards would also be affected ($Z = -2.31$, $p = 0.021$, $r = -0.24$) although this effect was also found to be small. Digit span backwards is an indication of working memory i.e. the ability to keep things in mind while performing a mental manipulation.

5.5 Results from the Mazes subtest (WISC-R)

The Mazes subtest was scored according to a time limit without making any errors. Errors were defined according to whether the participant entered a blind alley with partial credit allocated if the participant was able to solve the maze within the time limit but still made errors within the task (Weschler, 1974). Participants were also not penalised if they overshot a turn or for pencil lifts. Note that only the performance of 26 participants was available for analysis. Table 5.5.1 provides a summary of the performance of the participants in this task:

Table 5.5.1 Performance on the Mazes subtest , n = 26

	Mean	**Mdn**	**SD**	**Z-Score (Deviation from Contrast)**
Mazes Performance Scores	22.42	22.5	5.20	0.12

The Mazes subtest was intended to provide information pertaining to planning and forethought and involves the adoption of strategic mental processes in order to achieve a positive outcome. When compared to the contrast group, the performance of the HIV positive cohort was found to be undeviated (z = 0.12).

Table 5.5.2: Non-Parametric T-Test Mazes Subtest (n= 92)

	Wilcoxon *(Z)*	**p-value**	**effect size (r)**
Mazes Performance Score	0.643	0.52	0.07

A t-test analysis (Table 5.5.2) on the Mazes subtest further revealed that the performance between the HIV-positive group and the contrast group was not significant. In addition the effect of this difference was found to be weak (Z = 0.643, p = 0.52, r = 0.07). This result suggests that planning functionality and strategic processes needed for problem solving appear to have no difference from the contrast group. The findings of this subtest are discussed further in Chapter 6.

5.6 Results from the D-KEFS Colour Word Interference Test

Each of the trials in the D-KEFS CWIT is scored according to the speed of processing (with longer time taken associated with poorer speed of processing), and an error related processing task consisting of uncorrected errors and self-corrected errors. Uncorrected errors can be thought to be a reflection of poor sustained attention, while self-corrected errors refer to self-regulation and self-monitoring capabilities.

The first two trials of the D-KEFS CWIT ie the Colour Naming Trial (Trial 1 or CNT) and the Word Reading Trial (Trial 2 or WRT) are primarily evaluations of sustained attention and speed of processing. Table 5.6.1 provides a summary of the performance of the participants on these trials:

Table 5.6.1 D-KEFS Colour Word Interference Test – Colour Naming Test (CNT) & Word Reading Test (WRT), n = 29

	Mean	**Mdn**	**SD**	**Z-Score (Deviation from Contrast)**
TRIAL 1: CNT				
CNT Uncorrected Errors	1.14	1.00	1.43	0.54
CNT Self Corrected Errors	2.14	2.00	1.62	0.93
CNT Total Errors	3.28	4.00	1.91	0.99
CNT Time	51.55	49.00	10.54	1.54
TRIAL 2: WRT				

WRT Uncorrected Errors	0.41	0.0	0.73	0.17
WRT Self Corrected Errors	1.41	1.0	1.38	1.01
WRT Total Errors	1.83	2.0	1.75	0.93
WRT Time	38.76	37.0	12.16	1.00

Comparing the performances delivered by the HIV positive group and the healthy samples on both the CNT and WRT (Table 5.6.1) reveals that the HIV affected group made higher errors across the trials for the Colour Naming Test and the Word Reading Test. The experimental group also took longer to complete the trials than the contrast group – reflected in the positive z-score results. The z-score means of these differences was evaluated to be just within one standard deviation of the contrast group.

Table 5.6.2: t-tests D-KEFS Colour Word Interference Test – Colour Naming Test (CNT) and Word Reading Test (WRT), n = 95

	Wilcoxon Z	**p value**	**Effect Size (r)**
Trial 1: CNT			
CNT Uncorrected Errors	1.86	0.66	0.19
CNT Self Corrected Errors	3.28	0.001	0.34
CNT Total Errors	3.68	0.0002	0.38
CNT Time	4.83	< 0.0001	0.50
Trial 2: WRT			
WRT Uncorrected Errors	0.73	0.46	0.07

WRT Self Corrected Errors	3.78	0.002	0.39
WRT Total Errors	3.27	0.001	0.34
WRT Time	4.01	<0.000	0.41

The D-KEFS CWIT requires appropriate response selection and self-monitoring in order to correct errors. Significantly higher self-regulation performance (self-corrected errors) was picked up in the HIV positive group compared to the contrast group, however, this must be considered in light of the fact that they *made more errors* overall (total errors) as compared to the contrast group which explains the difference ($Z = 3.68$, $p = 0.0002$, $r = 0.38$). The effect of this difference is small to moderate. In the same trial, an evaluation of the t-tests depicted in Table 5.6.2, reveals that speed of processing (for the colour naming task) in the HIV-positive group ($Z = 4.83$, $p < 0.0001$, $r = 0.50$) was significantly longer than in the contrast group and that the related effect size was at least moderate. Likewise, in the Word Reading task, the participants made more errors overall ($Z = 3.27$, $p < 0.001$, $r = 0.34$), and once again the time taken to complete the task was longer ($Z = 4.01$, $p = 0.0001$, $r = 0.41$), than the contrast group. Not only were these differences statistically significant, but the effect of these differences was found to be small to moderate (Table 5.6.2).

The next two trials in the D-KEFS CWIT reveal the performance of the group in the Inhibition Trial (Trial 3) which calls on cognitive control i.e. the ability to shift attention from one feature of focus to another (eg. from colour to word) and the Inhibition/Switching Trial (Trial

4) (which requires inhibition and set shifting capabilities but demands more cognitive resources and better working memory functionality). Consider Table 5.6.3:

Table 5.6.3: D-KEFS Colour Word Interference Test – Inhibition Test (IT), n = 29

	Mean	**Mdn**	**SD**	**Z-Score (Deviation from Contrast)**
Trial 3: IT				
IT Uncorrected Errors	4.24	3.0	4.23	0.70
IT Self Corrected Errors	4.24	4.0	3.12	0.38
IT Total Errors	8.49	7.0	4.78	0.77
IT Time	95.24	94.0	23.97	1.36

The Inhibition trial requires additional resources ie. selective, divided and sustained attention as well as good monitoring skills. Due to the cognitive load imposed by these trials, it was predicted that poorer attentional mechanisms would compromise overall performance. Indeed, this was the case in the HIV positive group where the additional resources required to conduct the tasks resulted in more overall errors in the Inhibition Trial, although this difference was small (within one standard deviation of the contrast group, z (Total Errors) = 0.77); and they took a moderately longer time than the contrast group, z (IT-Time) = 1.36 to complete the task.

Table 5.6.4: t-tests D-KEFS Colour Word Interference Test – Inhibition Trial (IT) and Switching Test (ST), n = 95

	Wilcoxon Z	p-value	effect size (r)
Trial 3: IT			
IT Uncorrected Errors	2.03	0.04	0.21
IT Self Corrected Errors	0.83	0.41	0.09
IT Total Errors	2.33	0.02	0.24
IT Time	3.85	0.0001	0.40

T-test comparisons (Table 5.6.4) of Total Errors in Trial 3 further support statistically significant differences, Z = 2.33, p = 0.02 and the small effect size (r = 0.24), while the processing time (IT-Time) was also evaluated to be statistically significant, Z = 3.85, p = 0.0001 but the effect size moderate to large (r = 0.40).

The Switching/Inhibition Test (Trial 4) requires additional cognitive resources inclusive of attention, the ability to inhibit and continuous self-monitoring, working memory (in terms of keeping the rule in mind) and switching (cognitive flexibility). Table 5.6.5 provides a summary of the HIV positive group's performance on this task:

Table 5.6.5: t-tests D-KEFS Colour Word Interference Test –Inhibition/Switching Test (ST), n = 29

	Mean	Mdn	SD	Z-Score (Deviation from Contrast)
Trial 4: ST				
ST Uncorrected Errors	5.72	5.00	4.17	0.36
ST Self Corrected Errors	3.31	3.00	2.61	0.09
ST Total Errors	9.03	8.00	4.48	0.40
ST Time	98.83	101.00	24.40	1.12

As predicted, the HIV+ve cohort deviated from the contrast group ie. they made more Total Errors, z (ST Total Errors) = 0.40 (moderately more) and took (moderately) longer to complete the task, z (ST Time) = 1.12.

Table 5.6.6: t-tests D-KEFS Colour Word Interference Test – Inhibition/Switching Test (ST), n = 95

	Wilcoxon Z	p-value	effect size (r)
Trial 4: ST			
ST Uncorrected Errors	3.11	0.002	0.32
ST Self Corrected Errors	0.29	0.771	0.03
ST Total Errors	2.71	0.007	0.28
ST Time	3.90	<0.0001	0.40

T-test comparisons also reveal that these differences were statistically significant ie. with Switching/Inhibition Total Errors, $Z = 2.71$, $p = 0.007$ and where the effect was found to be

small (r = 0.28) – Table 5.6.6. In terms of processing time, once again the HIV-cohort emerged as taking a statistically significant longer time (Z = 3.90, p <0.0001) and further validating the moderately longer effect size (r = 0.40).

5.7 Results of the Trail Making Test-B

TMT-B is a mental tracking task which imposes a higher cognitive load and contrasts shifting of spatial locations with comparable non-shift control conditions (TMT-A) (Suchy, 2009). Consider Table 5.7.1:

Table 5.7.1: Trail Making Test -Trails B, n = 29

	Mean	**Mdn**	**SD**	**Z-score (Deviation from Contrast)**
Trails B Time	139.27	128.00	64.77	0.82
Trails B Errors	2.52	1.00	3.65	1.05
% Increase in TMT B	49.97	55.15	21.46	-0.25
Diff B – A (Errors)	2.06	1.00	3.31	0.93

Z-score results of the Trails-B Time reveal that the HIV-positive group took longer than the contrast group to complete the task, z (Trails-B Time) = 0.82 , they made more errors, z (Trails B Errors) = 1.05. It is also possible via the TMT-B task to differentiate between dual tracking and visuospatial processing. This can be done by assessing the percentage increase in time taken to complete the TMT-B as opposed to the TMT-A. In this task it was discovered that the experimental group were comparable to the contrast group in terms of the processing time, z (% Increase in TMT B) = - 0.25. Despite this, the cohort still made more errors ie. z (Diff B – A (Errors)) = 0.93. Although the effect size of this difference is small, it is an indicator of poorer visuospatial processing in the cohort.

Table 5.7.2: t-test results of the Trails B performance of the TMT, n = 95

	Wilcoxon Z	**p-value**	**effect size (r)**
Trails B Time	3.90	< 0.0001	0.4
Trails B Errors	2.23	0.026	0.23
% Increase in TMT – B	- 0.77	0.44	-0.08
Diff B – A (Errors)	2.00	0.048	0.21

T-test analysis show that the experimental group took a statistically significant longer time to complete the task Z= 3.90, p < 0.0001 and that the effect size of this difference was small to moderate (r = 0.40). The cohort were also found to make (statistically) significantly more errors Z = 2.23, p = 0.0026 but the effect size was found to be small (r = 0.23). While the percentage increase in the time taken to complete the TMT-B was found to be negligible (Z = -0.77, p = 0.44, r = -0.08) it is worth re-iterating that they were found to make more errors in the dual tracking aspect (Z= 2, p = 0.048, r = 0.21) but that this effect was small. Given the results from the D-KEFS CWIT as well as the observed attentional and working memory and processing speed deficits observed thus far, it was to be expected that performance on the TMT-B would be compromised when compared to the contrast group. This performance is therefore consistent with the results of the D-KEFTS CWIT, Inhibition and Switching/Inhibition trials.

5.8 Results of the Wisconsin Card Sorting Test

The WCST measures EF by ascertaining the set formation, set maintenance and set shifting capabilities. As discussed, set formation refers to generativity and involves aspects of initiation and volition as well as planning and reasoning capabilities. In the WCST this is operationalized by the number of trials to complete the first category (initiation and volition) while planning and reasoning was measured by the number of categories completed.

Table 5.8.1: Wisconsin Card Sorting Test, n = 29

	Mean	**Mdn**	**SD**	**Z-score (Deviation from Contrast)**
WCST Trials to First Category	14.55	11.00	17.72	-0.33
WCST Categories Completed	3.28	3.00	2.05	-0.18
WCST Correct Responses	49.18	55.00	19.08	-0.37
WCST % Conceptual Level Responses	37.44	38.00	20.14	-0.26
WCST No of Errors	50.88	45.00	19.01	0.36
WCST No of Perseverative Responses	38.00	30.00	24.71	0.18
WCST % Perseverative Errors	30.81	25.00	18.60	0.19
WCST Failure to Maintain Set	0.55	0.00	0.74	-0.25

No significant differences were found between the HIV-positive experimental group and the contrast group on any of the above-mentioned tasks (Table 5.8.1). Such were the results however, that it is definitely worth commenting that the mean differences between the HIV positive sample and the contrast group revealed small but **not** statistically significant differences. For example, the HIV positive group had less correct responses (z = -0.37), made more Errors (z = 0.36), made more Perseverative Responses (z = 0.18) and had more perseverative errors (z = 0.19) when compared to the unaffected group. The tendency to perseverate is associated with poorer self-regulation mechanisms and was predicted for the HIV-positive group. It was however noted that the experimental group's performance on the Failure to Maintain Set (z = - 0.25) was better than the contrast group. This performance is inconsistent with our hypothesis, however their performance on this aspect of the WCST may be an artefact of their slightly increased tendency to perseverate. This assertion is speculative at the moment due to the poorer sensitivity of the WCST to pick up executive function errors in this population. It is also possible that this is merely an emerging skill in this cohort and if this was followed up on an older age group the results might be different.

Table 5.8.2: t-tests Wisconsin Card Sorting Test, n= 92

	Wilcoxon Z	**p-value**	**effect size (r)**
WCST Trials to First Category	- 3.245	0.001	- 0.34
WCST Categories Completed	- 0.783	0.431	0.08
WCST Correct Responses	- 1.096	0.27	- 0.11
WCST % Conceptual Level Responses	- 0.916	0.357	0.10

WCST No of Errors	1.11	0.264	0.11
WCST No of Perseverative Responses	0.403	0.684	0.04
WCST % Perseverative Errors	0.39	0.693	0.04
WCST Failure to Maintain Set	- 1.091	0.274	- 0.11

In terms of the number of trials to complete the first category (Table 5.8.2), a statistically significant difference was found with the HIV positive group $Z = -3.245$, $p < 0.001$; but this effect was weak to moderate ($r = -0.34$). At first glance, this performance would suggest that the participants in the HIV positive group appear not to have problems with initiation and in fact had better volitional capabilities compared to an unaffected group. Possible explanations for this performance may lie in the design of the test as it does begin with the 'Colour' rule – which is perceived to be the most obvious, however despite this better than expected performance, the HIV-positive group was not able to complete more categories on the WCST (performance was marginally weaker but non-significant) when compared to the contrast group.

Set maintenance requires freedom from distractibility, response selection (thinking before acting) and cognitive control ie. the ability to inhibit the tendency to persist (evaluated as perseverative responses and perseverative errors on the WCST). Set Shifting on the other hand draws on a few processes ie. working memory (the ability to hold a changed rule in mind (observed via WCST Error response and number of Correct responses), planning and

reasoning at a conceptual level (Conceptual level Response) and most importantly cognitive flexibility ie. the ability to switch response sets or between operations (evaluated by the perseverative responses).

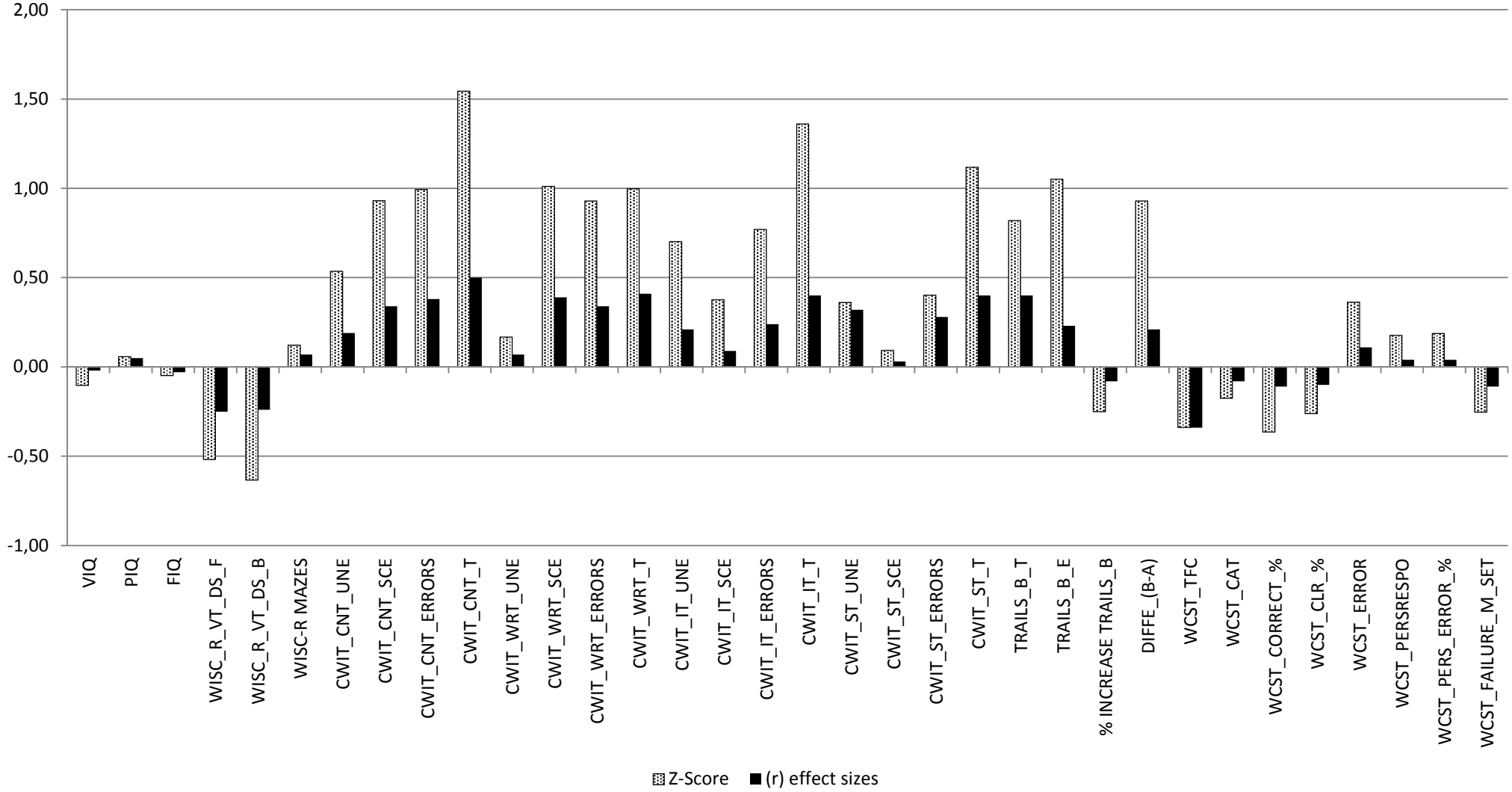


Fig 5.1: Collective Pattern of Performance

5.9 Results of Differences for Mood

As highlighted earlier on in this study, an additional test for mood related differences as evaluated by the Beck's Youth Inventory (BYI-II) was applied to establish the link to EF capability. The areas of importance for this study pertained to the Disruptive Behaviour Index and the Anger Index as they relate to disinhibition and the OFC-mediated circuitry. Analyses of the results reveal marginal differences between the HIV-positive group and the unaffected contrast group (Table 5.9.1):

Table 5.9.1: Anger and Disruptive Behaviour Index, n = 29

	Mean	**Mdn**	**SD**	**Z-score (Deviation from Contrast)**
Anger Index	21.12	22.00	9.51	0.26
Destructive Behaviour Index	10.46	8.00	9.67	0.26

Higher scores in these two dimensions might suggest that the HIV cohort are inclined to have higher Anger and Destructive Behaviour tendencies but these differences are so small ie. z (Anger Index) = 0.26 and z (Destructive Behaviour Index) = 0.26 that they are almost inconsequential.

T-Test comparisons support the initial interpretations as revealed in Table 5.9.2:

Table 5.9.2: t-tests of Anger Index and Destructive Behaviour Index, n = 92

	Wilcoxon (*Z*)	**p-value (p)**	**effect size (r)**
Anger Index	1.12	0.26	0.12
Destructive Behaviour Index	0.76	0.44	0.08

So, while the HIV-group had higher index scores for Anger and Destructive Behaviour, the difference is not statistically significant, and the effect size is negligible indicating that in this cohort, disinhibition as it relates to the OFC-mediated circuitry is comparable to the contrast group.

5.10 Results of Differences within the HIV-Positive Cohort

A further analysis was conducted on the experimental group test for differences in performance between gender, between the 13-14yr olds and 15 – 16yr old age categories, between viral load drops (significant vs non-significant drops), between the current states of immunosuppression (CD4 T-cell counts) as well as duration on HAART (established through the closest equitable split of $\leq$ 6years or > 6years). Once again, non-parametric statistical computations were conducted based on the smaller sample size, uneven split between groups and the skewed distributions.

Existing literature reveal that verbal performance in girls would be higher than in boys. Table 5.10.1 is an analysis of between gender differences within the experimental group (showing only significant differences):

Table 5.10.1: Significant performances by Gender in the HIV cohort

	Boys *Mdn (SD)*	***Girls*** *Mdn (SD)*
Digit span Backwards	2.00 (1.33), n = 13	3.5 (1.50), n = 16
VIQ	54.00 (7.79), n = 11	67.5 (10.30), n = 14
D-KEFS CWIT (Switching) Self Corrected Errors	2.0 (1.52), n = 13	4.0 (2.74), n = 16
D-KEFS CWIT (Switching) Total Errors	7.0 (2.44), n = 13	12.0 (4.43), n = 16
TMT –B (Time)	193.00 (71.99), n = 13	105.5 (37.05), n = 16
% Time Increase in TMT-B	0.60 (0.15), n = 13	0.42 (0.20), n = 16

Between the genders, girls were found to have better verbal IQ ($Z = -2.58$, $p = 0.0092$) with a moderate effect ($r = -0.516$) and better verbal working memory abilities (digit span backwards, $Z = -1.95$, $p = 0.049$) although the effect of this difference is weak to moderate ($r = -0.36$). Given the better VIQ, one would have expected the girls to have a statistically significant Digit Span Forward performance, however this was not found to be the case.

In the D-KEFS CWIT, no statistically significant differences were reported between the genders in the HIV-positive cohort, but for the Switching/Inhibition trial of the D-KEFS CWIT, where the boys made more self-corrected errors ($Z = -2.618$, $p = 0.0083$, $r = -0.486$) and contributed to a higher total errors performance ($Z = -3.16$, $p = 0.002$). When compared to the girls, this suggests poorer error-related processing – where the effect was moderate to large ($r = -0.586$).

In the dual tracking task (TMT-B Time), the boys' processing speed was considerably longer when compared to the girls ($Z = 3.09$, $p = 0.002$) with a moderate effect size ($r = 0.57$). After eliminating for visuo-spatial processing time and considering only dual-tracking and shifting capability (% Increase in TMT-B Time), it was noted that the boys took considerably longer than the girls ($Z = 3.00$, $p = 0.0025$) and this difference was moderate ($r = 0.55$). It is also noted that the boys made no more errors than the girls for the same task. In other words, the girls were not only faster but also did not have more errors than the boys suggesting better cognitive flexibility and speed of processing. Since girls develop faster than boys, these gender differences may only be temporary due to maturational differences between boys and girls and can be thought to be consistent with male/female differences at this age. It would be useful to establish these within group differences in the contrast group. These gender differences are expected but if it is to be assumed that boys are inclined to use more right hemispheric skills than girls then it is possible that HIV has more serious consequences for boys and the difference may be greater.

As indicated, the participants were split according to the number of years on HAART. We predicted that performance between the groups would differ based on duration on HAART. Since the bulk of the participants had been on HAART for at least 5 years, it was decided to split the group into those who had been on HAART for less than 6 years and those that had been on HAART for 6 years or more. Although not ideal, a 45:55 ratio was obtained with 45% (n =13) being on HAART for less than 6 years and 55% (n =16) on HAART for 6 years or more. Some participants were excluded for missing details. In the case of the WISC-R, 4

participants were not evaluated due to missing WISC-R results. Statistically significant differences based on HAART duration are indicated in Table 5.10.2:

Table 5.10.2: t-tests based on HAART duration

	Wilcoxon (*Z*)	**p-value (p)**	**effect size (r)**	**n**
VIQ	2.42	0.014	0.48	25
FIQ	2.21	0.025	0.44	25
D-KEFS CWIT (ST-ERRORS)	2.47	0.013	0.45	29
WCST (PERSEVERATIVE RESPONSES)	-2.15	0.030	-0.40	29

According to this division (Table 5.10.2), significant differences were noted for VIQ and FIQ. Participants who had been on HAART for under 6 years had statistically better VIQ performance as well as FIQ performance scores and this effect was at least moderate. All other subtests under the WISC-R were not significant. As noted, 4 participants were excluded as they were not evaluated on the WISC-R.

On the D-KEFS CWIT, the only significant difference was noted on the Switching Trial (Trial 4) –Errors performance. Here participants who had been on HAART for less than 6 years reported **more** errors than those who had been on HAART for longer. The size of the difference was also found to be moderate (r = 0.45). Once again, all other tests were not significant between the groups for this assessment.

Finally, it was found on the WCST-Perseverative Responses task that participants who had been on HAART for less than 6 years made significantly less perseverative responses than those who had been on HAART for longer and that the size of this effect was moderate.

Given that no significant differences were found when the group was split according to viral load drops, current CD4 T-cell counts, CD4 T-cell counts at HAART initiation and age category (13-14yrs vs 15-16yrs), it is possible that these effects may due to the effects of HAART medication – given that no significant differences were found based on Viral Load Drops. Since all other factors are non-significant, the efficacy of the ACC-OPFC circuitry appears to be the area of localisation, however further testing is required to confirm this conclusion.

Chapter 6: Discussion

Having deconstructed EF in the manner that we have provides fragments of information. IQ measurements between the cohort and the experimental group (as evaluated on the WISC-R) reveal comparable performances between the HIV-positive cohort and the unaffected group after considerations for age, education and socio-demographic factors. While IQ (as evaluated on the WISC-R) can be ruled out as a source of the neuropsychological differences between the HIV experimental group and the contrast group, it is also possible that the composite IQ performances (VIQ, PIQ and FIQ) alone is not sufficient to evaluate the more subtle neuropsychological deficits associated with HIV. In addition, since mood related factors were also found to be relatively comparable between the two groups, affect related differences were also ruled out as possible sources for the EF deficits.

The collective pattern that emerged from the Digit Span task is indicative of poorer attentional mechanisms and poorer memory (reduced short term memory and consequently poorer working memory functionality). While these differences exist, they are subtle. This performance is perhaps one of the first indicators of possible disruption of the circuitry of the DLPFC (responsible for the sequencing and organisation of information needed to facilitate a response) as well as the MPFC (ACC) which is associated with motivational aspects needed for selective and sustained attention. So, while global intelligence has been ruled out as a source of neuropsychological differences per se, the first clue that something is awry emerges from the digit span subtest. If the channels responsible for attentional processes and working memory are in any way compromised, then the

prediction is that EF will also be affected due to the higher attentional and working memory resources demanded by EF.

Results from the WISC-R Mazes subtest revealed no significant differences between the HIV positive cohort and the Contrast group. While the WISC-R Mazes subtest requires problem solving skills, planning and mental flexibility (needed to generate alternatives), the scoring system by itself was not deemed to be adequate as an evaluation tool of EF in this study. Indeed, Lezak et al (2004) admits that although the Mazes subtest is sensitive to eliciting planning deficits, it is not usually used "perhaps because the original set requires considerable time and administration challenges." (p. 616). As indicated, effective performance is based on the number of successful turns within a specified time period. Some participants were noted to have deliberated before attempting the task. This deliberation could be due to pre-planning before actual administration which might have adversely affected overall performance. Qualitative reports also indicate that some participants delved into the task without any deliberation – this time suggesting the proclivity towards impulsivity which may also have affected overall performance. The Mazes subtest by virtue of its scoring design and administration difficulties was consequently found to leave the researcher with more unanswered questions and points to the shortfalls in adopting the standardised test method used in this task – which in a clinical setting may not be sufficient for diagnostic purposes. This may well be an area of focus for further research.

The D-KEFS CWIT was found to be the tool that was most effective at assessing executive dysfunction in the cohort. As discussed, the first two trials evaluate sustained attention and speed of processing. Each trial also has a speed of processing portion (with the longer times taken associated with poorer speed of processing), and an error related processing task (which consists of uncorrected errors and self-corrected errors). Uncorrected errors are thought to be a reflection of poor sustained attention, while self-corrected errors refer to self-regulation and self-monitoring capabilities. Trials 3 and 4 of the D-KEFS CWIT viz. the inhibition and Inhibition/Switching task draws upon response selection and self-monitoring capacities in order to correct errors. In the results, we noted that the HIV positive group displayed significantly higher self-regulation performances (self-corrected errors), however, this must be considered in light of the fact that they ***made more errors*** overall (total errors) as compared to the contrast group which further explains the difference.

To enable a better understanding of how this performance plays out, it may be clearer to visualise the following schematic representation:

	Overall Monitoring & Attention	*Attention*	*Self-Regulation*	*Processing Time*
	Total Errors	**Uncorrected Errors**	**Self-Corrected Errors**	**Time**
Colour Naming Task	***S***	*NS*	**S**	**S**
Word-Reading Task	***S***	*NS*	**S**	**S**
Inhibition Task	**S**	**S**	*NS*	**S**
Switching/Inhibition Task	**S**	**S**	*NS*	**S**

Fig 6.1: D-KEFS performance schematic in the HIV-positive cohort

S = Significant, NS = Non Significant

In Fig 6.1, the various tasks have been plotted together with the respective performance in the cohort. The diagram pictorially reveals that if tasks are automatic and overlearned then attentional resources are not in as high demand (indicated by the non-significant Uncorrected Error measurements on the WRT task), however, once the cognitive load increases, greater attentional mechanisms are required. Should attentional mechanisms be compromised then poorer overall executive function performance can be expected – and indeed, was obtained. In general, the HIV sample made more errors overall and took longer to process the information when compared to the contrast group.

The word-reading task is fairly automatic and relies upon previous learning and skill to assure better performance. Automated tasks therefore require less attentional resources. In terms of the neuropsychological theory, automated tasks fall into the dimension of procedural memory and largely bypass executive function capability. It is also thought that the role of the association cortices (particularly the posterior parietal cortex) and cerebellum are activated to ensure optimal functioning (Strick, Dum, & Fiez, 2009).

The colour naming task is also an overlearned task, however the additional colour-to-word association is a little more taxing than the word reading task. Here, sustained attention is imperative for better performance. Areas that would be implicated in this process are once again the DLPFC and ACC although as indicated the white matter tracts and effectiveness of the associated circuitry are as important for errorless processing.

The inhibition task calls on the additional activation of the MFC as well as the OFC. That both groups performed equally in terms of the self-corrected errors suggests appropriate activation of the OFC. That the HIV-positive group made more uncorrected errors than the unaffected group suggests that self-regulation is not as effective as it should be. Moreover, despite taking a significantly longer time to complete the task, they still made significantly more errors. The same applied to the Inhibition/Switching task. Here again, the additional cognitive resources demanded by the task saw the HIV positive cohort faltering. It is also possible that the higher cognitive load coupled with poorer attentional functionalities and poorer working memory capability, ultimately led to poorer cognitive flexibility, poorer

mental control and reduced errorless processing. This is a key observation and has important ramifications for the HIV-positive cohort.

This research used three separate tests of EF – each of which evaluate error-related processing, attentional mechanisms, cognitive control and cognitive flexibility. The premise was that if the HIV-cohort had executive dysfunction then the primary measures of the various EF tests should validate the outcome on three different measures. Indeed, this was the case, with the D-KEFS CWIT and the Trail Making Test-B being the most sensitive of the three instruments in being able to clearly elucidate the differences in EF. It was noted that HIV-positive adolescents were as competent as their unaffected peers on tasks that were overlearned and automated. However, even on these tasks, their speed of processing was delayed suggesting that they took longer to do the same task, but made as many, if not more errors than their unaffected counterparts. It is important to note that although there are differences – these differences are small.

These results do not support the results obtained by Llorente, et al. (2012), who question the sensitivity of their tests (the NEPSY). The authors point out that the lack of differences in their study does not exclude the possibility of executive deficits in their sample (Llorente, et al., 2012).

Performance on the WCST did not reveal gross EF deficits but for the most part pointed towards the general direction of the EF weaknesses seen on the D-KEFS. It is also noted that

the retarded visual processing component in Trails B and the D-KEFS CWIT exhausted attentional resources which further explains these EF deficits. In general, the task was perceived to be quite complex with the cohort achieving less than 40% success for conceptual level responses (ie. the ability to problem solve). We therefore conclude that the WCST task by itself did not pick up differences in executive functioning. Similar responses have been noted by other researchers using the WCST (Minassian, et al., 2013; Salama, et al., 2013). We also note that given that this research was indeed tested on a small sample.

Evaluating the 'components' are useful but ineffectual on its own. Mapping the pieces back together however reveals a startling picture. Put very simply, the pattern that emerges is that the HIV-positive cohort *made more errors* despite *taking more time to process* information. Moreover, while their performance on automated tasks are comparable to the unaffected contrast group, this *pattern changes substantially once the cognitive load increases* making them less able to cope as effectively. This result supports the findings of Melrose et al. (2009) who came to a similar conclusion. In their study that asserted that "HIV disease induces a reorganisation of the attention network that results in cognitive impairment if the manageable load is exceeded" (p 345).

That poorer cognitive control abilities, poorer attentional mechanisms and poorer cognitive flexibility has been implicated highlights deficits to the PFC and/or its circuitry. This is consistent with previous research which identified impaired functioning particularly in the PFC and in the medial temporal lobe under fMRI conditions (Chang, Jovicich, Arnold &

Arnold, 2002). Melrose et al. (2009) however investigated the underlying fronto-striatal circuitry involved in executive function using a combination of neuropsychological measurements as well as fMRI data to establish activation differences on tasks in an adult population. Although they found mild cognitive deficits on their HIV-positive group, they failed to determine behavioural differences between the groups on the fMRI task. Furthermore, structural MRI analyses revealed no evidence of atrophy or cortical thinning but they did find attenuation activity differences on the fMRI data within the fronto-striatal areas in the HIV positive group on a sequencing task. The authors believed that functional changes in the fronto-striatal circuitry are prodromal to structural changes which underscore executive dysfunction seen in HIV positive populations (Melrose et al., 2009). More interesting and concurrent with our findings in this research, was that they effectively demonstrated that caudate activity normally associated with EF (and present in the control group) was absent in the HIV positive group (Melrose et al., 2009). This is of importance since the caudate nucleus has been found to be instrumental for successful goal directed behaviour through the activation of correct action schemas and contention scheduling while the putamen, appears to underlie those cognitive functions involved in stimulus responses and habit learning (Grahn, Parkinson & Owen, 2008). In our sample, this further explains the relative ease in automated tasks – which according to Melrose et al.'s (2009) research is mediated by the putamen, while those requiring attentional resources involve the caudate. Herein lay the key to understanding the effects of HIV – a disease that results in executive dysfunction by destabilising the neural circuitry to the PFC.

That the anticipated havoc that should occur is not observable at a gross level in asymptomatic HIV-positive adolescents was also observed in Melrose and colleagues research (2009) where fMRI revealed increased parietal activity in their HIV positive sample. This supports the neural plasticity of the brain that disruption to the fronto-striatal system is compensated by increased parietal attentional networks (Melrose et al.et al., 2009). This conclusion also provides a plausible explanation as to why longer speeds of processing were observed in the HIV positive group tested in our research as compared to the unaffected group. In Chapter 2, a conceptual diagram of EF was provided as a means of mapping EF to its neural correlates (Fig 2.2.4). Given the finding found in this research, the diagram has been re-conceptualised (Fig 6.2) as an indication of which pathways may be affected. It should be emphasised that this study ***does not assert*** that the pathways have been ***completely*** compromised. It is more a suggestion of 'less than optimal', since the statistically significant differences (to the contrast group) are small to moderate,

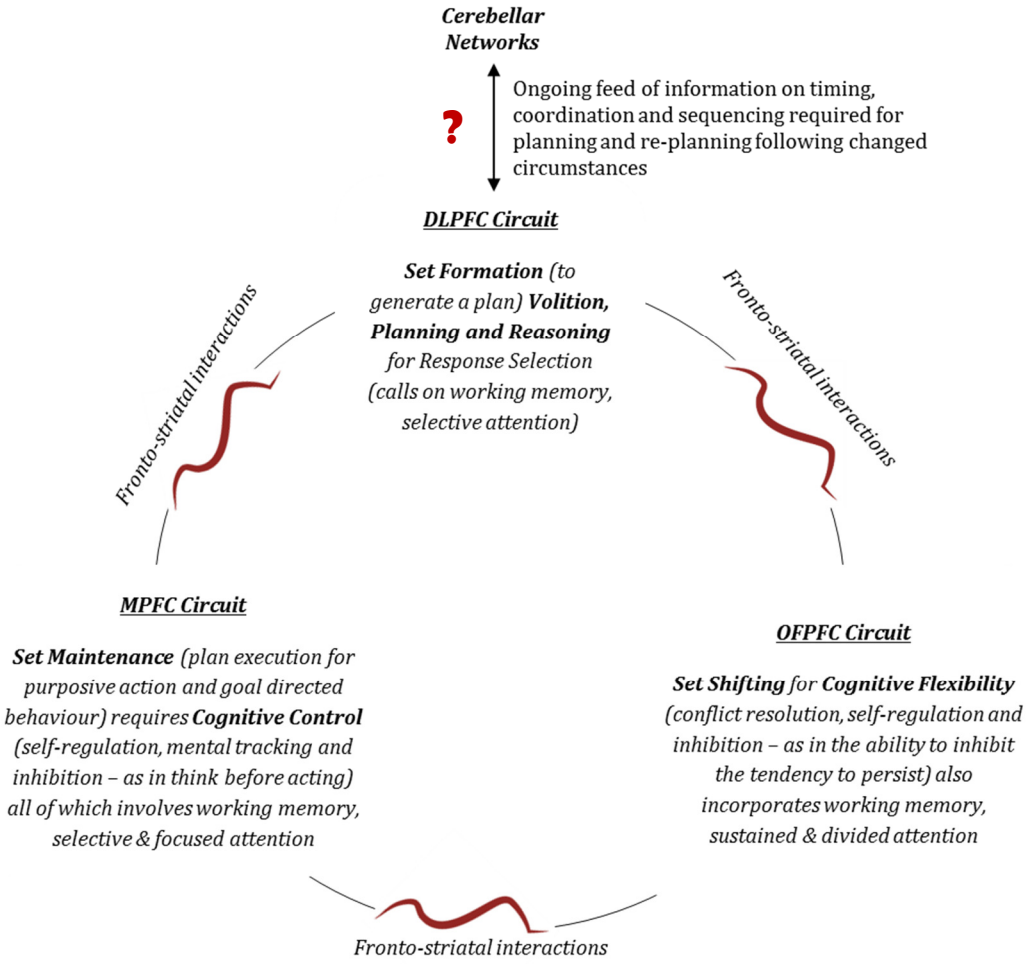


Fig 6.2: Conceptual diagram of affected circuitry

In the days before HAART, HIV Associated Dementia (HAD) was prevalent in HIV populations. HAD was considered to be a subcortical dementia by virtue of the mechanism of HIV penetration into the CNS causing neurodegeneration and astrocyte apoptosis either though the toxic gp 120 and tat proteins effects directly or due to inflammatory responses induced by the cytokine cascades to the neurons. The resulting neuronal degeneration presents clinically as encephalitis, however white matter neuronal apoptosis are less visible and present as clinical slowing and cortical effects (Joska, Hoare, Stein & Flisher, 2011).

Since the advent of HAART, HAD has become less prevalent, however, the literature has alluded to the increased incidence of HIV associated neurocognitive disorders (HAND) of varying degrees ie. asymptomatic neurocognitive impairment (ANI), minor neurocognitive disorder (MND) and HAD (Singh, 2012). While many of the participants in this cohort would be regarded as falling into the category of ANI, the mechanisms by which the pathogen enters and the pathways it affects have not changed. Against the results obtained in this study, HIV-associated executive dysfunction is a subcortical neurocognitive disorder following the same channels inherent in HAD. The pathogen has had 'some' effect but its rapid destructiveness has been minimised by the use of HAART.

Although not definitive, there were suggestions of neuropsychological differences between those participants who had been on HAART longer when compared to those who had been on HAART for shorter periods of time. Indeed, it was found that the HIV positive adolescents who had been on ARV's for more than 6 years had poorer VIQ, FIQ's and had poorer self-regulation/inhibition capacities than those who had been on HAART for under 6 years but they were inclined to perseverate less. As this study evaluated EF only, this conclusion does to some extent to support Mirza's and Rathore's (2012) research in terms of EF functionality being compromised but the evidence is unclear for the moment and therefore weak based on the smaller within group sample size. It does however hint at the potential neurotoxic effects of HAART as indicated by Liner, Meeker & Robertson (2010). Further investigation is needed to consider whether the pre-HAART pattern of higher levels of impairments in motor skills, speed of processing and verbal fluency was obtained or if the

post-HAART pattern of more impairment in memory and executive function typical of the post-HAART era was obtained.

Within the HIV-positive cohort, gender differences have been linked to maturational effects, however it was interesting to note that those participants that had been longer on HAART performed poorer in the areas of VIQ and FIQ. This performance is suggestive of two possibilities i.e. (1) that the virus targets the right hemisphere first but over time the left hemisphere becomes more compromised or (2) that the medication has an impact on the left hemisphere. The HIV positive group also tended to perseverate more but made less errors on selective tests of cognitive flexibility and processing speed. Given that the within group analysis was based on such a small group, we are led to question the generalizability of this result. Indeed, the reported literature does comment on the neurotoxic effects of CNS penetrant HAART medication, so this association is not unexpected. However, given the overwhelming benefits of HAART on overall well-being the risk to benefit ratio currently favours taking HAART than risk opportunistic infections, HIV associated dementia and rapid degeneration to full blown Stage IV.

Chapter 7: Limitations of the Study

Perhaps the greatest limitation of this study has been the small sample size that was obtained for the research. Due to strict exclusion parameters demanded by the study, access to qualifying participants was limited. In addition, it was decided to exclude children that were not in nuclear-type families to maintain socio-demographic factors. Since many of the children who visit the clinic emerged from orphanages and foster homes, the population size was even further reduced impacting upon the availability of participants. The distribution of the experimental population was consequently skewed especially since the contrast group was more than twice as large as the experimental group. While the use of non-parametric statistics was adopted it is thought to have less statistical power than parametric t-tests.

In order to keep the sample as homogeneous as possible, people that were on second line treatment were also excluded from the sample, as were those believed to be symptomatic at the time of the study. This selection was necessary based on the research design and for the elimination of additional confounders. It also meant that we were unable to empirically assess the additive effects of changed medication and opportunistic diseases on neurocognitive performance and offers an opportunity for further testing.

The battery of tests applied were extensive with the full battery lasting around 3 and ½ hours, so it required respondents to be motivated and have the endurance to continue.

Although efforts were made to mitigate for fatigue effects, it may have been better to have conducted the battery over two days. Even though the same conditions applied to the contrast group, the added effect of being on ARV's for the experimental suggests that fatigue effects could not be ruled out altogether.

The tools that were used were well tested and applied. However the WCST was thought to be less sensitive in establishing differences between the groups. It is prudent to add that current literature has noted that the original paper-and-pencil test format applied in this research, is 'ill-suited to offer an accurate description of the type and severity of cognitive deficits or the anatomical location of the lesions ultimately responsible for those deficits' (Bowden et al., 1998; Mountain & Snow, 1993; Reitan & Wolfson, 1994 cited in Nyhus & Barcelo, 2009, p 438). In addition, results from the Mazes (WISC-R) also proved to be insufficient.

There were limitations to the paradigmatic approach of the study – which was largely embedded in the scientific tradition. The scientific approach requires that the research be ontologically objective to allow for the research to be reproducible and reliable. Needless to say, it does limit the study outcomes to the specific group under investigation. It also reveals some 'holes' in the interpretation of the results. The Mazes subtest (WISC-R) for example would have provided better insights had the clinical impressions of the administrators been factored in.

A final limitation of the study is that it is believed that the contrast group was not affected by HIV. Under South African law enquiry into a person's HIV-status is illegal and the respondent is not required to respond to such enquiry. Participants from the contrast group were therefore screened according to whether they were currently taking any chronic medication or had any other central nervous system disorders (such as epilepsy) and if they had incurred any traumatic brain injuries, meningitis or encephalitis.

Chapter 8: Conclusion

This study set out to research executive function of HIV positive adolescents in Johannesburg, South Africa. We used a constructivist approach of understanding the functional aspects of EF and syndromic theory on how it manifests in the different parts of the CNS with lesion studies guiding our understanding of how the underlying circuitry ties this all together.

In assembling the 'parts' we revealed an image of EF – in line with our definition i.e. *those processes that allow people to shift their mind sets quickly and inhibit inappropriate actions so as to facilitate responses to an environment in constant flux* as posited by Jurado and Rosselli (2007). In this respect we predicted that **the HIV cohort** would **exhibit executive deficiencies in mental flexibility, self-regulation and inhibition** when compared to an unaffected group. Our hypothesis on all these aspects was effectively confirmed by the D-KEFS CWIT as well as the Trail Making Test – Part B which confirmed that HIV-positive adolescents struggled at tasks that required higher cognitive resources (such as inhibiting and switching) but were able to match the unaffected cohort on automated/overlearned tasks. Based on the findings of Melrose et al. (2009), as well as existing evidence on the route of HIV infection (as a subcortical infection) we posit that this may be a deficit in the white matter tracts linking the caudate nucleus to the frontal cortices. These statements would need to be confirmed by neuroimaging data with further studies linking caudate attenuation (or the lack of) in our experimental group.

We noted that the WCST did not pick up the executive deficits observed on the D-KEFS CWIT and the TMT-B. One theory is that the task may have been too complex for the adolescents since conceptual level responses were evaluated as less than 40% with no significant difference with the contrast group. Another explanation for the difference may be due to the fact that the WCST is not a timed-test observed by the statistically non-significant performance in the contrast group. For instance, no significant differences were noted for Self-Corrected Errors in the D-KEFS CWIT for the Inhibition and Inhibition/Switching task but significant differences were noted on the time it took i.e. even though they had the same self-monitoring capabilities, they took longer to process the information. The time taken to conduct the WCST was not measured hence this comparison could not be made on the WCST. Needless to say, we hypothesise according to Melrose et al (2009) that the added processing time may have been due to the (longer) compensatory parietal attentional route which may have been activated leading to comparable results for the contrast group. Once again, further research is required to validate this assertion.

In response to our earlier question – how has the effect of being placed onto HAART at a later age affected executive function? The answer appears to be that, although there are some differences, these differences are moderate to weak with those participants who have been on HAART for < 6 years performing better than their peers who had been placed on HAART earlier. The effects of the ARV's on executive function emerge as a possible reason for the deviation if one is to consider the evidence of the neurotoxic effects of HAART on the CNS. Be this as it may, this statement is however made with extreme caution as additional factors such as treatment adherence was not probed effectively, neither have the

interactional effects been considered. The finding is concerning and certainly suggests that more research is still needed to investigate the neuropsychological effects of HAART and the effects of increased titrations over the longer term.

This study effectively elucidated the subtle but ostensible deficits in specific processes of executive function. Based on these insights and existing literature of the route of pathogenic invasion, it postulated that these deficits may be localised to the frontostriatal circuitry underlying EF – and considered the role of caudate nucleus in terms of its role of facilitating goal directed behaviour through the activation of correct action schemas and contention scheduling. Although attentional deficits were noted, we ascribe these to BG-mediated ACC deficits but acknowledge that attentional processes are required at all stages of EF thus pockets of deficits would be picked up in the DLPFC (working memory), in the MFC (self-monitoring) or the OFC (for inhibition and flexibility). We *did not* pick up deficits with regard to planning and organisational activities except in the case of the sequencing task of the Digit span subtest. Other measures of strategy proved to be equivalent between the groups, however performance on tasks such as the ROCFT would help towards ruling out whether cerebellar mediation was also affected in some way. We note that cerebellar activity in EF is a separate circuit but required for effective planning, sequencing and timing intrinsic for optimal EF functionality. In this report however, and given the tests discussed in this paper, cerebellar circuitry was not investigated for its role in the pattern of executive dysfunction observed. This research also supports the research on post-HAART patterns of deficits, however delayed processing has also been noted and may contribute to a mixed pattern of motor-related deficits usually seen in pre-HAART research as outlined by Dennis et al.

(2011). The research does however highlight the impact of poorer attention and processing on EF.

We believe that the results obtained might suggest that HIV positive adolescents living in Johannesburg and on a managed treatment programme (which includes HAART) reflect executive function deficits that have ramifications for future adaptability. Barkley (2001) asserts an evolutionary perspective – with his reformulation of EF as those activities that "enable social exchange (reciprocal altruism), vicarious learning, tool utilisation, mimetic skill development and communication, self-regulation for self-defence and the governance of social behaviour using mental representations" (pg 24). The concepts we considered in our definition ie. mental flexibility, self-regulation and inhibition which incorporate planning and reasoning, response selection, working memory and attentional mechanisms are vital to effective EF as conceptualised by Barkley. Barkley's definition does however concretize the impact of poor EF and its socially devastating consequences. He asserts that planning and reasoning skills, for example, is not the outcome, but the means to a specific outcome (Barkley, 2001). Inadequate planning and reasoning capabilities would therefore diminish problem solving capability and by inference, survival or adaptivity.

In the HIV-positive cohort we investigated, we predict that with the slower rates of processing especially under conditions that demand increased cognitive resources, that asymptomatic HIV-positive adolescents' would falter. In terms of teaching and development, it is likely that the adolescents will find it more difficult to cope especially under conditions requiring greater cognitive resources. We also believe that the capacity to

learn would be impacted upon by the reduced attentional mechanisms as would problem solving abilities. Understanding that this might be the case, these results suggest that HIV-positive adolescents would benefit greatly from being taught strategic problem solving and organisational techniques (commonly used in rehabilitation type settings) in order to optimise EF. Teaching should also be clustered around introducing new concepts gradually rather than overwhelming students and focus on *skill acquisition* and repetition as a means of optimising performance.

Chapter 9: Future Directions

As it stands, the study shows that HIV has a detrimental impact on cognitive development and that it may lead to deficits in a range of functions including the ability to form (planning functionality obtained through initiation and working memory), maintain (response selection and the ability to self-regulation and inhibit) and switch (cognitive flexibility, mental tracking, organization and sequencing) mental processes in order to effect a positive outcome. In summary, the adolescent's ability to problem-solve under novel conditions or high cognitive load will be less than optimum.

We acknowledge that the study was done on a relatively small sample in order to adhere to the strict exclusion criteria and to keep the sample as homogeneous as possible. However, the research does point out areas of concern that need to be addressed further. Certainly, there is clearly a need to repeat the protocol on a much larger group in order to validate many of the findings.

The conclusions arrived at in this research opens other doors for further investigation. In a country that is infamous for its large HIV positive population, it is important to realise the ramifications of compromised EF. For the current cohort who would soon be developing into young adults. While the EF continues to develop over the adolescents life span and into their early thirties, it is important to realise that teaching programmes should be developed so as to 'teach' problem solving skills, adaptivity, stress management skills and coping skills as part of the educational curriculum – both in primary and secondary schools. It may also

be necessary that this scaffolding continues at tertiary level so as to support the development of competency. It is as important to realise that skills that can be taught via the procedural memory system may also be a way in which to enhance learning. In other words, if it is possible to introduce certain tasks so that they become automated, thereby reducing the cognitive load and enables better coping under periods of stress /novel situations.

Care management of HIV affected populations should also include detailed information on medication changes, the appropriate combination of medication and the impact of increased HAART dosages. This information would be useful towards monitoring the effect of neurotoxicity on neurocognitive functioning and quality of life.

EF deficits not only lead to cognitive deficiencies but also amplify psychological problems. Poorer EF can diminish self-esteem and self-confidence. In so doing it increases the person's vulnerability to psychiatric conditions including many of the mood disorders, anxiety, depression, phobias and so forth. It can thus also act as an underlying diathesis that can trigger further problems. Failing to address EF development in an HIV positive can therefore lead to greater social, psychological and cognitive problems. Addressing these issues when they have already occurred is already a little too late. The economic strain it causes may be by this time too much. In a country such as South Africa, riddled with the challenges of poverty, malnutrition and crime – **this** economic burden is something better prevented than cured. Indeed, this research asserts that policy makers, educators and health professionals

alike have a responsibility to assist in finding intervention programmes that can better aid EF deficiencies in affected populations.

Chapter 10: References

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Chapter 11 : Appendices

Appendix 1: 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

Medical Ethics number: ***M120268***

Appendix 2: Parental Consent Form (Empilweni Group)

UNIVERISTY
OF THE
WITWATERSRAND,
JOHANNESBURG

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

I, Mother/Father/Legal Guardian of

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

I understand that:

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

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

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

Signed: _____ Date: _____

Assigned Participant Number: _____

Appendix 3: 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 memory, judgement, processing and reasoning.

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

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

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

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

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

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

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

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

Thank You and Kind Regards,

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

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

Medical Ethics number: ***M120268***

Appendix 4: Participant Assent Form (Empilweni Group)

UNIVERISTY
OF THE
WITWATERSRAND,
JOHANNESBURG

School of Human and Community Development

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

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

Hello,

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

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

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

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

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

☐ Yes, I am willing

☐ No, I do not want to

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

Thank you very much,

Signed (You can just write your name): _____

Date: _____

Assigned Participant Code: _____

Medical Ethics number: ***M120268***

Appendix 5: Parental Information Sheet (Contrast group)

School of Human and Community Development

Private Bag 3, Wits 2050, Johannesburg, South Africa

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

Dear Parent/Guardian,

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

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

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

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

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

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

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

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

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

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

Thank You and Kind Regards,

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

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

Medical Ethics number: ***M120268***

Appendix 6: Parental Consent Form (Contrast Group)

UNIVERISTY

OF THE

WITWATERSRAND,

JOHANNESBURG

School of Human and Community Development

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

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

Medical Ethics number: ***M120268***

I, Mother/Father/Legal Guardian of

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

I understand that:

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

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

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

Signed: _____ Date: _____

Assigned Participant Number: _____

Appendix 7: Participant Information Sheet (Contrast Group)

School of Human and Community Development

Private Bag 3, Wits 2050, Johannesburg, South Africa

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

Hello!

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

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

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

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

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

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

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

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

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

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

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

Thank You and Kind Regards,

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

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

Medical Ethics number: ***M120268***

Appendix 8: Participant Assent Form (Contrast group)

UNIVERISTY

OF THE

WITWATERSRAND,

JOHANNESBURG

School of Human and Community Development

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

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

Medical Ethics number: ***M120268***

Hello,

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

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

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

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

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

☐ Yes, I am willing

☐ No, I do not want to

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

Thank you very much,

Signed (You can just write your name): _____
Date: _____

Assigned Participant Number: _____

Appendix 9: Biographical Questionnaire

PART A: Participant Screening

To be completed by Case Manager/Doctor

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

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

Date…… Code……..

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

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

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

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

PART B: Biographical Questionnaire

Collateral/Home Information

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

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

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

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

14. Who lives at home with the child?

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

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

Mother	1
Father	2
Grandmother	3
Grandfather	4
Aunt	5
Uncle	6
Sister	7
Brother	8
Mother's boyfriend	9
Father's girlfriend	10
Other	11……

16. Do the parents or guardians work?

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

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

	Is there:	Yes	No
24.	a TV that is working at home?	1	0
25.	a radio that is working at home?	1	0
26.	a hot water tap inside your home?	1	0
27.	a flush toilet?	1	0
28.	a parent/guardian who has their own car?	1	0
29.	a vegetable garden at home?	1	0
30.	electricity in the home?	1	0
31.	gas at home?	1	0
32.	a fridge at home?	1	0
33.	a bed that the child/ward sleeps on by himself/herself?	1	0
34.	a bedroom that the child sleeps in?	1	0
	If not, in what room does he/she sleep in?		
35.	Is he child sleeping alone in the bedroom?	1	0
	If not, who do you share it with?		

Does the child eat:

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

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

		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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