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Zondo, Sizwe

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Neurocognitive Rehabilitation for an Adolescent HIV Population: The Case of Sustained Attention

SIZWE ZONDO

0317404Y

A PhD Thesis Submitted to the Faculty of Humanities,

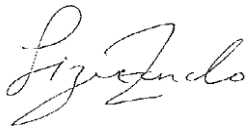
For the Degree of Doctor of Philosophy

University of the Witwatersrand, Johannesburg,

2024

DECLARATION

I declare that this dissertation is my own unaided work. The thesis is being submitted for the degree of Doctor of Philosophy at the University of the Witwatersrand, Johannesburg, and has not been submitted before, for any degree or examination at another University.

Signature: 

Date: 28 October 2024

DEDICATION

This thesis is dedicated to my late grandmother, ‘ugogo’ Regina Tshabalala-Zondo, the matriarch of the Zondo family. Thank you for your selfless love and believing in me. You were the epitome of the Proverb: *“*She opens her arms to the poor and extends her hands to the needy. When it snows, she has no fear for her household; for all of them are clothed in scarlet.” Proverbs 31:20-21.

ACKNOWLEDGEMENTS

- I acknowledge the fountain of my life, Jesus Christ, thank you for being my source of strength and joy.

I would like to express my gratitude to all the people who made this research study possible:

- Prof Susan Malcolm-Smith, for planting the love of neuroscience and statistical analysis within me.
- Professor Obianuju Njoku, for encouraging me to always take risks and reach for my dreams beyond the current manuscript.
- To the children at Red Cross Children's Hospital (RXH), who continue to inspire my research trajectory in pediatrics, and adolescent health.
- To my supervisors, Prof Aline Correia-Ferreira and Prof Kate Cockcroft, for supporting me and allowing me to run with the study idea.
- To Gail Johnson, Kim de Allende, and Bridgette Bond for trusting me with the children in their care.
- To the children who participated in the study, thank you!
- To Sibongile Ngomane, thank you for assisting me with data collection!
- To Dr Armin Heinecke at NIRX, Germany, for always answering my questions on the analysis of functional near-infrared spectrometry data.
- To the National Research Foundation [grant number TTK200408511634]; Rhodes University [grant number PGSD05/2022], University of the Witwatersrand [Research Incentive Funding provided to Profs Ferriera-Correia and Cockcroft], and Harvard University, for funding my research.

ABSTRACT

The Human Immunodeficiency Virus (HIV) continues to be a significant disease burden. In terms of neurocognitive health, HIV crosses the blood-brain barrier, resulting in neuronal dysregulation and compromised neurocognition. Of further import, antiretroviral drugs are indicated to have limited permeability in the central nervous system and do not reverse compromised neurocognition, sequent HIV neuroinvasion. The objectives of the study were to investigate the efficacy of HIV cognitive rehabilitation therapy (HIV-CRT) in adolescent HIV. The first aim was to investigate the evidence for the cognitive rehabilitation of HIV in adolescent and geriatric samples, sequent neuroHIV. This investigation resulted in the publication of a meta-analysis detailing the efficacy of attention remediation in neuroHIV. The second aim was to examine the efficacy of fNIRS neuroimaging in measuring hemodynamic responses in the prefrontal cortex in adolescents neuroHIV. This investigation resulted in the publication of an article detailing the efficacy of fNIRS in detailing changes in oxygenated haemoglobin in adolescents living with neuroHIV. The third aim was to pair fNIRS optical neuroimaging with behavioural data to investigate changes associated with brain training at a cortical and behavioural level. The execution of the above aim resulted in the publication of an article detailing the procedures and methods to achieve the enquiry. The fourth article, under review, details findings related to neural efficiency and attention training. The final manuscript, under preparation, details functional connectivity outcomes related to attention training.

To enable the analysis of the published articles, an initial cohort of 42 adolescents (mean age = 17.28) living with HIV participated in the study. Following attrition, the sample was reduced to 26 participants. Thirteen participants were assigned to the treatment group (n = 13; mean age = 16; SD = 1.2), which received cognitive rehabilitation to remediate attention. Thirteen children acted as controls (mean age = 17; SD = 1.3). Pre- and post-intervention data were analysed using behavioural and optical imaging data.

Findings indicated that HIV-CRT (attention) is associated with decreased oxygenated haemoglobin (HbO) and increased functional connectivity in the Central Executive Network (CEN). Contrary to expectation, HIV-CRT was associated with minimal behavioural gains, as indicated by neuropsychological assessments. Taken together, findings seem to suggest that in adolescent neuroHIV, customised HIV-CRT promotes cortical efficiency. However, brain training does not translate to immediate behavioural improvements at post-assessment. Summarily, findings suggest that cortical plasticity may precede near-and-far cognitive transfer gain in adolescents neuroHIV.

Keywords: Adolescent neuroHIV, HIV-CRT, Brain Plasticity, Attention, fNIRS.

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LIST OF PUBLICATIONS

1. **Zondo, S**. The cognitive remediation of attention in HIV-Associated Neurocognitive Disorders (HAND): A meta-analyis and systematic review [version 1; peer review: 2 approved]. F1000Research, 2023, 12: 1133 (https://doi.org/10.12688/f1000research.132166.1)

2. **Zondo, S**., Cockcroft, K., & Ferreira-Correia, A. (2024). Brain plasticity and adolescent HIV: A randomised controlled trial protocol investigating behavioural and hemodynamic responses in attention cognitive rehabilitation therapy. *MethodsX*, *13*, 102808. (https://methods-x.com/article/S2215-0161(24)00261-9/fulltext)

3. **Zondo, S**., Ferreira-Correia, A., & Cockcroft, K. (2024). A Feasibility Study on the Efficacy of Functional Near-Infrared Spectrometry (fNIRS) to Measure Prefrontal Activation in Paediatric HIV. *Journal of Sensors*, *2024*, 4970794. (https://onlinelibrary.wiley.com/doi/10.1155/2024/4970794)

Manuscript Under Review

4. **Zondo, S**, Cockcroft, K, da Silva Ferreira Barreto & Ferreira-Correia, A. Shining Light into Adolescent HIV Neuroplasticity: A Behavioural and Neuroimaging Study of the Prefrontal Cortex Using Functional Near Infrared Spectrometry (fNIRS) (*Neuroimage*).

Manuscript Under Preparation

5. **Zondo, S**. (2024). Cortical Neuroplasticity and Seed Based Functional Connectivity in Adolescent neuroHIV: An fNIRS Investigation. Target Journal, *Behavioural Brain Research*.

CHAPTER 1
INTRODUCTION

1.1 Background

Optimal health and neurocognitive function are integral to human well-being. Consequently, exploring physical and biological states that disturb optimal function is imperative. Viruses, specifically viral infections of the central nervous system, have been extensively studied due to their adverse effect on health. Significantly, the Human Immunodeficiency Virus (HIV), a virus that causes Acquired Immunodeficiency Syndrome (AIDS), has been indicated as a significant cause of behavioural, neurocognitive, immune, and motor dysfunction in human populations. Exploring the pathogenic effects of HIV on neurocognitive function is crucial, not only for optimal health outcomes but also for the development of effective interventions and therapies to mitigate impairments due to the virus.

Global estimates from UNAIDS (2023) indicate approximately 39 million people living with the virus, with Sub-Saharan Africa accounting for 20.8 million of these estimates. South Africa bears the highest disease burden of HIV, with approximately 14% of the population, equivalent to approximately 7.9 million people living with the virus (UNAIDS, 2023). Concerning children (0-9 years old) and adolescents (10-19 years old), the population interest of the thesis, (UNICEF, 2023), estimates 1.8 million children and adolescents living with HIV in Sub-Saharan Africa by the end of 2022 (UNICEF).

Virologically, two types of HIV have since been isolated, namely HIV-1 and HIV-2 (Zayyad & Spudich, 2015). HIV-1 type is found in most regions and has more pathogenic consequences. HIV-2, which is rare and considered benign, is predominantly restricted to West Africa and Southeast Asia (United Nations Joint Programme on HIV/AIDS (UNAIDS), 2019). This dissertation concentrates on the HIV-1 type. HIV belongs to the Retroviridae family and is part of the genus Lentivirus, first isolated in 1983 (van Heuvel et al. 2022). Based on viral

classification, HIV is a positive sense, ribonucleic acid (RNA) virus, which is enveloped (Poltronieri et al., 2015). Akin to other Retroviridae, the virus replicates in a host cell via reverse transcription. Unlike typical replication, where DNA is converted into RNA, HIV converts its RNA genome into DNA, causing a long duration in the CNS leading to long incubation periods in the infected host. Once HIV enters the host, it targets cells in the immune system, causing AIDS.

Biochemically, HIV targets cluster of differentiation (CD) cells, namely CD4+ lymphocytes and CD8 (cytokine) white blood cells, crucial for immune function (Poltronieri et al., 2015). After its integration in the host genome, HIV undergoes a series of biochemical processes, including transcription and translation of viral proteins, assembly of new virus particles, and the release of mature viral particles of proviral DNA. Overtime, proviral DNA may remain latent or become actively transcribed, further depleting CD4 cells, resulting in HIV/AIDS (Ellero et al., 2017). Summarily, in terms of cognition and HIV, the cognitive effected are differentiated as, HIV-associated neurocognitive disorders (HAND), which encompass a range of neurocognitive impairments linked to HIV infection, spanning from mild to severe manifestations of HAND. The most severe form of HAND is known as HIV-associated dementia (HAD), which is characterized by disabling cognitive deficits. On the other hand, 'HIV encephalopathy' is used to describe the brain damage resulting from HIV, which may overlap with the clinical presentation of HAD (Brew, 2018; Elbirt et al., 2018).

1.2 Statement of the Problem

The Trojan Horse Hypothesis postulates that during its incubation in the central nervous system (CNS), HIV crosses the blood-brain barrier (BBB) and enters the cerebral cortex (Das et al., 2016). Physiologically, the BBB is composed of capillary endothelial cells. A basement membrane encased with astrocytes enables passive diffusion of substrates, such as oxygen,

glucose, and amino acids, to diffuse the barrier and offer physiological protection against harmful substances, such as microbes, toxins, bacteria, and viruses (Abbott et al., 2006; Gonzalez et al. 2020). Through a mechanism not entirely understood, HIV permeates the BBB by differentiating monocytes into macrophages (Wilmshurst et al., 2018). Macrophages thus act as a cellular reservoir for HIV infection within the cortex, leading to neuroinflammation and neuronal perturbations (Churchill et al. 2016; Ellero et al., 2017).

Significantly, HIV-induced neuroinflammation is thought to dysregulate neuronal transmission; mainly, catecholamines where it leads to the deletion and overexpression of dopamine and tryptophan precursor metabolites, namely L-DOPA (L-3,4-dihydroxyphenylalanine)**,** and 5-Hydroxytryptophan (5-HTP), integral for attention and working memory function (Elbirt et al., 2015; Nolan & Gaskill, 2019). Biochemically, 'catecholamines' are monoamine, organic compounds that contain a catechol ring that is linked to an amino side chain are derived from the amino acid, tyrosine (Nolan & Gaskill, 2019). Primarily, catecholamines are thought to be responsible for executive function and attention (Logue & Gould, 2014), and their impairment can result in the dysregulation of immune responses (e.g., cytokines, monocytes) in the CNS, affecting cognitive processes, such as executive functions and sustained attention (Nolan & Gaskill, 2019). In relation to HIV, the virus not only affects catecholamines, but leads to HIV-induced neuroinflammation, which is further associated with white matter loss (Jensen et al., 2019), neuronal apoptosis (Smail & Brew 2018), and frontostriatal dysregulation (Du Plessis et al., 2019).

Noteworthy, combination antiretroviral drugs (cARTs), introduced to foster optimal cognitive and health outcomes in neuroHIV, have been found to manifest significant limitations (Lanman et al., 2019; Yuan & Kaul, 2019). Firstly, ARVs have been found to cause

neurotoxicity[1] in the CNS, further exacerbating HIV-induced neuroinflammation in the CNS (Gonzalez et al., 2020). Secondary to the above, ARVs have been noted to have limited permeability in the CNS to induce cortical integrity (Letendre et al., 2008; Yuan & Kaul, 2019). To this effect, ARVs, such as efavirenz[2], have been associated with mitochondrial toxicity and limited cognitive improvement sequent neuroHIV (Lanman et al., 2019).

Most significantly, for the present study, due to limitations associated with ARVs and neuronal dysregulation sequent neuroHIV, the virus is associated with compromised neurocognition in children (Wilmshurst et al., 2018) and adults (Cody & Vance, 2016). Specific to children and adolescents, the focus of the present study, HIV is associated with neurodevelopmental delay (Debeaudrap et al., 2018), delays in scholastic development (Abubakar, 2014; Anabwani et al., 2016), poorer academic outcomes (Pufall et al., 2014), and compromised higher-order functions in domains such as attention (Boivin et al., 2017; Rice et al., 2014; Walker et al., 2013b; Watkins et al., 2000), working memory (Cockcroft & Cassimjee 2020) and executive functions (Nichols et al., 2015; Walker & Brown, 2018), expressive language (Brahmbhatt et al. 2017; Chaudhury et al. 2017), and motor coordination (Jantarabenjakul et al., 2019).

1.3 Motivation for the Study

Provided the limitations of cARTs and cognitive decline sequent neuroHIV, clinicians have since enquired: *Is it possible to eradicate HIV from the brain?* (Brew et al., 2013. p. 403). The converging literature seems to suggest that it is not possible to eradicate HIV once in the cerebral cortex (Gonzalez et al. 2020; Green et al. 2019). Given this reckoning, clinicians have called for the optimization of non-cART interventions to supplement ARTs post-neuroHIV. To this end, based on brain plasticity principles, premised on the malleability of the cerebral

[1] Neurotoxicity deficits have been found to be cell-specific (astrocytes and nerve cells) (Gonzalez et al. 2020).
[2] A protease inhibitor.

cortex, researchers have voiced an urgent ‘call to action’ (Weber et al. 2013.p. 17) for the development of empirical studies to investigate the cognitive rehabilitation of HIV associated cognitive decline (HAND).

In response to this ‘call to action’, cognitive neuroscience researchers have begun to study the effect of brain neuroplasticity protocols in adolescent neuroHIV in cognitive domains such as attention (Basterfield & Zondo, 2022), working memory (Fraser & Cockcroft 2020), executive functions (Boivin et al., 2010; Boivin et al., 2019), and processing speed (Giordani et al. 2015). Notwithstanding this progress, there continues to be a dearth of studies pairing behavioural changes emanating from the brain training protocols with objective biomarker data, such as those gleaned from neuroimaging techniques, such as functional magnetic resonance imaging (fMRI) or functional near-infrared spectrometry (fNIRS); to study HIV brain training interventions, in paediatric and adolescent HIV (Benki-Nugent & Boivin, 2019; Musielak & Fine, 2016). Given this dearth, Chapter 4 expands on the application of fNIRS to study brain plasticity in neuroHIV.

In addition to the absence of neuroimaging correlates to complement behavioural changes sequent HIV cognitive training, there is a dearth of cognitive theoretical models used to investigate HIV brain plasticity protocols. The present study adopted a ‘top-down’ ‘bottom-up’ theoretical model (Sarter et al., 2001a) to study attention remediation in paediatric neuroHIV, an approach lacking in the literature.

Further motivation for the study stems from a quest for social justice in mental health. Due to South Africa’s adverse colonial history and planned segregation policies, critical services, such as mental health services, tend to be disproportionally apportioned to urban regions of the country (Lund et al., 2012; Sukeri et al., 2014; Vergunst, 2018). For this reason, there is a disproportional scarcity of mental health professionals providing psychological

services to children living with HIV/AIDS in the country's poor regions, including informal settlements, rural and 'township[3]' areas (RuDASA, 2015; Sukeri et al., 2014; Vergunst, 2018). To this effect, the dearth of mental health services in rural and 'township' South Africa has been described as 'dehumanising' (RuDASA, 2015) and a human rights issue that needs urgent attention (Burns 2011).

1.4 Statement of Originality

Given the 'call to action' for empirical studies investigating brain plasticity in adolescent HIV, the present study introduced optical neuroimaging technique (fNIRS) to investigate brain plasticity outcomes sequent brain training. Implementing optical neuroimaging methods in the form of fNIRS neuroimaging is a novel contribution to the field. Notably, the fNIRS technique employed in the study was grounded on theoretical models of 'attention' (top-down vs bottom-up). The extant literature investigating the symbiotic nature of neuroHIV, HAND, and neurorestoration has not employed cognitive neuroscience models (top-down vs bottom-up models of attention) to investigate modality-specific cognition and brain plasticity in neuroHIV. Most modality-based investigations (e.g., sustained attention, executive functions) have been restricted to animal models such as HIV-1 transgenic mice (e.g., Moran et al., 2019).

Studies may not have investigated modality-based functioning in neuroHIV because the hypothesis is that the cortex, within its broader constitution, is wholly affected by the HI-virus. There is, however, merit in investigating cognition-based and/or cortical-specific neurocognition as it pertains to HIV neurocognition (Moran et al., 2019; Weber et al., 2013), as it allows for an in-depth neuroscience approach to the analysis of HIV neurocognition. The current study thus deviates from a general purview of neurocognition as it pertains to neuroHIV and focuses on the nature of attention as it pertains to the Central Executive Network (CEN).

[3] In South Africa, the term 'township' refers to dwelling places that were historically designated for non-white South Africans, during the apartheid era (RuDASA, 2015).

As such, the study grounds the investigation of attention on the theoretical understanding that an anticorrelation mediates attention, namely an anticorrelation between the Central Executive Network (CEN) and the Default Mode Network (DMN), as detailed in Chapter 2.

Collectively, the originality of the study arises from answering a novel empirical question on the efficacy of brain plasticity processes, in pediatric and adolescent neuroHIV, using a novel theoretical approach (top-down, bottom-up, CEN), grounded on a novel design, that pairs optical imaging (fNIRS), and behavioural outcomes, to investigate brain plasticity in an underrepresented research population.

1.5 Research Aims

The general aims of the study were (a) to conduct a meta-analysis investigating the effect of attention training in neuroHIV, based on behavioural outcomes, pre and post attention remediation. Secondly, the study undertook a longitudinal investigation, examining the effect of attention training within a cohort of children and adolescents living with HIV in South Africa. The study used a customised brain training program (ACTIVATE^{TM}) (Wexler et al., 2021) to remediate attention skills. To address a major imitation cited within the neuroHIV literature, the study sought to corroborate behavioural outcomes emanating from attention training with objective imaging techniques, namely, fNIRS optical imaging to investigate brain plasticity in neuroHIV.

1.6 Objectives of Study

The objectives of the study were as follows:

1. To conduct a meta-analysis investigating evidence for the efficacy of attention-focused brain training (ACTIVATE^{TM}) to remediate attention deficits in neuroHIV.

2. To evaluate the efficacy of functional near-infrared spectrometry (fNIRS) to measure hemodynamic responses in the prefrontal cortex, a key node within the central executive network (CEN), in adolescent neuroHIV.
3. To determine whether attention training (ACTIVATE^{TM}) induces near and far cognitive transfer (if any) on neuropsychological measures, pre-and post-brain training.
4. To investigate whether cognitive gains emanating from brain training (if any) can be corroborated with changes in hemodynamic responses as measured by fNIRS neuroimaging.
5. To evaluate whether attention brain training is associated with neural efficiency and increased functional connectivity in the CEN.

1.7 Overarching Conceptual Framework

The principal theoretical framework anchoring the research is premised on mammalian neuroplasticity. Neuroplasticity postulates the malleability of the cortex, precisely its intrinsic capacity to undergo structural and functional change. Neuroplasticity theory posits that the human cortex (by extension, the mammalian cortex) has an inherent capacity to adapt and change throughout life. Neuronal changes at a molecular and dendritic level enable the cortex to form new neural connections, reorganize existing ones, and modify its structure and function with repeated exposure to novel and demanding cognitive tasks, especially within an enriched stimulating environment (Anderson et al., 2011; Hebb, 1949).

Linked to the above, Bach-y-Rita (1990) notes that brain plasticity is facilitated by physiological mechanisms that "unmask relatively inactive pathways" (p. 547) and wire active pathways, leading to increased functional connectivity, neuronal sprouting and increased synaptic scaling of distant, and proximal cortical networks. Merzenich (2013) highlights that a range of factors propel or inhibit plasticity, including, but not limited to, psychosocial

depravity, motivation and personality factors traits. Chapter Three further expands on the principles of neuroplasticity.

With specific reference to HIV and neuroplasticity, Green et al. (2019) note that plasticity at a neuronal level is facilitated by homeostatic scaling – a process under which neurons establish network connections – which can either be mediated by negative plasticity (HIV neurotoxicity and neural death) or positive plasticity (synaptic scaling). Succinctly, Green et al. (2019) argue that in neuroHIV, neuronal networks can be strengthened to become less susceptible to neuroHIV, subsequently preserving the neuronal and functional integrity of the cortex in the context of neuroHIV, the aim of the current investigation. Consequently, this study was guided by the following research questions:

1.8 Research Questions

The following broad research questions guided the study:

1. Does meta-analytic data provide evidence for improved behavioural outcomes on attention measures sequent HIV brain training?

2. Do HIV+ participants in the experimental group (ACTIVATE^{TM}) indicate improved behavioural scores post-intervention compared to controls?

3. If experimental participants receiving the active ingredient (ACTIVATE^{TM}) indicate improvements in behavioural measures sequent attention training, are these corroborated by fNIRS neuroimaging?

4. Do HIV+ participants in the experimental group (ACTIVATE^{TM}) indicate improved neural efficiency in the CEN in response to receiving the attention training?

5. Do HIV+ participants in the experimental group (ACTIVATE^{TM}) indicate improved functional connectivity in the CEN in response to receiving brain training?

1.9 Overview of Research Methods

1.9.1 Research Design

Since all published articles in this thesis contain comprehensive methodological sections, this section briefly includes other pertinent details that may have been omitted from the articles due to space limitations. The first research article (Chapter 4) was a meta-analysis of pre - and post-attention measures (Edmonds & Kennedy, 2013) which was analysed using standardized mean differences (SMD). It is worth detailing that as expedient as SMD meta-analysis approaches are, they have significant limitations. Firstly, SMDs compare the effect sizes of studies that measure the same outcome (i.e., attention) but use different scales or measurement units. As such, SMDs are challenging to interpret intuitively because they depend on estimates of variability. Differences among studies, such as participant characteristics, can affect SMD estimates, rendering them susceptible to bias due to SMDs, combining studies that use distant assessments to measure the same cognitive construct (i.e., attention).

Subsequent articles (Chapters 7 and 8) took the form of a longitudinal pre-and-post-quasi-experimental design (Edmonds & Kennedy, 2013), incorporating an experimental and passive control group. Due to the nature of longitudinal studies, the study experienced various internal validity threats. For example, the study experienced high attrition rates in the latter parts, which necessitated switching from a passive control group to a treatment-as-usual (TAU) group, thus taking an approach least favoured in brain plasticity research (Simons et al., 2016). A similar threat to internal validity is that the longitudinal study took the form of a ‘multi-site’ investigation, spanning three child centres, requiring standardization across sites in the form of screening, recruitment, matching, and group allocation. Given that multi-site investigation requires greater study quality control across sites (Hart & Bagiella, 2012) and greater resources,

there was, unfortunately, not always homogeneity in consistently implementing standardisation around participant screening and group allocation.

Notwithstanding these limitations, other threats to internal validity, such as instrumentation and maturation, were minimal. Significantly, participants who completed the measures during the pre-test phase, also completed post-assessment, following the rehabilitation. Moreover, age was not found to have a significant maturation effect when completing neuropsychological assessments at pre and post-testing.

With reference to materials, the study employed various materials detailed in the published studied. Summarily, behavioural measures used in the study included the Stroop Colour Word Test (SCWT), the NEPSY-II and BRIEF. Reliability and validity measures of the SCWT in relation to fNIRS are detailed in the published studies. Briefly, the psychometric properties of the NEPSY-II, are well attested, and include reliability and validity Moreover, due to its psychometric properties, the NEPSY has been indicated for wide clinical and research usage in low-and middle-income countries, amongst adolescent population in South Africa (e.g., Fraser & Cockcroft, 2020; Rochat et al., 2017). Summarily, the *Behaviour Rating Inventory of Executive Function* (BRIEF; 6 to 18 years) an 86 item questionnaire evaluated behavioural and executive functions in participants (Gioia et al., 2000). The BRIEF is indicated to have high construct validity (Gioia et al., 2000), and is divided into two broad categories: (a) behaviour regulation, and (b) metacognition indexes. The combined global executive composite (GEC) score indicates day-to-day behavioural problems related to executive functions. Higher scores on the GEC indicate behavioural and executive challenges. Neuroimaging measures were obtained in the form of functional near infrared spectrometry.

1.9.2 **Selection of HIV Home Shelters**

All research participants (HIV+ experimental group and HIV+ controls) were recruited from three HIV shelters[4] (centres) that were selected using convenience sampling. The selection bias was consequent to the candidate having professional links with the HIV care centres. There were no obvious exclusion criteria applied to the study in terms of HIV sites, as the researcher did not have access to other HIV care homes at the time of the study.

1.9.3 **Research Participants**

Data regarding research participants is detailed in the published studies. Significantly, power analysis for the study was estimated using (Fraser & Cockcroft, 2020; n=63), who obtained an effect size (ES) of $d = 0.649$, with an alpha = 0.05 and power = 0.80. From these estimation, it was projected that to reach a similar effect, my study would need a sample size of n = 42 (Experimental = 26; Control = 26) (GPower 3.1: Faul et al., 2007). Following study attrition in 2022 (n = 9) and 2023 (n = 7), the final sample size for data analysis was n = 26. Notably, although the sample size appears small, it is similar to experimental studies published in the neuroHIV and brain training field (e.g., Cody et al., 2015; Fazeli et al., 2019; Hossain et al., 2017). All participants were either isiXhosa, or isiZulu primary speakers, with a proficient grasp of English as a second language. Given this demographic, all participants were able to complete most of the study tasks, such as the Stroop Colour Word Test (SCWT), as detailed in the published papers.

1.10 Outline of Dissertation

Chapter One (this chapter) details the background of the research study, including the research aims, methods, and key research questions that guided the study.

[4] These care shelters care for orphans, and children living with HIV/AIDS, and other developmental challenges.

Chapter Two briefly details the cognitive neuroscience of attention, specifically sustained attention. The chapter further details the neural correlates of sustained attention, including the 'top-down' and 'bottom-up' attentional systems. The chapter concludes by describing the effect of HIV on attentional control.

Chapter Three briefly expands on the brain plasticity theory and details early studies investigating brain training in attention. The chapter concludes by detailing evidence for the neurorehabilitation of attention in paediatric HIV.

Chapter Four details findings from a meta-analysis investigating the relationship between HIV brain training and behavioural outcomes on attention assessments, pre- and post-training.

Chapter Five details the Methods undertaken to investigate the relationship between functional near-infrared spectrometry (fNIRS) and behavioural measures. The Chapter is placed after the Meta-analysis chapter to allow for a seamless transition of subsequent Chapters detailing the study methods.

Chapter Six describes the feasibility of employing fNIRS techniques to investigate hemodynamic changes in adolescent neuroHIV.

Chapter Seven details the effect of attention training (ACTIVATE^{TM}) as determined by behavioural data from the Stroop Colour Word Test (SCWT) and hemodynamic responses as assessed by fNIRS. Hemodynamic responses, focus on neural efficiency changes within the CEN.

Chapter Eight details the effect of attention training (ACTIVATE^{TM}) as determined by behavioural findings (NEPSY-II and SCWT) and hemodynamic responses based on seed-based functional connectivity investigations.

Chapter Nine summarises the study findings and provides recommendations for future research.

1.11 Roles and Responsibilities

The candidate conceptualized the study based on his clinical and research work in adolescent neuroHIV. Upon conceptualization, the research supervisors provided logistical support for the registration of the PhD study. The candidate wrote and completed all ethical considerations of the projects, which were reviewed at the Departmental and Faculty levels. The candidate sourced funding for the study from the South African National Research Foundation (NRF Thuthuka Track), Rhodes University, the Harvard University South Africa Fellowship Program, and the University of the Witwatersrand. All secured funds were used to purchase research equipment (fNIRS) and to reimburse research assistants during the data collection phase between November 2022 and August 2023. Funds from the University of the Witwatersrand assisted with the purchase of licenses used during the intervention.

The candidate was the primary author for all publications enlisted in the thesis. Upon feedback, he executed all primary aspects for manuscript publication, including conceptualization, data analysis, and writing of the initial and subsequent drafts. The candidate was also responsible for submitting manuscripts for journal consideration and acting as the correspondent for published manuscripts.

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CHAPTER 2

The Cognitive Neuroscience of Attention and its Relation to neuroHIV

2.1 Attention

Attention is defined as the cognitive process of selectively focusing on specific aspects of the environment while disregarding others (Treisman & Gelade, 1980). Within cognitive neurosciences, attention is postulated to be the primary modality for cognition, with other cognitive processes, such as executive functions, speed processing, cognitive control, and working memory, underpinned by attentional processes (Hopfinger & Slotnick, 2020; Malia et al., 2004; Posner et al., 1990). To this end, William James, a pioneer in cognitive neuroscience, defined attention as "the taking possession by the mind, in clear and vivid form, of one out of what seem several simultaneous objects or trains of thought. Focalization, concentration, of consciousness are of its essence" (James, 1890, p.971).

Concerning attention and consciousness, James emphasizes that countless stimuli are present in the sensory environment. Still, not all stimuli enter conscious awareness unless an individual wilfully chooses to attend to specific stimuli (James, 1890). The selective process of attending to stimuli in the context of an overwhelming influx of sensory input underscores the importance of attention. While James provided insights into attention processing, advances in cortical network systems and subsequent theoretical models have refined the cognitive neuroscience of attention.

Regulation of Attention: Network Systems and Catecholamines

Complex systems involving multiple anatomical structures have been suggested to undergird attention. By and large, the primary systems of attention divide attention into neural networks centred around the alerting network, the sensory orienting network, and the executive attention network (Borders, 2020; Parasuraman & Davies, 1984; Petersen & Posner, 2012; Raz, 2004;

Sarter et al., Bruno 2001b). According to Posner and Petersen's (1990) model of attention, the (a) alerting network[5] is responsible for maintaining a state of alertness. Moreover, this network arises from the reticular activating system in the brainstem and prepares the parietal lobe and the right prefrontal areas to detect target stimuli while neglecting other stimuli (Fan et al., 2009; Kolb & Whishaw, 2015; Sarter et al., Bruno 2001a).

Secondly, (b) the visual orienting network controls the selection of information from sensory input and is mediated by the superior parietal lobe and temporal-parietal junction. Lastly, the (c) executive attention network is responsible for resolving conflicts among varied responses and other stimuli affecting attention. Moreover, this network is activated when there is a conflict of stimuli, where dominant responses (primary responses) must be chosen over subdominant responses (i.e., less important responses in divided attention tasks). The executive attention network is mediated by cortical regions in the medial frontal and lateral prefrontal cortex (Fan et al., 2009; Parasuraman & Davies, 1984; Martin et al., 2001b).

2.2 Top-Down and Bottom-Up Systems in Regulating Attention

As noted above, attention is not a single concept but encompasses various aspects that interact to shape human perception and processing of information. To arrive at a comprehensive understanding of attention, it has been suggested that researchers develop models that coalesce disparate features of attention into unified frameworks. 'The Feature-Integration Theory of Attention' espoused by Treisman and Gelade (1980) offers valuable insights into how attention operates and influences cognition. According to the theory, attention operates through selective processing and integrating *features* within a stimulus. Features may encompass colour, shape, location, and other visual or auditory attributes. In accordance with this theory, attention acts akin to a spotlight that accentuates specific features while actively uniting these features to

[5] This attention network is sometimes referred to as the *vigilance network* in the cognitive neuroscience literature (e.g., Sarter et al., 2001b).

construct a cohesive perception of one's surroundings. This theoretical framework further suggests a dual stage in attention processing, namely, the *preattentive* stage and the *focused*-attention stage. Cognitive science scholars have since expanded on this theoretical contribution to arrive at a dual process of attention involving 'top-down' and 'bottom-up' attentional processing (Katsuki & Constantinidis, 2013).

The 'top-down' model of attention requires a wilful and effortful cognitive process to enable attention. This active and effortful process relies on encoded information stored in memory and must be manipulated with working memory to enable sustained and divided attention (Katsuki & Constantinidis, 2013). On the other hand, 'bottom-up' attention processes are thought to rely on salient, automatic features that "pop out" into consciousness, such as identifying a chair by its shape and orientation. Converging evidence suggests that effortful cognitive processes that govern 'top-down attention' are dependent on the activation of the Central Executive Network (CEN) and deactivation of the Default Mode Network (DMN) (Clark & Noudoost, 2014; Sarter et al., 2001; Treisman & Gelade, 1980).

2.3 The CEN and DMN in Attention

The research primarily investigated the cognitive rehabilitation of sustained attention in adolescent neuroHIV. To this end, attention is divided into (a) sustained, (b) divided, and (c) selective attention (Chaudhari et al., 2021). According to Posner and Peterson's model (1990), the alerting network mediates sustained attention and alertness and is critical in detecting relevant stimuli to focus upon. Sustained attention is described as the ability to maintain alertness to a task or stimulus (auditory or visual sensation) over a prolonged period. Theoretical advances in neuroimaging research indicate that in addition to the alerting network, attention, particularly sustained attention, is mediated by a network anticorrelation, which enables the activation of the CEN and deactivation of the DMN. To this extent, the converging

data suggests that ‘top-down’ attention processing maintained by a dual neuronal network (↑ CEN, ↓ DMN) (Esterman & Rothlein, 2019; Rosenberg et al., 2016; Martin Sarter et al., 2001a), maintains peak attentional processing, either by training or regulation of this dual system.

For optimal ‘top-down’ attention processing, the CEN is thought to recruit cortical regions responsible for cognitive control, enabling task-relevant responses, whilst the DMN activates and suppresses task-irrelevant thoughts (i.e., mind wandering) (Sarter et al., 2001). Summarily, the CEN is thought to be regulated by cortical nodes located in the dorsolateral prefrontal cortices (DLPFCs) (bilaterally) and the parietal cortices (bilaterally) (Denkova et al., 2019; Gratton et al., 2018; Sridharan et al., 2008). At a neurochemical level, the CEN is maintained by catecholamines, namely, dopamine and norepinephrine, which regulate attentional control and maintain cognitive engagement on cognitive tasks (Arnsten, 2011; Panichello & Buschman, 2021). Relevant to my research, cognitive systems governing attention, namely the vigilance and alerting network associated with the CEN, are aberrant in neuroHIV.

2.4 Attention Systems and neuroHIV

A growing body of research implicates Posner and Petersen's (1990) attention network in neuroHIV. For example, compared to controls (HIV-), Wang et al. (2017) indicate that synaptodendritic damage due to neuroHIV affects the alerting network, whose primary function is to inhibit unnecessary stimuli and sustain attention. Similarly, magnetoencephalography (MEG) research indicates that the orienting network, which links orienting senses to attention and is a conduit to the alerting systems, is affected in neuroHIV (Arif et al., 2020). Significantly, Arif et al. (2020) noted that aberrant orienting circuity due to neuroHIV compromised the interpretation of sensory inputs in the temporoparietal regions,

which may have upstream effects on the alerting network. In the subsequent paragraphs, I briefly expand on the impact of neuroHIV on attention in paediatric and adolescent populations, which is not detailed in the published articles due to space limitations.

2.5 Attention and Adolescent neuroHIV

There is a growing body of evidence detailing the effects of neuroHIV in pediatric and adolescent populations. In one of these studies, not cited in the published journals, 93 HIV+ children and 106 HIV-negative controls engaged in 'The Test Variables of Attention'. Data obtained from the study indicated that HIV+ children performed significantly worse in tasks that required high levels of attention, such as visual reaction time tasks, compared to controls (Ruel et al., 2012). These research findings are further supported by similar studies, such as Sorenson et al. (1992), who sampled 27 HIV-seropositive and 13 HIV-controls and found deficits in selective and divided attention in HIV-seropositive participants when compared to controls. Similarly, Watkins and colleagues (2000) examined the effects of HIV/AIDS on attention between (a) HIV seronegative controls, (b) HIV seropositive participants (CD 4 counts = > 200), and (c) immune comprised HIV seropositive participants (CD 4 count less than 200). Findings indicated that seropositive children performed significantly poorly on the ‘Continuous Performance Test’ (CPT), a measure of sustained attention, and on the ‘Span of Apprehension’ (Span), a measure of general attention skills (Watkins et al., 2000). These findings and others cited in the thesis (e.g., Ipser et al., 2015; Rice et al., 2014; Posada et al., 2012) indicating compromised neurocognition, particularly in attention, provided the primary ethos for the investigation of brain plasticity, to remediate attention deficits in adolescent neuro-HIV.

2.6 Conclusion

Attention is a critical component of neurocognition and is mediated by a complicated neuronal system that involves the alerting network system and the CEN. Subsequent to crossing the BBB, neuroHIV leads to adverse consequences in attentional circuitry, where it is noted to affect critical nodes in the CEN, especially in the frontostriatal and dorsolateral prefrontal cortex (Ipser et al., 2015). To date, no studies have investigated 'top-down' attention processes in the context of HIV and how brain plasticity mechanisms may ameliorate compromised attention in adolescent HIV, sequent HIV neuroinvasion. The next chapter details the evidence for brain plasticity, broadly in the domain of attention remediation, and links this data to the neurorehabilitation of attention in neuroHIV.

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CHAPTER 3
Cortical Plasticity and Attention

3.1 Cortical Neuroplasticity

From an early period in medical history (~1890s), the nervous system has consistently been recognised as the 'apparatus of biological plasticity' (Lamb, 2019, p.1359). Concerning cortical injury, William James and others (e.g., Hebb, 1949; Luria, 1970) noted that the cerebral cortex in human species is imbued with an inherent capacity to undergo structural and functional change over a lifetime, resulting in positive morphological change in response to learning, experience, and cortical training in enriched environments. To this end, regarding neural plasticity, James, in the 'Principles of Psychology' (1890), noted:

> 'Plasticity, then, in the wide sense of the word, means the possession of a structure weak enough to yield to an influence, but strong enough not to yield all at once. … Organic matter, especially nervous tissue, seems endowed with a very extraordinary degree of plasticity of this sort…' (James 1890).

3.2 Brain Plasticity and Attention Processes

The principles of neural plasticity and their relevance to attention processes have been widely studied in neurosciences. A review of the literature seems to indicate that investigations around attention plasticity have been primarily centered around (a) attention plasticity and genetics, (b) attention plasticity and personality traits, and (c) the effect of brain stimulation to enhance attentional processing (Nobre & Kastner, 2014). The thesis briefly provides examples of often-cited studies detailing the role of neuroplasticity based on the above variables (a, b, c).

3.2.1 **Genetics and Attentional Plasticity**

Voelker et al. (2017) explored the effect of genetics on attention training by examining diverse alleles of the MTHFR (methylenetetrahydrofolate reductase), DBH (dopamine beta-hydroxylase), and COMT (catechol O methyltransferase) gene, in relation to attention training, and learning. The sample of interest were children (n=70) between the ages of 7 and 8 years of age in the United States of America (USA). Attention training was provided based on multiple training sessions using the Attention Network Test (ANT). Findings indicated a significant interaction between MTHFR and COMT on reaction time outcomes. Specifically, children with the CC genotype for MTHFR and the AA genotype for COMT showed improved differentiated reaction time and prolonged attention to the ANT. Interestingly, concerning age, 7-year-old, and not 8-year-old, homozygous for the C allele of MTHFR showed significantly more improvement in overall reaction time and conflict resolution tasks with regular practice on ANT.

Based on the above findings, the authors state that independent of culture and environmental factors, genetic alleles may determine behavioural performance (i.e., reaction time and conflict resolution outcomes) when paired with attention training protocols. The study further suggested that epigenetic factors may influence synaptic plasticity resulting from attention training, which invariably influences cortical network connectivity due to genetics (Voelker et al., 2017). The influence of genetics on attention training, independent of cultural experience, has been reported elsewhere (e.g., Posner et al., 2006; Rueda et al., 2005).

3.2.2 **Personality Traits and Attentional Plasticity**

In a slight departure from epigenetics, Della Libera et al. (2017) investigated the link between attention, reward-based plasticity cortical maps, and personality traits. The study included 48 university students (Males = 24; females = 24; mean age = 21.9 years; SD = 2.3 years). The

authors hypothesised that reward-based plasticity maps will reflect brain regions traditionally associated with cognitive processes involved in attentional selection. Reward-based plasticity was defined as rewards anchored on the ability to modulate neural mechanisms underlying attention and decision-making. Reward-based plasticity was measured using a visual search protocol involving presenting participants, with a circular array of eight white squares measuring 1.54° × 1.54° each. Eight geometric shapes would appear inside the white squares at various intervals of five hundred milliseconds, making one stimulus, the target stimuli, and the other seven distractors. The primary task for participants was to detect the target and respond quickly and accurately to its identification. To enhance reward values, each of the eight locations was arrayed, with specific probabilities of receiving high or low rewards.

Findings indicated that reward-based learning led to selective enhancement of cortical regions associated with spatial prioritisation for attention. Specifically, greater reward was associated with more efficient attention allocation and cortical maps related to attention. Concerning personality, the authors found that reward-based allocation was best predicted by personality types who were reward-sensitive, internally driven, and fun-seeking by nature (Della Libera et al., 2017).

According to the authors, the findings imply that personality may predict attentional learning and attention training. The authors further posit that individual differences may play a role in how individuals allocate attention and that future attention training protocols may benefit from personalized cognitive training approaches, especially with clinical subjects in conditions such as ADHD, where research indicates that neural networks in these populations may be characterized by altered reward processing which may affect attentional control (Della Libera et al., 2017).

3.2.3 **Cortical Stimulation and Attentional Plasticity**

Lastly, researchers have investigated the effect of transcranial alternating current stimulation (tACS) on enhancing attentional regulation. Hopfinger et al. (2017) conducted a within-subjects study (n=23, Mean Age, 23 years), inclusive of three tACS conditions (alpha tACS[6], gamma tACS[7], and sham tAC[8]), to modulate neural activity and improve attentional reorienting. Arrays were placed in the inferior parietal cortex, a region implicated in top-down and bottom-up attention control.

Findings indicated that alpha range stimulation enhanced 'endogenous' attention, while gamma stimulation enhanced 'exogenous' attention. The authors defined endogenous attention as voluntary attention directed by internal goals to attend to relevant information while ignoring irrelevant information selectively. Exogenous attention, on the other hand, was defined as involuntary attention that is triggered by external stimuli. These types of attention processes are akin to 'top-down' and 'bottom up', attention, as described in *Chapter 2.2*. Concerning neuroHIV, transcranial stimulation has been successfully applied to enhance attention in geriatric patients, with arrays placed in the dorsolateral prefrontal cortex, a cortical region implicated in the CEN and 'top-down' attention (e.g., Fazeli et al., 2019; Ownby & Acevedo, 2016; Pope et al., 2018).

3.3 Brain Plasticity and Adolescent neuroHIV

Given the above evidence, linking attention to cortical plasticity, Ismail et al. (2017) posit that the adolescent cortex presents a quintessential 'window of opportunity' due to its malleability and cellular adaptation. To this end, due to its heightened adaptivity to experience-dependent learning, clinicians have applied neuroplasticity principles to adolescent neuroHIV. Primarily,

[6] (10 Hz).
[7] (40 Hz).
[8] (25 Hz).

due to limitations of antiretroviral drugs (ARTs), particularly their limited permeability in the cerebral cortex (Morgello, 2018), coupled with their neurotoxicity (Nightingale et al., 2023), brain plasticity measures, in the form of HIV brain training,[9] have taken an added pre-eminence to reverse cognitive impairment, in adolescent neuroHIV. For example, brain training protocols have been applied to remediate attention (Basterfield & Zondo, 2022), working memory (Fraser & Cockcroft, 2020), and executive functions (Boivin et al., 2010; Boivin et al., 2019) in adolescent HIV. Notwithstanding these strides, there continues to be a dearth of research pairing behavioural outcomes with neuroimaging measures to investigate brain training in children and adolescents living with HIV in Sub-Saharan Africa (Benki-Nugent & Boivin 2019; Musielak & Fine 2016). To address limitations in the literature, my thesis, through the subsequent chapters, provides a meta-analysis investigating the effects of attention brain training to reverse neuroHIV (Chapter 4). Chapter 5 is a Methods chapter detailing the use of fNIRS neuroimaging and behavioural protocols to investigate attention remediation in adolescent HIV. Chapter 6 is a feasibility study examining the use of fNIRS optical technology in adolescent HIV. Chapter 7 details hemodynamic and behavioural changes associated with attention training in adolescent HIV, with Chapter 8 providing a functional connectivity analysis of the above training. Chapter 9 provides a summary of the study.

[9] The neuroscience literature uses the terms, HIV brain training, HIV adaptive training, HIV cognitive rehabilitation, HIV cognitive remediation, HIV cognitive intervention, and HIV computerised cognitive training, interchangeably. In the article, the terms HIV brain training and HIV cognitive training will be preferred.

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CHAPTER 4

The Cognitive Remediation of Attention in HIV associated Neurocognitive Disorders (HAND): A Meta-Analysis and Systematic Review

Reprinted with permission from Zondo, S. (2023). The cognitive remediation of attention in HIV associated neurocognitive disorders (HAND). *F1000Research* 2023, 12:1133 (https://doi.org/10.12688/f1000research.132166.1)

Abstract: Despite medical advances in Highly Active Antiretroviral Therapy (HAART), patients living with HIV continue to be at risk for developing HIV-associated neurocognitive disorders (HAND). The optimization of non-HAART interventions, including cognitive rehabilitation therapy (CRT), shows promise in reversing the impact of HAND. No data exist indicating the efficacy of CRT in remediating attention skills following neuroHIV. This paper presents a meta-analysis of randomised and non-randomised controlled trials (RCTs) to remediate attention skills following HIV CRT. The database search included literature from Google Scholar, ERIC, Cochrane Library, ISI Web of Knowledge, PubMed, PsycINFO, and grey literature published between 2013 and 2022. Inclusion criteria included studies with participants living with HIV who had undergone CRT intervention to remediate attention skills following neuroHIV. Exclusion criteria included case studies, non-human studies, and literature reviews. To assess study quality, including, randomisation, allocation concealment, participant and personnel blinding, the Cochrane Collaboration ratings system was applied. A total of 14 studies met the inclusion criteria (n = 532). There were significant pre- to post-intervention between-group benefits due to CRT in the experimental group relative to control conditions for the remediation of attention skills following HIV acquisition (Hedges g = 0.251, 95% CI = 0.005 to 0.497; $p < 0.05$). No significant effects ($p > 0.05$) were demonstrated for subgroup analysis.

Keywords: HIV, HAND, Attention Rehabilitation, Neuroplasticity, meta-analysis, meta-regression

4.1 Introduction

The Human Immunodeficiency Virus (HIV) continues to be a significant global pandemic with no known cure. Latest figures from UNAIDS (2021) indicate that by the end of 2021, approximately 38.4 million people were living with the virus, with 1.5 million newly reported cases in 2021 alone. Virologically, HIV is a ribonucleic acid (RNA), single-stranded retrovirus (Poltronieri et al., 2015) that targets cells in the immune system. Through pathobiology yet to be understood, following transmission to the host, HIV permeates the blood-brain barrier (BBB), where it leads to the differentiation of monocytes into macrophages. This differentiation leads to the infection of cells in the CNS, namely microglia and astrocytes (Filipowicz et al., 2016; Sillman et al., 2018). In breaching the BBB, HIV is thought to dysregulate the brain's intrinsic nerve cell architecture, leading to aberrant neural transmission, including excess glutamate levels and decreased dopaminergic transmission (Elbirt et al. 2015a; Nolan & Gaskill 2019a). Markedly, HIV's viral penetrance and persistence in the CNS is implicated in neuronal apoptosis, leading to a milieu of neurocognitive impairments associated with HIV (Das, et al., 2016; Smail & Brew 2018).

Neurocognitive impairments resulting from HIV are well-documented and include HIV Dementia (Hussain et al. 2022; Mattson, et al., 2005), HIV-associated neurocognitive disorder (HAND) (Elbirt et al. 2015a; Smail & Brew 2018), and HIV encephalitis (Morgello, 2018). Specific to HAND[10], although no reliable worldwide estimates exist, the prevalence rates are estimated to range from 25% to 59% of HIV cases (Bonnet et al. 2013; Elbirt et al. 2015a; Kinai et al. 2017). According to updated criteria, HAND is diagnosed if a patient performs more than one standard deviation (SD) below his or her normative mean, on standardized neuropsychological measures, in two or more cognitive domains (*e.g.*, attention, speed of

[10] Within the extant literature, the terms 'HAND' and 'neuroHIV' are used concurrently to indicate cognitive impairment following HIV (Saloner and Cysique 2017).

processing, verbal memory, executive functioning) (Antinori et al. 2007; Bruce et al., 2018; Chan et al., 2019; Chan & Wong 2013; Saloner & Cysique, 2017).

4.1.1 **Problem statement**

Pharmacological interventions, namely Highly Active Antiretrovirals (HAART), have improved cognitive outcomes in HIV (Benki-Nugent & Boivin 2019; Jantarabenjakul et al. 2019). However, to date, their efficacy in treating or reducing the impact of HAND remains variable (Alford & Vera, 2018b; Lanman et al. 2019; Yuan & Kaul, 2019). For example, Underwood et al. (2015) found that prolonged treatment with efavirenz (a non-nucleoside reverse transcriptase inhibitor) (NNRTI) and raltegravir (integrase inhibitor) may play a role in HIV-associated cognitive decline and poorer cognitive function in children living with HIV. A cognate study by Hammond et al. (2019) found that children in a South African study showed no cognitive gains after receiving efavirenz. The study hypothesised that efavirenz, due to its pharmacokinetic profile (genetically slow metabolites), may be a risk factor for neurotoxicity, leading to the poor neurocognitive outcomes associated with HAND.

Correspondingly, Crowell et al. (2015), in their study involving 396 children living with HIV, found an association between early viral suppression and improved neurocognitive outcome; however, they found no association between a high CNS Penetration-Effectiveness score (CPE)[11] and neurocognitive improvement in the children. These findings are similar to those reported by Ellis et al. (2014), who found no association between high CPE and gains in neurocognition in a longitudinal study conducted among adults living with HIV. Similarly, Puthanakit et al. (2013), found no improvement in neurocognitive outcomes amongst 139 Thai and Cambodian children living with HIV after a three-year initiation of cARTs. Other studies (Das, et al., 2016; Iglesias-Ussel & Romerio 2011; Kumar et al. 2018) indicate that when

[11] CPE ranks all ARVs on four categories (a) physicochemical properties, (b) concentrations achieved in the CSF, (c) efficacy based on CSF virologic suppression, and (d) neurocognitive improvement (Letendre et al. 2008).

antiretrovirals (ARVs) act upon the brain HIV viral reservoir, they are indicated to significantly cause neurotoxicity, leading to further neurocognitive and psychiatric impairments (Alford & Vera 2018b; Das, et al., 2016; Lanman et al. 2019; Vázquez-Santiago et al. 2014; Wilmshurst et al. 2018).

4.1.2 **Brain plasticity and cognitive rehabilitation**

Given the pharmacological limitations associated with ARVs, including limitations in viral reservoir penetration in the brain and neurotoxicity, studies have begun investigating the efficacy of alternative non-pharmaceutical therapies, namely cognitive rehabilitation therapy (CRT)[12], to reverse HAND. The principles of CRT are based on neuroplasticity. Neural brain plasticity posits that the human cortex is malleable and has the inherent capacity to undergo structural and functional change (Bach-y-Rita, 2003; Noggle, 2019; Wilson et al., n.d.). Within the mammalian cortex, structural and functional change is attendant to continued and repeated exposure to cognitively demanding brain training exercises, purposed to rewire and improve neuronal connectivity, increase blood supply and improve brain function (Hebb, 1949; Luria, 1948; Merzenich, 2013). Luria, (1970) particularly notes that brain plasticity and cognitive training allow for axonal and synaptic connections reintegrating. Accordingly, through dendritic outflow, synaptic connections are thought to stimulate neuronal density and cortical enrichment in near and distant neuronal networks responsible for disparate cortical functions.

Given the promise of positive neuroplasticity to harness neurocortical networks and ameliorate brain function, the extant literature has documented the efficacy of brain training exercises to reduce the risk of cognitive impairment sequent HAND. For example, data indicate improvements in cognitive domains such as executive functions (Boivin et al. 2016; Frain and Chen 2018), attention (Basterfield, & Zondo, 2022; Boivin et al., 2010; Towe et al., 2017),

[12] Within the extant literature, the terms ‘cognitive rehabilitation therapy’, ‘cognitive-training intervention’, and ‘brain training’, are used interchangeably (Shawn Green *et al.*, 2019; Simons *et al.*, 2016a), and this sequence will be equally applied in the manuscript.

processing speed (Cody et al. 2020; Vance et al. 2012), and working memory (Fraser & Cockcroft 2020; Towe, et al., 2017), following intensive brain training exercise in neuroHIV.

Despite the above early promising findings, contradictory findings have been reported. For example, Vance et al. (2012) used a computerized CRT program (InSight) to investigate processing speed in adults. Although the experimental group showed significant baseline-to-post-test improvements in speed processing, speed processing deficits are not prevalent in the post-cART era (Heaton et al. 2011). In another study, Pope et al. (2018) found that a computerised program (Posit Science: BrainHQ) could improve abstraction and executive functions, whereas Fazeli et al. (2019), reported that the same software enhanced other cognitive domains, such as attention, working memory, and information processing in the experimental group. Moreover, some studies returned insignificant findings (*e.g.,* Vance et al., 2018; Fazeli et al. 2019) when comparing the effect of the cognitive rehabilitation on the experimental group, compared to the control, despite utilizing brain training programs and techniques that have proven to improve cognition in HIV.

Given contradictory findings within the literature, Vance et al. (2019), conducted a systematic review of 13 computerised cognitive rehabilitation (CCT) studies investigating the efficacy of cognitive rehabilitation to reverse HAND. The review by Vance et al. (2019) found that, for the most part, CRT in HIV was associated with improved cognitive outcomes that translated to improvements in quality of life. Nonetheless, although the systematic review provides summary data on the effect of CRT on working memory, processing speed, and ageing, it does not provide effect size data for each of the reviewed cognitive domains. Most importantly, it does not provide information on the cognitive rehabilitation of attention skills, although deficits in attention are the foremost and common consequence of HIV (Posada et al., 2012; Wang et al., 2017). Moreover, since the review did not provide effect size data, it did not provide data detailing the effect of moderator variables or subgroup meta-analytic data on HIV

cognitive rehabilitation outcomes. Given these limitations, the current study aimed to conduct a meta-analysis investigating the efficacy of CRT in remediating attention skills among people living with HIV. Significantly, the study aimed to (1) provide effect size data detailing pre- and post-intervention improvement in attention due to CRT among people living with HIV. Secondly, the study sought to (2) investigate the effect of moderator variables by conducting subgroup analyses of the effect size (if significant). Lastly, the study aimed to provide clinical suggestions for implementing HIV CRT interventions in low-to medium-income countries with a high number of HIV cases.

4.2 Methods

This study was registered on Protocols.io (dx.doi.org/10.17504/protocols.io.5jyl8jqm7g2w/v1; 01/03/2023). Although the study was not registered in PROSPERO the review protocol can be found in the extended data. The study followed the Preferred Reporting Items for Systematic Reviews and Meta-analyses (PRISMA) reporting guidelines for meta-analyses (Moher et al., 2009).

4.2.1 Search strategy

The units of analysis were chosen from published literature containing medical subject headings (MeSH) and text words related to: 'HIV and attention rehabilitation' or 'HIV and cognitive rehabilitation', 'HIV and/or attention', 'HIV and attention remediation', 'HIV and executive attention remediation'. These were combined with terms related to outcome research such as: 'effect', 'efficacy' 'evaluation', or 'outcome'. To identify relevant studies, journal articles, books, dissertations, and electronic databases were searched. Electronic database searches included Google Scholar (RRID:SCR_008878), ERIC (RRID:SCR_007644), Cochrane Library (RRID:SCR_013000), ISI Web of Knowledge, PubMed (RRID:SCR_004846), and PsycINFO (RRID:SCR_014799). Grey literature and

unpublished papers were searched based on indices of conference proceedings and dissertation abstracts to minimise publication bias (Higgins & Green, 2008). A complete breakdown and description of the search strategies are available as *Extended data* (Zondo, 2023).

4.2.2 **Inclusion criteria**

The inclusion criteria for studies included in the meta-analysis were included based on the PICOS criteria. The population and condition of interest were patients diagnosed with HIV, receiving cognitive rehabilitation to remediate attention. Participants in the experimental group should have undergone an intervention to remediate attention skills following neuroHIV. Studies should have included a comparison between the experimental group and at least one control group (passive control group[13], or active control group[14]). Studies should also have reported outcome data in the form of pre-and post-intervention attention scores using validated neuropsychological measures of attention[15]. Lastly, studies were included if they used random and non-random control trial study designs. In addition to the PICOS criteria, studies should have reported sample sizes to enable effect size weighting (Borenstein et al., 2021).

The above inclusion criteria were combined with the 27-item PRISMA checklist to produce a four-phase PRISMA flow diagram as suggested by Moher *et al.* (2009). The complete PICOS criteria accompanied by the PRISMA checklist can be found as *Extended data* (Zondo, 2023). The PRISMA flow diagram is indicated below in Figure 4.1. All duplicate studies for the meta-analysis were removed using Mendeley Data (RRID:SCR_002750) Software, Version 1. The author (S.Z) and two researcher assistants (K.S and T.C), independently assessed the titles and abstracts retrieved from literature searches for relevance.

[13] A passive control group is a group of research participants that does not receive any form of intervention, treatment, or activity related to the study (Salkind, 2015).
[14] An active control group is a group of participants that receives a treatment or activity that is not the active ingredient, yet is still designed to control for factors like time, attention, and expectations (Salkind, 2015)
[15] Valid measures of attention were cross checked and validated based on (Lezak et al. 2004; Strauss, Sherman, and Spreen 2006).

After the initial assessment, the same reviewers determined the eligibility of all full-text relevant for the meta-analysis. Any disagreements (three articles) were resolved by a third research assistant (N.M) with expertise in meta-analytic research. Relevant but excluded studies from the reviewed literature are indicated in the *Extended data* (Zondo, 2023).

4.2.3 **Data extraction**

Data extraction was done by the author and cross-checked (by K.S. and T. C.) using an Excel spreadsheet (Microsoft Corporation) (RRID:SCR_016137). The relevant summary statistics to investigate attention outcomes due to cognitive rehabilitation included individual data points linked to: (a) The number of participants in each of the groups, (b) relevant statistical data such as means, and standard deviations, for both the experimental and control groups (active or passive control) on the attention measures, pre and post the intervention (Field and Gillett 2010; Lee 2018).

The extraction of attention outcomes (dependent variable) for each of the studies used in the meta-analysis are available as *Extended data* (Zondo, 2023). Other key moderator data extracted from each of the studies included in the meta-analysis included data related to: (a) the duration of the cognitive training exercises (< 10 sessions; 10 sessions; > 10 sessions in each study; (b) the type of cognitive training received (computerised; pencil and paper, mixed); (c) the setting of the cognitive training (individualised training; group intervention); (d) the type of research design employed (random control trial *vs.* non-random control); (e) the socio-economic setting of the study (High *vs.* Low); (f) the data quality of the study (Low, Medium, High); (g) the type of sample (pediatric HIV *vs.* geriatric HIV); (h) the type of control group utilised (active, passive, both) and (g) whether participants were blind or aware to their condition (experimental or control). The above variables were included in the subgroup meta-

analysis to investigate the influence of pertinent moderator variables on the overall effect size of the cognitive rehabilitation.

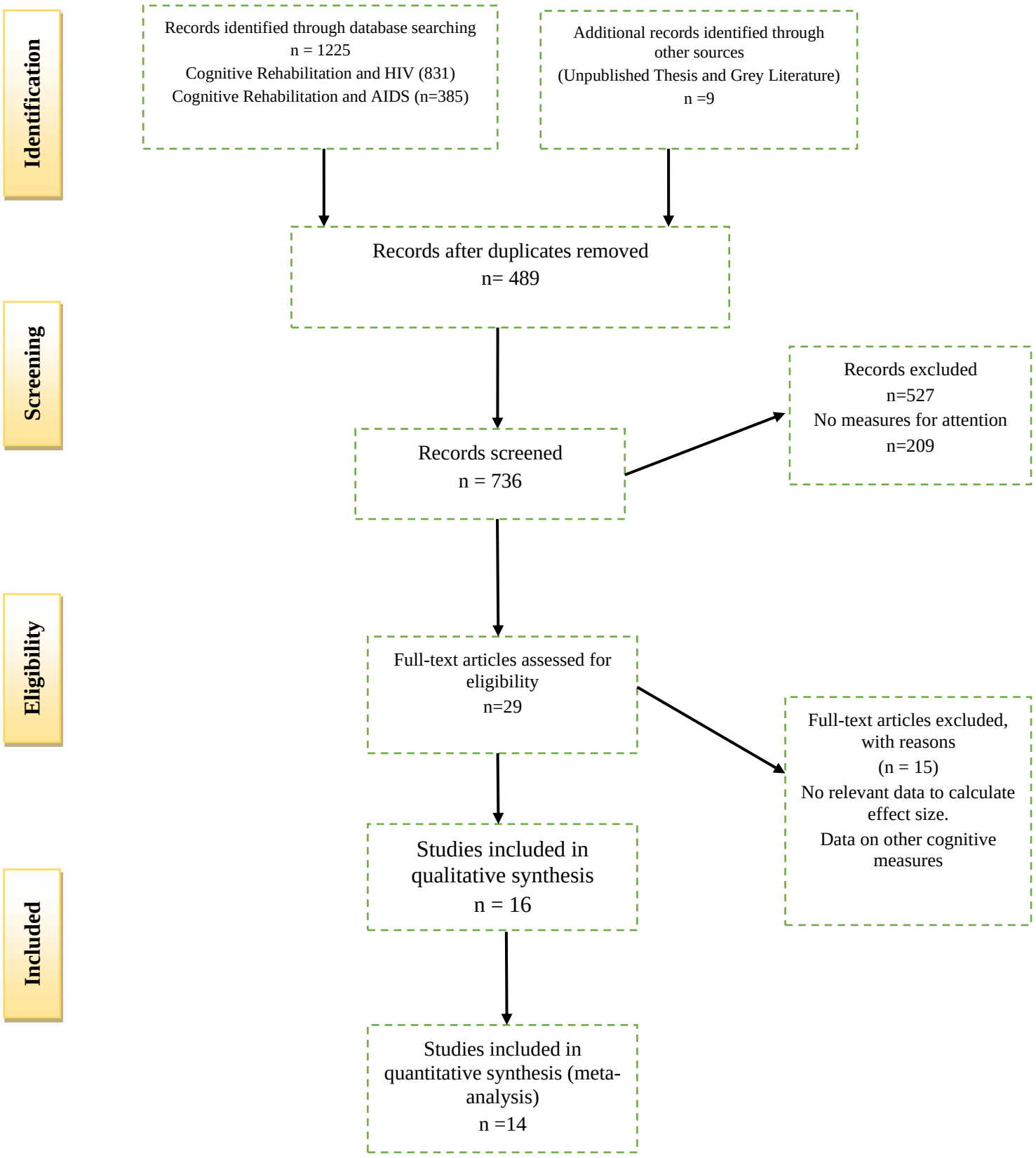


Figure 4.1. Flow Diagram depicting the selection of studies for the meta-analysis.

4.2.4 **Data analysis**

The meta-analysis was performed using Stata 17 (StataCorp. 2021. Stata Statistical Software: Release 17. College Station, TX. StataCorp, LLC) (RRID:SCR_012763) (free alternative, RStudio). The overall effect size was determined by measuring attention scores pre-and-post the CRT to investigate the effectiveness of the attention intervention. Given the heterogeneity across all studies, the random effect model was used to estimate the pooled effect (Borenstein et al., 2009). Effect sizes were calculated based on the standardised mean difference (SMD) sizes for the individual studies, weighted according to the relevant sample size. Briefly, when using SMD, effect is calculated as the mean change in pre-intervention scores compared to post-intervention scores in the intervention group minus the mean change from pre-intervention to post-intervention scores in the control group, divided by the combined pre-intervention standard deviation scores (Borenstein et al., 2009; Field & Gillett, 2010).

Following suggestions from Borenstein et al. (2021), the inverse variance method was used to interpolate the SMDs of each study. As suggested by Borenstein et al. (2021), since the SMD model also corrects for the use of different outcome measures (*i.e.*, different neuropsychological outcomes used to assess attention), it, however, fails to account for differences in the direction of the participants' behavioural performance (neuropsychological performance) within the various outcome measures used in the meta-analysis (neuropsychological assessments). Stated differently in certain assessments, an increase in mean scores may represent a decline in disease severity, whereas, in some neuropsychological assessments, a decrease in mean scores represents a decline in disease severity (Borenstein et al., 2009). To correct these differences, mean scores from studies in which a decrease in mean scores represents a decline in disease severity were multiplied by -1, ensuring conformity of direction for all the scales used in the meta-analysis calculation (Borenstein et al., 2009). Based on the above recommendations, the mean scores for both the control and experimental group

from the following studies Fazeli et al. (2019), Zondo and Mulder, (2015) were corrected by multiplication of -1.

The H^2 and I^2 statistic (based on the *Q* statistic) was used to assess the proportional significance of heterogeneity (Borenstein *et al.*, 2009). The author tested for publication bias using a funnel plot, which is a type of scatterplot with treatment effect size (Cohen's D) plotted on the x-axis, and the standard error (variance) plotted on the y-axis (Borenstein et al., 2009). Statistical significance for all analyses was set at a threshold of $p < 0.05$.

4.3 Results

4.3.1 Search results

Since the inclusion criteria of the studies are detailed in the methods section, a PRISMA flow chart indicating the decision process and study selection is described in Figure 4.1. In summary, the study included a total of 1,225 records; after removing duplicates (489), 736 records were screened. A further 527 records were excluded based on title searches, abstracts, and methodological considerations (*i.e.*, case studies and qualitative designs). A total of 15 studies were deemed relevant but were excluded from the analysis due to reasons provided as *Extended data* (Zondo, 2023). In total, 29 studies were assessed for eligibility with the final selection including 11 randomised control studies (Basterfield, & Zondo, 2022; Boivin et al., 2010; Casaletto et al., 2016; Cody et al., 2020; Fazeli et al., 2019; Frain & Chen, 2018; Fraser & Cockcroft, 2020; Livelli et al., 2015; Ownby & Acevedo, 2016; Pope et al., 2018; Vance et al., 2012) and three non-randomised studies (Cody, Fazeli, and Vance 2015; Ezeamama et al. 2020; Zondo and Mulder 2015).

4.3.2 Study characteristics

The characteristics of all studies included in the meta-analysis are detailed in Table 4.1. The analysis included data from South Africa (Basterfield, & Zondo, 2022; Fraser & Cockcroft,

2020; Zondo & Mulder, 2015), Uganda (Boivin et al. 2010; Ezeamama et al. 2020), Italy (Livelli et al. 2015), and the US (Casaletto et al., 2016; Cody et al., 2015, 2020; Fazeli et al., 2019; Frain & Chen, 2018; Ownby & Acevedo, 2016; Pope et al., 2018; Vance et al., 2012). In total, the study comprised 532 participants (255 participants in the intervention group and 277 participants in the control group).

As indicated in Table 1, participant ages for adults ranged from a mean of 47.5 years (Livelli et al., 2015) to 59.7 years (Ezeamama et al., 2020) in the intervention group; and 50.0 years (Livelli et al., 2015) to 62.12 years (Cody et al., 2020) in the control group. Participant ages in the pediatric HIV groups ranged from a mean of 10.34 years (Boivin *et al.*, 2010) to 12.0 years (Fraser & Cockcroft, 2020) in the intervention group and 9.36 years (Boivin *et al.*, 2010) to 12.41 years (Fraser & Cockcroft, 2020) in the control group. The proportion of female participants ranged from 0% (Frain & Chen, 2018) to 66% (Boivin et al., 2010) in the intervention group and 0% (Zondo & Mulder, 2015) to 90% (Boivin *et al.*, 2010) in the control group.

The 'types' of attention intervention implemented varied extensively and included selective attention training (Basterfield, & Zondo, 2022), divided attention training (Casaletto et al., 2016), selective and divided attention training (Fazeli et al., 2019), selective, divided, and sustained attention training (Fraser & Cockcroft, 2020; Livelli et al., 2015), visual attention (Frain & Chen, 2018; Vance et al., 2012), and simple attention training (Ezeamama et al., 2020; Ownby & Acevedo, 2016). Nine of the studies (Boivin et al., 2010; Casaletto et al., 2016; Ezeamama et al., 2020; Fazeli et al., 2019; Frain & Chen, 2018; Livelli et al., 2015; Ownby & Acevedo, 2016; Pope et al., 2018; Vance et al., 2012) reported participant biomarker data, in the form of CD4+ T-cell count, pre-and post-the intervention. CD4+ T-cell counts in the treatment group ranged from 552 cells/μL (Casaletto et al., 2016) to 833 cells/μL (Fazeli et al., 2019). None of the studies reported biomarker data in the form of neuroimaging data (i.e., MRI,

EEG, fNIRS) detailing the effects of the intervention from baseline to post-intervention changes.

Table 4.1: Study and participant characteristics. CRT, cognitive rehabilitation therapy; HIV, Human Immunodeficiency Virus; HAART, Highly Active Antiretroviral Therapy; ARV, antiretroviral; HAND, HIV-associated neurocognitive disorders.

	Sample								**Attention Remediation Group**					
	Sample size			Age mean in years		Female (n)		Overall Description of Participants	Training received	Number of sessions[b]	Sessions per week	Follow up duration	Type of attention training	Control condition
Study	Total	CRT	Control	CRT	Control	CRT	Control							
Basterfield & Zondo (2022), SA	5	3	2	11.27	11.23	2 (66)	1(50)	Children[a] (aged 10 -15 yrs.) with HIV receiving HAART.	BrainWaveR	8	3	None	Selective	Microsoft Word Exercises
Boivin *et al.*, (2010), Uganda	60	32	28	10.34	9.36	21(65.6)	15(53.6)	Children (aged 6 - 16 yrs.) with perinatal transmission of HIV on HAART.	Captain's Log	10	2	None	Simple	Non-Active Cognitive Training
Casaletto *et al.*, (2016), USA	90	30	30 x 2	50.1	47.8	3 (10)	7 (23)	Adults (47 - 51 yrs.) with HIV and Substance Use Disorder and Dysexecutive Syndrome	Goal Management & Metacognition Training	1	N/A	None	Divided	Paper Origami Exercises
Cody *et al.*, (2015), USA	20	13	24	50.22	52.9	4 (25)	(7) 29	Adults (47 - 51 yrs.) with asymptomatic HIV	PositScience	5	N/A	1 - 2 Months	Selective& Divided	No Contact
Cody *et al.*, (2020), (USA)	33	17	16	58.82	62.12	7 (33.3)	5 (31)	Adults (>55 yrs.) with and without HIV, and no Hx of brain trauma.	PositScience Transcranial Deep Stimulation (tDCS)	10	2	N/A	Selective& Divided	Sham tDCS

(Continued)

Study	Sample								Attention Remediation Group					
	Sample Size			Age, Mean Years		Female sex, %		Overall Description of Participants	Training Received	Number of Sessions	Sessions per week	Follow Up Duration	Type of Attention Training	Control Condition
	Total	CRT	Control	CRT	Control	CRT	Control							
Ezeamama *et al.*, (2020), Uganda	81	41	49	59.7	60.0	24 (59)	25 (50)	Elderly adults (>50 yrs.) with HIV and without other mental or health disorders.	Captain's Log	10	2	5 Weeks	Simple	Standard of Care (SOC)
Fazeli *et al.*, (2019), USA	33	17	16	56	55.63	6 (35)	5 (31)	Adults (>50 yrs.) with HIV, and without a history of brain trauma, and/or mental health disorders.	PositScience BrainHQ	10	N/A	4 Weeks	Selective & Divided	Sham tDCS
Frain & Chen (2018), USA	22	10	12	58	54	0 (0)	3 (25)	Adults (>50 yrs.) with HIV, on ARVs	PositScience BrainHQ	N/A	3	2 and 4 Months	Visual Attention	Nonactive Cognitive Training
Fraser & Cockcroft (2020), SA	63	31	32	12.0	12.41	16 (52)	16 (50)	Adolescents (aged 10 -15 yrs.) diagnosed with Clad C HIV on HAART.	Jungle-Memory Computer Exercises	32	4	6 months	Selective & Sustained	Microsoft Paint Exercises
Livelli *et al.*, (2015), Italy	32	16	16	47.5	50.0	5 (31)	3 (19)	Adults (>50 yrs.) with HAND receiving care (Amedeo di Savola Hospital)	Mixed: Pencil and Paper & Computer Exercises	36	N/A	6 months	Selective Divided Sustained Divided	Standard Care (SOC)

(Continued)

	Sample								Attention Remediation Group					
	Sample Size			Age, Mean Years		Female sex, %		Overall Description of Participants	Training Received	Number of Sessions	Sessions per week	Follow Up Duration	Type of Attention Training	Control Condition
Study	Total	CRT	Control	CRT	Control	CRT	Control							
Ownby & Acevedo (2016), USA	11	5	6	50.3	52.8	0	2 (40)	Adults (>51 yrs.) with HIV, and self-reported cognitive impairment in at least 2 cognitive domains.	GT Racing2 Game & tDCS	6	N/A	N/A	Simple Attention	Sham tDCS
Pope *et al.*, (2018), USA	30	15	15	55.3	53.7	5 (33)	6 (40)	Adults (>50 yrs.) with HIV, and without a history of brain trauma, and/or mental health disorders.	PositScience	10	4	N/A	Divided & Selective	Sham tDCS
Vance *et al.*, (2012), USA	46	22	24	50.1	52.9	5 (23)	(7) 29	Adults (47 - 51 yrs.) with asymptomatic HIV.	PositScience	10	N/A	N/A	Visual Attention	No Contact
Zondo & Mulder (2015), SA	6	3	3	11	11	0	0	Children (11-year-old) with HIV receiving HAART.	BrainWaveR	8	2	N/A	Selective	No Contact

Note: [a] The definition ‘child’, is based on age guidelines from the UN Convention of the Rights of the Child that describe the child / pediatric age as ranging from birth to adolescence (16-19 years) (UN Convention Assembly, 1989).

Note. [b] In most studies (e.g., Fraser and Cockcroft, 2020), a session lasted for a period of 30-45 mins.

The total number of rehabilitation sessions ranged from 1 (Casaletto et al., 2016) to 36 sessions (Livelli et al., 2015). There was much variability within the studies regarding the duration of each rehabilitation session, with some sessions, ranging from 10-15 minutes per session (Casaletto et al., 2016) to others ranging from 30-45 minutes per session (Fraser & Cockcroft, 2020). Training frequency within studies ranged from two sessions per week (Boivin et al., 2010) to four sessions per week (Fraser & Cockcroft, 2020; Pope et al., 2018). For most studies, the control conditions were divided into one of two control types: either active controls (six studies: Basterfield & Zondo, 2022; Casaletto et al., 2016; Cody et al., 2020; Ezeamama et al., 2020; Fazeli et al., 2019; Fraser & Cockcroft, 2020; Livelli et al., 2015), or passive controls (five studies: Boivin et al., 2010; Cody et al., 2015; Frain & Chen, 2018; Vance et al., 2012; Zondo & Mulder, 2015). None of the reviewed studies included both active and passive controls, to assess the impact of the active ingredient (cognitive rehabilitation), compared to the influence of a sham activity (active control) and/or passive interaction (passive control).

Overall, 10 of the studies implemented computerised cognitive rehabilitation (CCT) protocols (Boivin et al., 2010; Cody et al., 2016, 2020; Ezeamama et al., 2020; Fazeli et al., 2019; Frain & Chen, 2018; Fraser & Cockcroft, 2020; Ownby & Acevedo, 2016; Pope et al., 2018; Vance et al., 2012, 2018); two utilised pencil and paper protocols (Basterfield & Zondo, 2022; Zondo & Mulder, 2015), whereas one study employed a mixture of computer and paper-pencil protocols (Livelli et al., 2015), whilst another used a mixture of Goal Management and individualised metacognition training (Casaletto et al., 2016). Of the 10 studies that implemented computerised CRT, two (Cody et al., 2020; Fazeli et al., 2019) coupled computerised training with transcranial deep brain stimulation (tDCS). Moreover, of the studies that utilised computerised interventions, six used the PositScience-BrainHQ system (Cody et al., 2015, 2020; Fazeli et al., 2019; Frain & Chen, 2018; Pope et al., 2018; Vance et al., 2012), whereas two employed the Captain's Log (Boivin et al., 2010; Ezeamama et al.,

2020), which trains multiple cognitive domains including working memory and executive skills, and one made use of Jungle-Memory (Fraser & Cockcroft, 2020), which trains working memory.

4.3.3 **Meta-analysis of attention**

The analysis was carried out using the standardized mean difference as the outcome effect measure. As indicated in Figure 4.2, a random-effects model was fitted to the data. The amount of heterogeneity (tau^2) was estimated using the restricted maximum-likelihood estimator (Viechtbauer 2010). In addition to the estimate of tau^2, the Q-test for heterogeneity and the I^2 statistic was conducted on a total of 14 studies included in the analysis. The observed standardized mean differences ranged from -1.129 to 1.115, with the majority of estimates being positive (71%). The estimated average standardized mean difference based on the random-effects model was Hedges, g = 0.251 (95% CI: 0.005 to 0.4977).

The average outcome for attention rehabilitation differed significantly from zero (z =2.00, p = 0.045). According to the Q-test, the true outcome of the effect size appears to be heterogeneous (Q (13) = 24.70, p = 0.025, tau^2 = 0.097, I^2 = 44.89%). A 95% prediction interval for the true outcomes of the intervention ranged from - 0.3901 to 0.8579. Although the average outcome for the rehabilitation was estimated to be positive (Hedges g = 0.251, p = 0.045), the data indicate that in some studies the true outcome of the rehabilitation may in fact be negative. Further examination of the studentized residuals revealed that none of the studies had a value larger than ± 2.9137. Hence, there was no indication of outliers in the context of this model. As further indicated by the Forest Plot (Figure 4.3), there was greater variability in the 95% CIs in studies with smaller sample sizes and larger weights in studies with post-intervention follow-ups and larger sample sizes.

Meta-analysis summary — Number of studies = **14**
Random-effects model — Heterogeneity:
Method: REML — tau2 = **0.0937**
I2 (%) = **44.89**
H2 = **1.81**

Study	Hedges's g	[95% conf.	interval]	% weight
Basterfield & Zondo (2022)	**-1.129**	**-2.607**	**0.348**	**2.38**
Boivin et al., (2010)	**0.766**	**0.247**	**1.285**	**9.64**
Casaletto et al., (2016)	**0.272**	**-0.230**	**0.774**	**9.91**
Cody et al., (2015)	**0.227**	**-0.382**	**0.837**	**8.29**
Cody et al., (2020)	**0.001**	**-0.665**	**0.667**	**7.55**
Ezeamama et al., (2020):	**-0.626**	**-1.257**	**0.004**	**8.00**
Fazeli et al., (2019)	**0.412**	**-0.261**	**1.086**	**7.45**
Frain & Chen (2018)	**0.870**	**0.059**	**1.681**	**5.96**
Fraser & Cockcroft (2020)	**0.386**	**-0.106**	**0.879**	**10.07**
Livelli et al., (2015)	**0.700**	**0.003**	**1.397**	**7.17**
Ownby & Aceved (2016)	**0.433**	**-0.667**	**1.533**	**3.86**
Pope et al., (2018)	**-0.122**	**-0.819**	**0.575**	**7.17**
Vance et al., (2012)	**-0.140**	**-0.709**	**0.429**	**8.86**
Zondo & Mulder (2015)	**1.115**	**-0.021**	**2.250**	**3.68**
theta	**0.251**	**0.005**	**0.497**	

Test of theta = 0: z = **2.00** — Prob > |z| = **0.0459**
Test of homogeneity: Q = chi2(**13**) = **24.70** — Prob > Q = **0.0253**

Figure 4.2. Mean Differences: The overall standardized mean difference was estimated using the restricted maximum-likelihood estimate (REML).

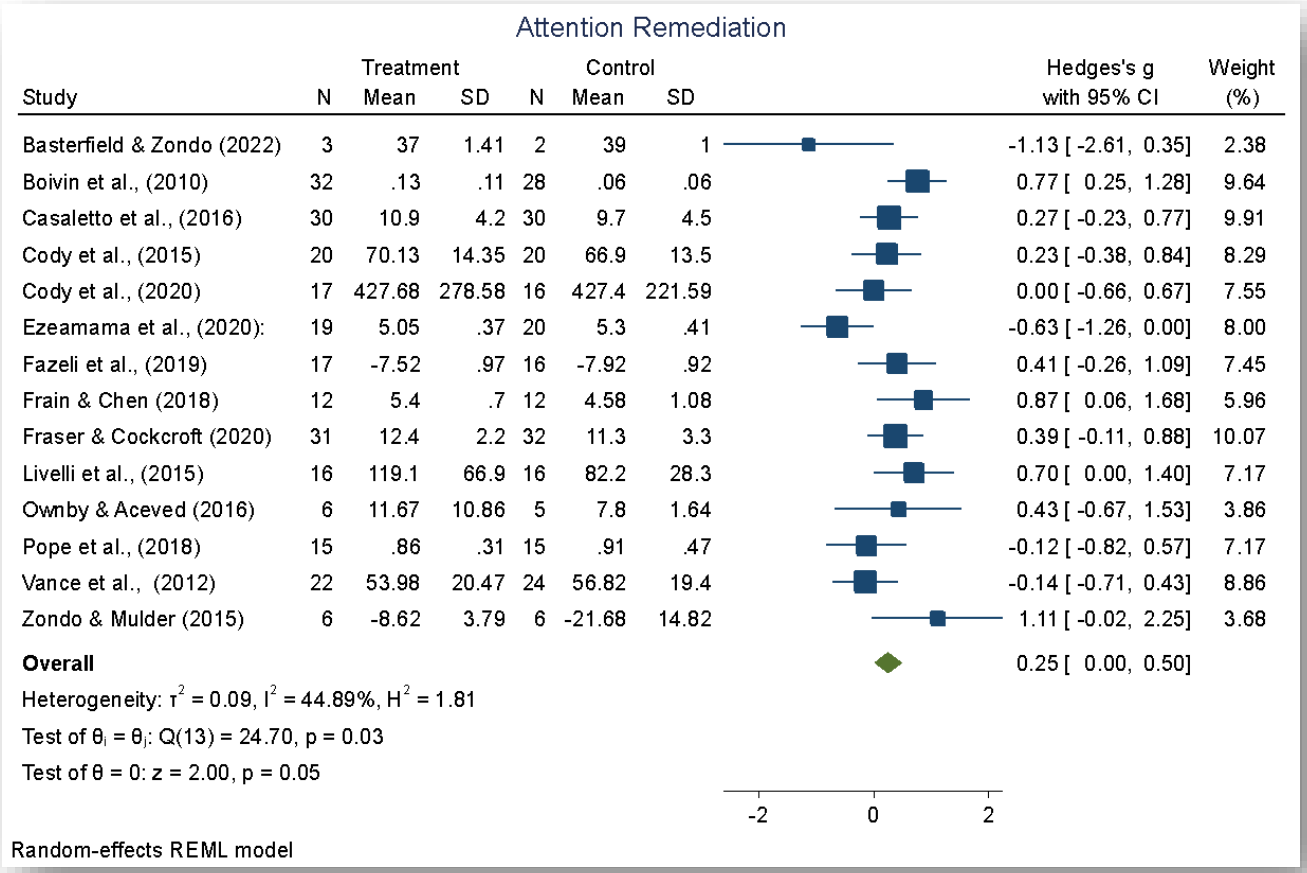


Figure 4.3. Forest plot. The overall effect of the cognitive rehabilitation to remediate attention skills following neuroHIV was significant, $z = 2.00$, $p < 0.05$.

4.3.4 **Subgroup analysis**

Subgroup analyses are presented in Table 4.2. These were conducted to investigate the effect of key moderator variables, namely (a) the duration of the intervention (< 10 sessions, 10 sessions, > 10 sessions), (b) the type of rehabilitation (computerized, pencil and paper, mixed), (c) the setting of the rehabilitation (individualized or group), (d) the type of research design employed (randomized, non-randomised), (e) data quality rating (Low median, high), (f) the population of the study (pediatric HIV or geriatric HIV), (g) the type of control group in the study (active control, passive control), and (h) the blinding of subjects (aware or blind). No significant subgroup differences were found on any of the moderator variables. Further meta-

regression analysis could not be conducted on the data, despite the significant outcomes of the cognitive rehabilitation (Hedges $g = 0.25$, $p < 0.05$).

Table 4.2: Subgroup analysis.

Table Moderator Effects (Post Test)					
Outcome Measure	**Criteria**	**Subgroup (study)**	**n**	**Hedges' g (95% CI)[ns]**	**Test of Subgroup Differences[a]**
Remediation of Attention	Duration	<=10 session	6	0.47 (0.15–0.78)	Q=2.43, df=2 (p=0.31)
		10 Sessions	6	0.06 (-0.34–0.47)	
		>=10 Session	3	0.23 (-0.53–0.99)	
	Type of Rehabilitation	Computerised	12	0.24 (-0.01–0.49)	Q=1.52, df=2, (p=0.46)
		Pencil and Paper	2	0.04 (-2.15–2.24)	
		Mixed	1	0.27 (0.03–1.40)	
	Setting	Individualised	5	0.38 (-0.20–0.96)	Q=0.17, df=1, (p=0.68)
		Group Rehabilitation	10	0.25 (-0.04–0.53)	
	Research Design	Randomization	12	0.33 (0.10–0.56)	Q=0.14, df=1, (p=0.71)
		None Randomized	3	0.15 (-0.77–1.07)	
	Socio Economic Setting	High	10	0.26 (0.05–0.48)	Q=0.06, df=1, (p=0.81)
		Low	5	0.17 (-0.55–0.89)	
	Data Quality	Low	4	0.37 (-0.5–1.24)	Q=0.73, df=2, (p=0.68)
		Medium	4	0.07 (0.59–0.73)	
		High	7	0.37 (0.15–0.60)	

(Continued)

Table Moderator Effects (Post Test)					
Outcome Measure	**Criteria**	**Subgroup (study)**	**n**	**Hedges' g (95% CI)[ns]**	**Test of Subgroup Differences[a]**
	Population	Pediatric	4	0.48 (-0.04–1.00)	Q=0.94, df=1, (p=0.33)
		Geriatric HIV	11	0.19 (-0.07–0.46)	
	Type of Control	Active	8	0.11 (-0.22–0.44)	Q=2.15, df=2, (p=0.34)
		Passive	4	0.51 (-0.02–1.05)	
		No Control	3	0.43 (-0.06–0.91)	
	Blinding	Aware	11	0.17 (-0.13–0.46)	Q=3.27, df=2, (p=0.19)
		Blind	3	0.57 (0.10–1.04)	

Note: ns: All the subgroup analysis were not significant at the 0.05 level of significance.

Note: a: Heterogeneity measures for the each of the group analysis.

Note: HIV: Human Immunodeficiency Virus.

4.3.5 **Study quality and risk of bias**

Study quality assessment ratings were conducted on all studies based on criteria established by the Cochrane Collaboration (Cumpston et al. 2019; Higgins and Green 2008). The criteria for quality assessment were as follows: (1) adequate randomization concealment of participants to either the treatment or control group (by the Primary Investigator (s); (2) Blinding of participants to either the treatment or control condition(s)[16]; (3) Baseline comparability, detailing whether the experimental and control group(s) were comparable on all outcome measures from baseline to post-intervention; (4) Power analysis: Did the study have adequate power and/or at least 15 participants per group for comparative analysis (experimental *vs.* control)? (5) Completeness of follow-up data: Was there adequate follow-up of at least three months post the intervention, with clear attrition analysis of data? (6) Handling of missing data: Were multiple imputation analysis and/or maximum likelihood analysis (or other advanced statistical techniques) applied to account for missing data and high attrition rates? Each of the above criteria was rated as 0 (the study does not meet criterion) or 1 (the study meets criterion). In summary, all studies were rated as Low (score 1 or 2), Medium (score 3 or 4), and High (Score 5 or 6) following suggested guidelines by Cochrane collaboration.

Based on the above criteria, five studies (Boivin et al., 2010; Casaletto et al., 2016; Fazeli et al., 2019; Fraser & Cockcroft, 2020; Livelli *et al.*, 2015) had high-quality evidence. Six studies (Cody et al., 2020; Ezeamama et al., 2020; Frain & Chen, 2018; Ownby & Acevedo, 2016; Pope et al., 2018; Vance et al., 2012) had moderate-quality evidence, and three studies (Basterfield & Zondo, 2022; Cody et al., 2015; Zondo & Mulder, 2015) had low-quality evidence. Summary data for the quality assessment of each study are available as *Extended*

[16] Following personal correspondence with multiple authors, the blinding of assessors to the experimental condition was not possible in most cases due to (a) resource constrains, (b) limited time frames to conduct research, and (c) pilot nature of most studies in the field.

Data (Zondo, 2023). The studies with low-quality ratings primarily presented with small sample sizes and had no follow-ups of at least three months post-intervention and presented large 95% CIs (*e.g.*, Basterfield & Zondo, 2022; Zondo & Mulder, 2015). Expectedly, the studies with high-quality ratings implemented randomisation, including blinding research participants to group allocation, and had adequate follow-up assessments of at least three months post-intervention. Further indication for study quality and publication bias based on Cook's distances indicated that one study (Ezeamama et al., 2020) could be overly influential on the meta-analysis effect. Nonetheless, in terms of publication bias, neither the rank correlation nor the regression test indicated any funnel plot asymmetry (p = 0.6265 and p = 0.3459, respectively), but one study was identified with publication bias as indicated in Figure 4.4.

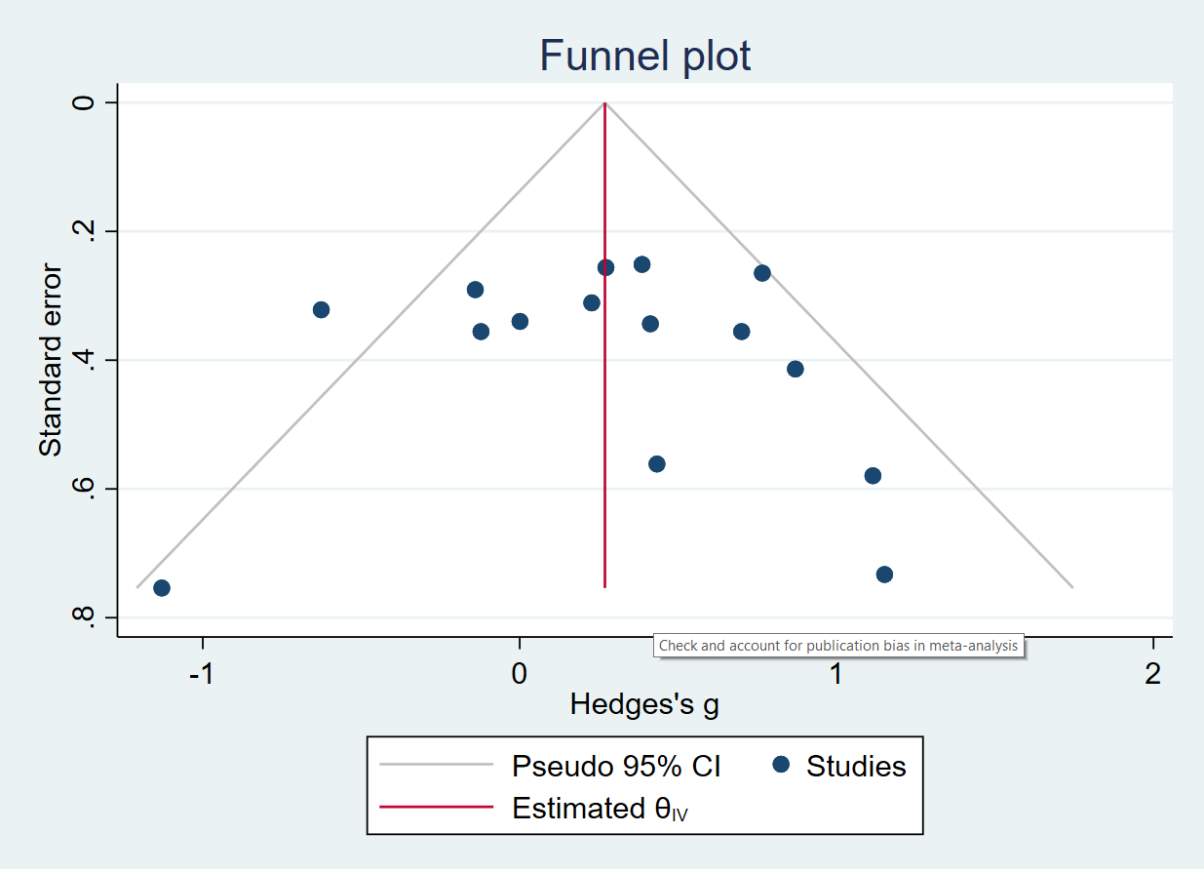


Figure 4.4. Funnel Plot Publication bias: Only one study indicated publication bias.

4.4 Discussion

4.4.1 Main findings

To the author's knowledge, this is the first meta-analysis to specifically investigate the efficacy of cognitive rehabilitation therapy as it pertains to brain training to remediate attention in neuroHIV. The nascent brain plasticity literature indicates intrinsic functional connectivity, particularly within the frontoparietal brain network, following attention and working memory cognitive rehabilitation training (Astle et al. 2015; Marek & Dosenbach, 2022; Spreng et al. 2010, 2013). Based on the scalability of attention and working memory cognitive training, the current meta-analysis found a small but significant effect (*Hedges g* = 0.25, $p < 0.05$) for the cognitive rehabilitation of attention following HIV acquisition, pre- and post-the rehabilitation.

Findings from this meta-analysis are consistent with previous studies indicating the efficacy of cognitive rehabilitation to train and remediate attention skills in patients with attention deficit-hyperactivity disorder (ADHD) (Bikic et al. 2018a; Wexler et al. 2021), autism (Spaniol et al. 2018), as well as children (Astle et al. 2015; Schrieff-Elson et al. 2017), and adults (Rosenbaum *et al.*, 2018; Spreng *et al.*, 2010) without ADHD. Nonetheless, despite the significant findings indicated in the overall meta-analysis regarding the efficacy of attention remediation in HIV, insignificant effects were noted on key sub-group moderator effects contrary to expectation.

Noteworthy research (*e.g.*, Azouvi, 2015; Shawn Green et al., 2019; Shoulson et al., 2012; Simons *et al.*, 2016a) indicate that multiple moderator effects, including methodological standards, such as the type(s) of the control group employed, randomization and blinding of subjects, and other contextual factors (the social environment of the rehabilitation), including the setting of intervention (group *vs.* individual rehabilitation) (Lincoln et al. 2020; das Nair et al. 2016), influence cognitive rehabilitation outcomes in brain training protocols.

Within the current meta-analysis, presumably, the null effect observed at the subgroup level may be a result of (a) the limited number of studies and the small number of participants in some of the studies, which might have resulted in insignificant findings being noted at the subgroup level. Secondary to the above, given the variegated nature of 'attention types' remediated in the various studies (*i.e.*, sustained, selective, divided, and simple attention) may have led to a lack of uniformity in the analysis, despite controlling for, and applying the standardised mean difference (SMD) as suggested in the meta-analysis literature (Borenstein *et al.*, 2009).

4.4.2 **Study limitations**

There continues to be a dearth of research investigating the efficacy of cognitive rehabilitation therapy in neuroHIV, and as such, there were limitations on the number of studies that could be included in the analysis. It is thus possible that the strict inclusion criteria (data points reporting 'attention' rehabilitation), permitted a weak interpretation of the treatment effect of the cognitive rehabilitation in the current study. The above observation is particularly significant, given that most studies investigating cognitive rehabilitation in the current era of neuroHIV have tended to focus on re-establishing cognitive functions related to 'executive functions', 'working memory', 'processing speed', and 'aging' (Vance *et al.*, 2019). As such, in some studies (*e.g.*, Ezeamama *et al.*, 2020; Fraser & Cockcroft, 2020), the cognitive rehabilitation of attention was a secondary consideration to the study's main objectives (*e.g.*, to remediate executive functions' or working memory in neuroHIV).

Moreover, considering the somewhat limited evidence base for the cognitive rehabilitation of attention in neuroHIV, the current study included data from both pediatric and geriatric HIV populations. Resultantly, the age-heterogeneous nature of participants may have affected the results as indicated by high 95% confidence intervals of some pediatric studies

(*e.g.*, Basterfield & Zondo, 2022). To this end, although research indicates that younger brains (ages 6 years to 25 years) have a greater susceptibility to cognitive training compared to adult brains (ages 18 years to 65 years) (Merzenich, 2013; Luria, 1970), conducting a meta-analysis on a composite 'group' (pediatric and geriatric) at different levels of brain plasticity may have resulted in different magnitudes of observed effects within the analysis. Additionally, as noted within the brain science literature (*e.g.*, Boot et al., 2013; Simons et al., 2016b), there continues to be a preponderance of cognitive rehabilitation studies to compare the effects of the cognitive intervention to passive, inactive controls. As noted by Boot *et al.* (2013), although this approach is expedient, it limits the vigorous interpretation of the 'active ingredient' within the rehabilitation and fails to control for the placebo effect that may be present within the intervention group. Significantly, the inclusion of 'active control groups', in brain research serves the dual purpose of mitigating the placebo effect and subsequently aids in matching perceived expectations of the cognitive rehabilitation within the treatment group. Unfortunately, none of the studies included in the meta-analysis had active control groups in order to match 'the active ingredient' within the intervention group in order to establish causal inference and treatment potency resulting from the intervention, resulting in a major limitation in the current meta-analysis.

4.5 Conclusion

Based on the current body of literature, coupled with findings from the current meta-analysis, there appears to be reasonable evidence to suggest the efficacy of cognitive rehabilitation to remediate attention dysfunction in neuroHIV. Nonetheless, more studies are required to confirm these nascent findings, especially in contexts such as Sub-Saharan Africa, where the high incidence of HIV/AIDS continues to be a significant risk factor for HAND. Following a review of the HIV literature, the suggestions below should be considered when designing

cognitive rehabilitation protocols in Sub-Saharan Africa (SSA) and other low-to medium-income countries with a high number of HIV cases.

4.5.1 **Clinical implications and recommendations for future research**

Although the reviewed literature indicates that random control trial studies incorporating individualized interventions coupled with intensive intervention protocols (*i.e.*, 30 sessions of 30-45 minutes per session) (*e.g.*, Frain & Chen, 2018; Fraser & Cockcroft, 2020) generate larger effect sizes, the nature of brain training intervention research tends to be taxing, time-consuming, and resource heavy, and tends to be associated with high attrition rates (Ballieux et al., 2016; Dean, 2019; Salkind, 2015; Schrieff-Elson et al., 2017).

It is thus suggested that future studies could benefit from adopting the Single Case Experimental Designs (SCED) to study the efficacy of CRT as it pertains to neuroHIV in SSA. The benefits of the SCED approach include in-depth rehabilitation sessions (30–45 min) with a limited number of participants (6-8) for prolonged periods of intervention. Their adoption could help mitigate high attrition rates often observed with pediatric intervention research, further improving the internal validity of neuroHIV rehabilitation studies.

Closely linked to the above, due to the limited number of participants required in SCEDs, the adoption of SCEDs could help address research design limitations within the rehabilitation literature by enabling the incorporation of *both* active and passive control groups in the same analysis in so doing, enabling the evaluation of the 'active ingredient' within the treatment arm (Evans et al. 2014; Krasny-Pacini & Evans 2018). Additionally, due to SCED's individualised and meta-cognitive nature, these designs have the added benefit of incorporating shorter intervention sessions (15 minutes), interspaced with longer sessions (30-45 mins), thereby allowing for regular follow-up of shorter periods (two weeks), juxtaposed with longer

follow-ups (four to eight weeks) (Evans et al. 2014; Krasny-Pacini & Evans 2018; Manolov & Moeyaert 2016) to evaluate the efficacy of neuro-rehabilitation protocols.

The reviewed further literature indicates that a limited number of studies report biological marker data, such as patient viral loads, before and after cognitive rehabilitation intervention. To this end, previous studies (*e.g.*, Benki-Nugent & Boivin, 2019) have found that (a) people living with HIV with CD4+ T-cell counts lower than 500 cells/μL are more likely to indicate HAND. Conversely, data suggests that (b) participants with lower viral loads and higher CD4+ T-cell counts may experience significant benefits from cognitive rehabilitation therapy (Brahmbhatt et al. 2017). It is therefore recommended that future studies conducting cognitive rehabilitation in the era of neuroHIV, report objective bio-marker data, such as viral load data, to complement neuropsychological measures indicating changes due to the cognitive rehabilitation. In line with the above observation, it is recommended that cognitive rehabilitation studies further supplement post-rehabilitation findings with objective brain imaging techniques such as functional near-infrared spectrometry (fNIRS), EEGs or other affordable neuroimaging markers to ascertain the efficacy of brain training protocols.

Lastly, several of the reviewed studies highlight the evolving nature of HIV/AIDS, especially the fact that the neuropsychological and neurobiological sequelae of HIV differ from population to population (Brahmbhatt et al., 2017; Bruce et al., 2018). Consequently, it is recommended that cognitive interventions implement context-specific population norms, paired with specific cognitive rehabilitation protocols, supplemented with specific objective biomarker evaluations (*e.g.*, fNIRS or CD4 viral load data). These context-specific norms could form the blueprint for cognitive rehabilitation studies regarding expected trajectories or outcomes related the implementation of cognitive rehabilitation protocols within the specific context of interest, for example, in SSA or other low to middle-income settings with a heavy burden of neuroHIV.

4.6 Acknowledgments

The author acknowledges the assistance of three research assistants (Ms. Kate Solomons, Ms. Tatenda Chivuku, and Ms Nike Mes) in cross-checking all studies included in the meta-analysis. All mentioned individuals have given permission to be named in the publication.

4.7 Conflict of Interest

There are no conflicts of interest to declare. Copyright permission for the use of all images, has been obtained from the appropriate publishing house.

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CHAPTER 5

Brain Plasticity and Adolescent HIV: A Randomised Controlled Trial Protocol Investigating Behavioural and Hemodynamic Responses in Attention Cognitive Rehabilitation Therapy

Reprinted with permission from Zondo, S, Cockcroft, K., & Ferreira-Correia, A. (2024). Brain plasticity and adolescent HIV: A randomised controlled trial protocol investigating behavioural and hemodynamic responses in attention cognitive rehabilitation therapy. *MethodsX*, *13*, 102808. https://doi.org/https://doi.org/10.1016/j.mex.2024.102808

Abstract: Despite advances in antiretroviral pharmacology, neuroHIV in the central nervous system (CNS), causes neuronal dysregulation, which is associated with compromised neurocognition. Non-pharmaceutical interventions such as HIV cognitive rehabilitation training (HIV-CRT), have shown potential to partially reverse cognitive deficits, sequent HIV neuroinvasion. Nonetheless, no studies exist pairing cognitive outcomes with objective neuroimaging biomarkers in adolescent HIV-CRT. This longitudinal pre-post-quasi-experimental protocol examined cognitive outcomes, paired with optimal neuroimaging outcomes following customised attention training in adolescent HIV. Twenty-six adolescents living with HIV were randomly assigned to either the treatment group, which received attention CRT using ACTIVATE^{TM}, (n=13), or to the treatment as usual group (n=13). Cognitive outcomes were examined using the NEPSY-II, and BRIEF; whilst neuroimaging outcomes were determined by changes in oxygenated hemoglobin (HbO), as determined by functional near-infrared spectrometry (fNIRS). Functional connectivity fNIRS measures were evaluated using seed-based correlation analysis, located in the central executive network (CEN). This study serves to guide the development and identification of objective biomarkers for adolescent neuroHIV, sequent CRT amongst children living with HIV in Sub-Saharan Africa.

Keywords, Brain Plasticity, neuroHIV, adolescent HIV, fNIRS, HbO, Central Executive Network.

5.1 Introduction

The Human Immunodeficiency Virus (HIV) has a detrimental effect on the body's immune and central nervous system (CNS). Markedly, with reference to the CNS, once HIV infiltrates the CNS, it is indicated to permeate the blood-brain barrier (BBB), and enter the cerebral cortex, where it leads to the differentiation of monocytes into macrophages, promptly resulting in pathogenetic neuroinflammation, (Morgello, 2018) which is associated with aberrant neuronal transmission (Brew, 2018), white matter loss (Jensen et al., 2019), neuronal apoptosis (Das et al., 2016), and catecholaminergic dysregulation (Nolan & Gaskill, 2019). Collectively, the cognitive and motors deficits associated with HIV neuroinvasion are referred to as HIV associated neurocognitive disorder (HAND), which is observed in both adult (Cody & Vance, 2016) and adolescent (Hoare et al., 2016) populations. Concerning adolescents, the focus of the current protocol, cognitive fallouts are characterized by deficits in working memory (Fraser & Cockcroft, 2020), attention (Rice et al., 2014), executive functions (Bugarski Ignjatovic et al., 2018), and response inhibition (Du Plessis et al., 2019).

Despite the development of highly active antiretroviral drugs (ARVs), HAND persists, namely due to the limited permeability of ARVs once in the CNS (Nightingale et al., 2023) and their associated neurotoxicity (Gonzalez et al., 2020). Given these limitations, there has been an urgent 'call to action' (Weber et al., 2013), for experimental studies, investigating the efficacy of non-pharmaceutical interventions, such as HIV cognitive rehabilitation (CRT)[17] to remediate cognition, sequent HIV neuroinvasion. With reference to adolescent HIV, there has been a steady rise of experimental studies, to remediate attention (Basterfield, & Zondo, 2022), working memory (Fraser & Cockcroft, 2020), and executive functions (Boivin et al., 2016). Notwithstanding these , no studies have paired behavioural outcomes sequent HIV-CRT, with

[17] The terms cognitive rehabilitation therapy and brain training are used interchangeably in the literature, and in the protocol.

objectives biomarker data, such as neuroimaging techniques, to investigate brain plasticity in adolescent neuroHIV, a major limitation of the current HIV-CRT literature (Benki-Nugent & Boivin, 2019; Musielak & Fine, 2016).

Due to the exorbitant costs associated with technologies such as fMRI and transcranial Doppler (TCD), (Boivin, 2013; Ogbole et al., 2018), there is a need for experimental studies, describing and implementing cheaper, portable technologies investigating brain outcomes in Sub-Saharan Africa contexts (Kwikima, 2024). With reference to neuroHIV, given the dearth of studies pairing behavioural and objective neuroimaging biomarkers, to investigate HIV-CRT, the present protocol details how functional near-infrared spectrometry (fNIRS) technology may be paired with behavioural measures from the NEPSY-II, to investigate attention training, in the context of adolescent HIV. The protocol further presents details of how seed-based correlation analysis can be pursued to investigate functional connectivity in this domain of study. The protocol, specifically details the use of fNIRS, specifically when paired to investigate oxygenated hemodynamic responses, in the central executive network (CEN), a critical cortical network, implicated in neuroHIV (Ipser et al., 2015; Wilmshurst et al., 2018).

5.2 Research questions

(1) Compared to controls, do HIV+ participants receiving attention brain training indicate improved cognitive outcomes on behavioural measures, at post intervention?

(2) Compared to controls, do HIV+ participants receiving attention brain training indicate greater functional connectivity in the CEN, post intervention, as indicated by seed-based functional connectivity analysis?

5.3 Methods

5.3.1 **Ethical approval**

The study was conducted in line with recommendations from the Declaration of Helsinki and received ethical approval from the Ethics Committee of the University of the Witwatersrand, South Africa [M211073].

5.3.2 Study sample and participant recruitment

Purposive sampling was used to recruit children living with HIV, residing at three shelters[18], caring for orphaned and abandoned children in South Africa. At study conception, G power analysis estimated using Fraser and Cockcroft (Fraser & Cockcroft, 2020) (n=63), indicated that to provide 80 % power, and detect a medium to high effect size (d = 0.649) at alpha 0.05, using independent samples analysis, a projected sample size of n = 42 was required (Experimental = 26; Control = 26) (GPower 3.1: Faul et al., 2007). Forty-three participants were initially recruited for the study (Experimental, n=22; Control, n=21), with 15 participants in the experimental and 15 participants in the control group, completing all pre-assessments. Sequent baseline assessment: one participant in the experimental group withdrew citing a lack of interest. Six participants in the control group dropped out, citing clashes of the study time with their school timetable (n = 2), a lack of interest (n = 2), no longer residing at the care shelter (n = 1), or illness (n = 1). At post brain-training and after all post-training assessments were obtained, data was deleted from a further three participants for the final analysis. Data deletions occurred either, due to low fNIRS signal data (n = 1), or corrupted imaging data due to internet loss (n = 2).

[18] The shelters (or Homes) were located in 'townships' located in Johannesburg and Makhanda, South Africa. Townships refer to dwellings previously designated for non-white residents during the apartheid era.

The final study sample consisted of 26 participants, 13 HIV+ participants in the brain training group and 13 HIV+ participants in the active control group. Participants constituted indigenous Africans, coloured and white participants, aged between 14 and 18 years of age (*M* = 17.28, *SD* =1.94). All participants were on a course of cART and were either attending primary or secondary schooling at the time of the study. Participants were excluded if they presented with (a) TBI, (b) CNS-related ailments (e.g., cerebral palsy, meningitis), or (c) learning difficulties. Written informed consent was obtained from the Directors of the shelters and, where possible, from guardians of the children. Assent was obtained from all participants aged 14 and older. Once assent and consent was determined, participants were randomly assigned to either the experimental or control group using the Research Randomizer Software (Urbaniak & Plous, 2013).

5.3.3 **Study protocol**

Experimental Design

The study took the form of a longitudinal pre-and-post-quasi-experimental design. This design enabled us to collect behavioural and fNIRS neuroimaging data, at pre- and post-treatment to allow for the investigation of the HIV-CRT, on outcomes measures, detailed below.

5.3.4 **Behavioural outcomes pre and post attention training**

Demographic questionnaire assessed participants' age, sex, level of education, general medical history, and medication.

A Developmental Neuropsychological Assessment: Second Edition (NEPSY-II) (Korkman et al., 2007), was administered to determine, near and far transfer gains, emanating from the attention training. The NEPSY is a standardized neuropsychological battery developed for children (3–16 years) that assesses cognitive function across six domains,

namely, executive function, and attention, memory and learning, language, visuospatial processing, and social perception (Korkman et al., 2007). The study used selected subtests from the NEPSY-II, as detailed in Table S1 (Supplementary).

Behaviour Rating Inventory for Executive Function (BRIEF): The school-age version of the BRIEF (6 to 18 years; 86 items) (Gioia et al., 2000), was administered to evaluate, behavioural and regulation outcomes emanating from the brain training. The behavioural regulation index (BRI), and metacognitive index (MI) were administered, respectively. Higher scores on the BRI and MI indicate behavioural and executive challenges.

5.3.5 **Imaging Outcomes Pre and Post Brain Training**

Neuroimaging data was collected using fNIRS optical neuroimaging techniques. We specifically designed an fNIRS-Stroop Colour Word Test (SCWT), adapted from Schroeter et al. (2002). Participants completed a computerised version of the SCWT at pre - and post-assessment. The SCWT was built using PsychoPy (Peirce & MacAskill, 2018). Before completing the computerised version of the SCWT, participants completed a pencil and paper version of the SCWT and received feedback on their performance (Supplementary Material Table S2). The SCWT took the form of an fNIRS block design as opposed to the event related design. The former has been indicated to show stronger statistical power and elucidate greater hemodynamic responses.

In the classical SCWT, a color word, such as blue, is written in an ink colour, which may or may not be the same as the colour word. First, the participant must name the colour of the word while ignoring the actual word. Then, the participant must read the word and ignore the colour (Stroop, 1935). The Stroop interference effect occurs when reading the word interferes with naming the colour (incongruent condition). Generally, the interference effect requires greater attentional capacity. Responses on the incongruent task have been associated

with slower responses, less accuracy, and greater cortical activation in the central executive network (Schroeter et al., 2002, 2004).

For the SCWT, participants answered the following question: “Does the colour ink of the top word match the meaning of the bottom word?”. As indicated in Figure 5.1, two conditions were implemented to answer this question, namely, Condition 1, which was a Congruent Block (the colour of the top word was the same as the meaning of the bottom word), and Condition 2, which was an Incongruent Block (colour of the top word differed from the meaning of the bottom word).

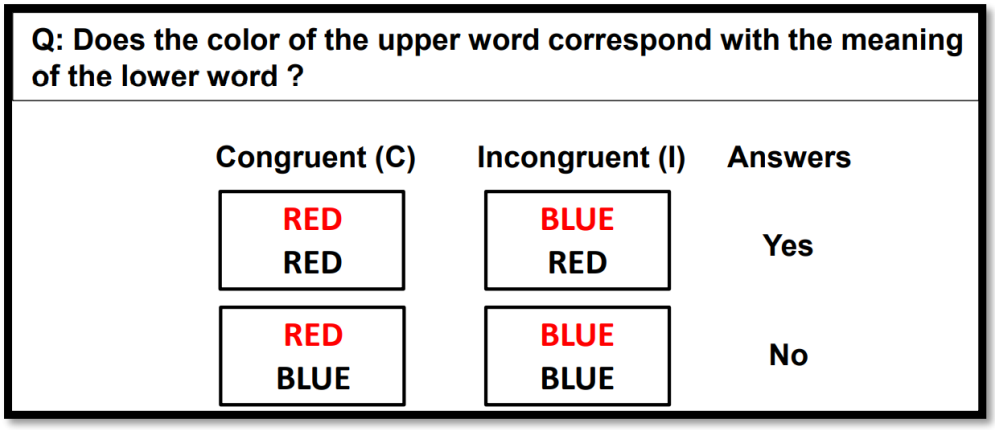


Figure 5.1. The Stroop Colour Word Test (SCWT). Adapted from Schroeter et al. (2002).

As indicated in Figure 5.2, blocks (Congruent, Incongruent) were randomly assigned, with each block presented for 10 seconds, interspaced with 15 seconds of rest, where participants had to stare at a ‘+’ sign before responding to the block condition. Each block condition was presented five times for a maximum of ten blocks, during which participants were required to press *q* on the computer keyboard in response to congruent stimuli and *p* in response to incongruent stimuli. All event markers (triggers) were programmed on PsychoPy and sent to the Aurora Acquisition Software (NIRx, Medical Technologies, LLC, Berlin, Germany), via lab streaming layer (LSL).

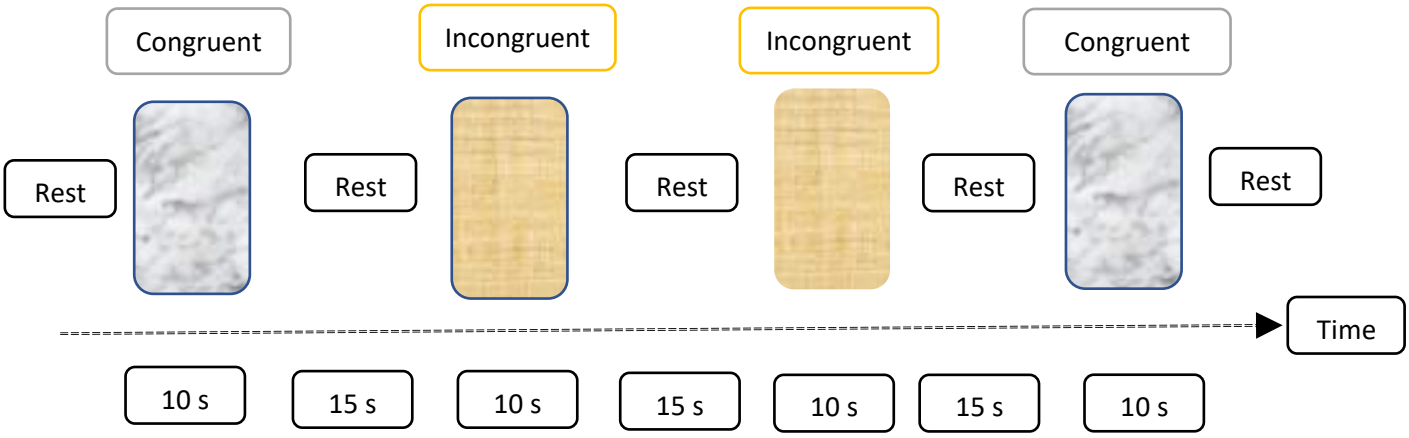


Figure 5.2. Stroop Colour Word Test: In total, 10 blocks (five congruent and five incongruent) lasting ten seconds each were interspaced with 15 seconds of rest.

5.3.6 **Functional Near-Infrared Spectrometry**

Data acquisition and montage

We measured cerebral activity based on concentration changes in oxygenated (HbO) and deoxygenated hemoglobin (Hb). Data were collected using the NIRxSport2 (NIRx, Medical Technologies, LLC, Berlin, Germany), a portable continuous wave fNIRS device, while participants completed the SCWT. As indicated in Figure 5.3, we used eight LED emitters (sources), paired with seven photodiode detectors, covering the prefrontal cortex. The optodes were placed according to the 10-20 system (Jasper, 1958), using a standardized prefrontal fNIRS Headband (EasyCap, NIRx, Medical Technologies, LLC, Berlin, Germany).

Probe placement (sources and detectors) to identify the most sensitive placement for each optode location was determined using the 'fNIRS Optodes Location Decider' (fOLD) software (Zimeo Morais et al., 2018) (Figure 5.4). These locations were paired with relevant Montreal Neurological Institute (MNI), coordinates (Table 5.1). Please note that the optode placement, and reporting of MNI coordinates used in the current protocol differ from our feasibility study (Zondo et al., 2024). Importantly, placement of sources and detectors corresponded with cortical regions implicated in attention, and working memory within the

central executive network (CEN), inclusive of the frontopolar, orbitofrontal, and dorsolateral prefrontal cortices (Esterman & Rothlein, 2019; Rosenberg et al., 2016; Sarter et al., 2001). In total, signals were captured from twenty-two channels covering the prefrontal cortex. The distance between sources and detectors was set at 2.5 cm, following guidelines for data acquisition with paediatric and adolescent samples (Pinti et al., 2019). Data were recorded at a sampling frequency rate of 10.2 Hz, based on two wavelengths, 760 and 850 nm.

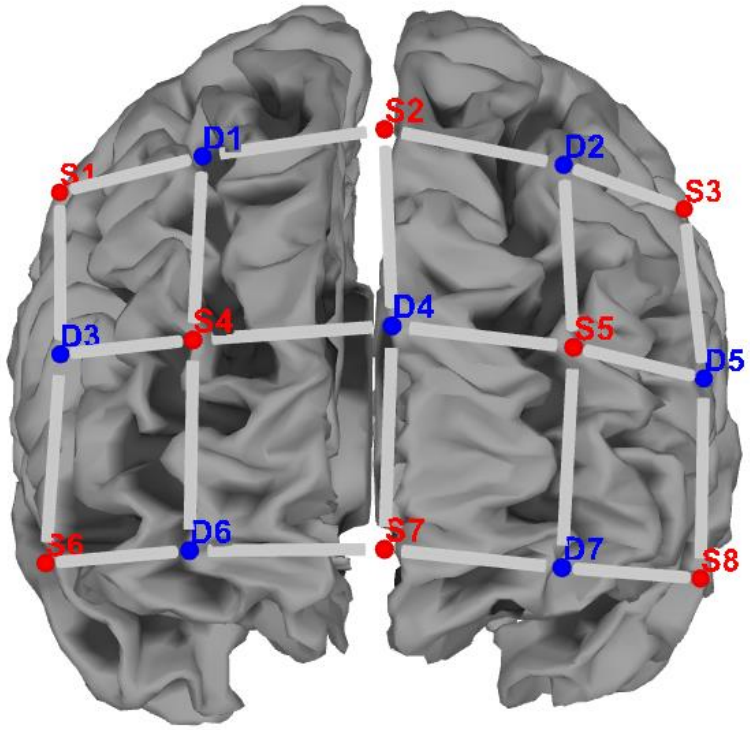


Figure 5.3. Optode placement montage. Regions of interest were concentrated on regions in the CEN. Optode placements followed the 10-20 system. Red = sources. Blue = detectors.

fOLD

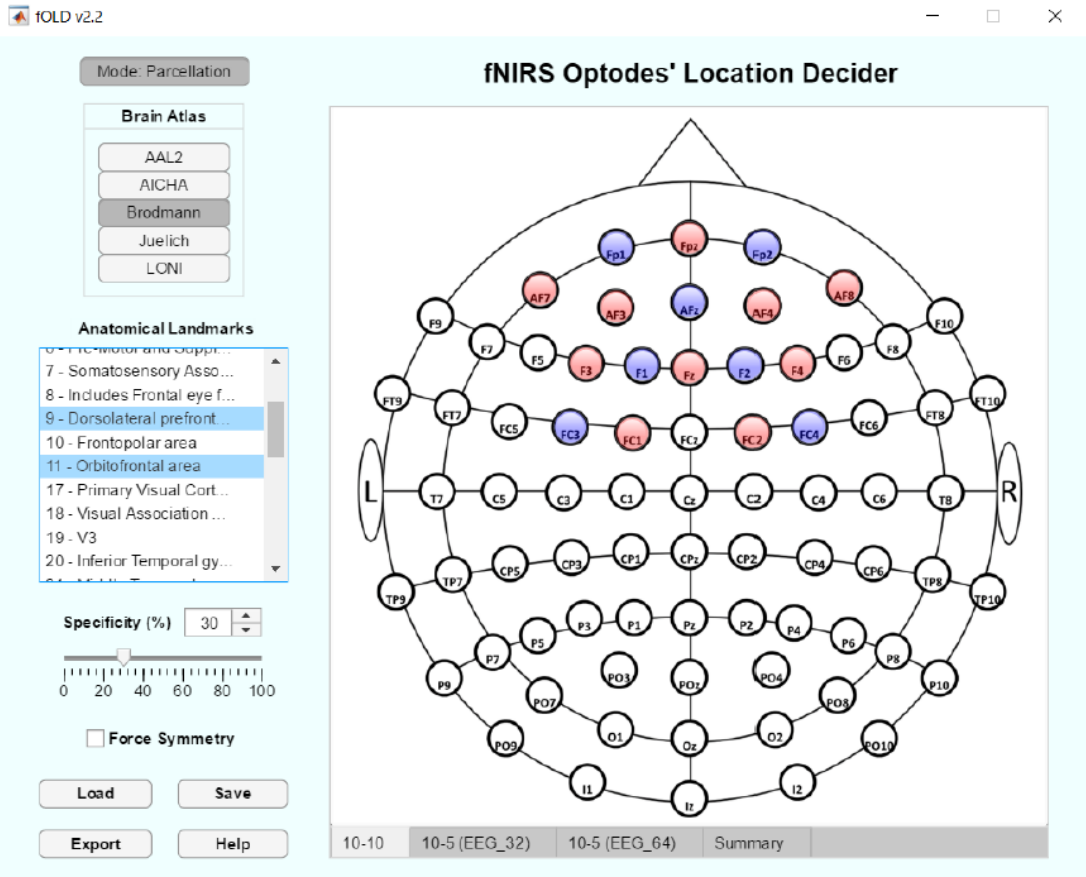


Figure 5.4. Screen shot of the fOLD software. The software enabled the location for optode placement for regions within the central executive network (DLPFC, Orbitofrontal).

Table 5.1. fNIRS Optodes and corresponding brain regions

Channel	Optode name	MNI Position			BA	Anatomical Location (Specificity %)
		x	***y***	***z***		
CH 1	S1- D1	30	40	41	9	Right dorsolateral prefrontal cortex (69)
					46	Right dorsolateral prefrontal cortex (22)
CH 2	S1 - D3	46	38	24	45	Right pars triangularis Broca's Area (71)
					46	Right dorsolateral prefrontal cortex (24)
CH 3	S2- D1	10	41	50	9	Right dorsolateral prefrontal cortex (68)
					8	Right includes frontal eye fields (29)
CH 4	S2 - D2	-9	41	50	9	Left dorsolateral prefrontal cortex (63)
					8	Left includes frontal eye fields (35)
CH 5	S2 - D4	2	50	39	9	Medial dorsolateral prefrontal cortex (62)
					10	Medial Frontopolar Area (20)
CH 6	S3 - D2	-31	39	41	9	Left dorsolateral prefrontal cortex (67)
					46	Left dorsolateral prefrontal cortex (25)
CH 7	S3 - D5	-46	39	26	45	Left pars triangularis Broca's Area (73)
					46	Left dorsolateral prefrontal cortex (22)
CH 8	S4 - D3	40	50	16	46	Right dorsolateral prefrontal cortex (47)
					45	Right pars triangularis Broca's Area (30)
					10	Right frontopolar area (19)
CH 9	S4 - D4	13	61	24	10	Right frontopolar area (72)
					11	Right orbitofrontal area (17)
CH 10	S4 - D6	22	52	33	9	Right dorsolateral prefrontal cortex (51)
					46	Right dorsolateral prefrontal cortex (26)
CH 11	S6 - D5	-39	50	17	46	Left dorsolateral prefrontal cortex (49)
					45	Left pars triangularis Broca's area (32)
CH 12	S5 - D4	-12	62	23	10	Left frontopolar area (76)
					9	Left dorsolateral prefrontal cortex (15)
CH 13	S5 - D7	-24	63	9	10	Left frontopolar Area (70)
					11	Left orbitofrontal area (20)
					46	Left dorsolateral (9)
CH 14	S6 - D3	48	46	5	45	Right pars triangularis Broca's Area (44)
					46	Right dorsolateral prefrontal cortex (43)
CH 15	S6 - D6	25	63	9	10	Right frontopolar area (69)
					11	Right orbitofrontal area (22)
CH 16	S7 - D4	1	64	14	10	Medial frontopolar area (88)
CH 17	S7 - D6	13	67	0	10	Right frontopolar area (53)
					11	Right orbitofrontal area (45)
CH 18	S7 - D7	-12	67	0	10	Left Frontopolar area (54)
					11	Left orbitofrontal area (45)
CH 19	S8 - D5	-47	46	6	45	Left pars triangularis Broca's area (49)
					46	Left dorsolateral prefrontal cortex (43)
CH 20	S8 - D7	-23	62	23	9	Left dorsolateral prefrontal cortex (48)
					46	Left dorsolateral prefrontal cortex (32)
					10	Left Frontopolar Area (17)

5.3.7 **Imaging Procedures**

All participants were tested individually in a quiet room, fitted with a desk, computer, and chair, at the children's shelter. Upon arrival, participants were first seated at a desk equipped with a computer (screen diameter: 22 centimetres; height: 33.2 centimetres) and were requested to verify their demographic data, collected during study recruitment. Participants then read and signed the Study Information Sheet and completed the fNIRS protocol as detailed below.

fNIRS Protocol

Step 1 Placement of Optodes by Fiducial Points

- Detection optodes (Table 5.1), were placed 25-30 mm, above the midpoint of the eyebrow of participants, in accordance with the 10-20 electrode system.

- To ensure consistency of optode placement, a red marker was used to indicate positions, 'Fpz', 'Oz', (Figure 5.5), 'T3', and 'T4' (Figure 5.6). The establishment of these fiducial positions helped establish cap placement, for each participant.

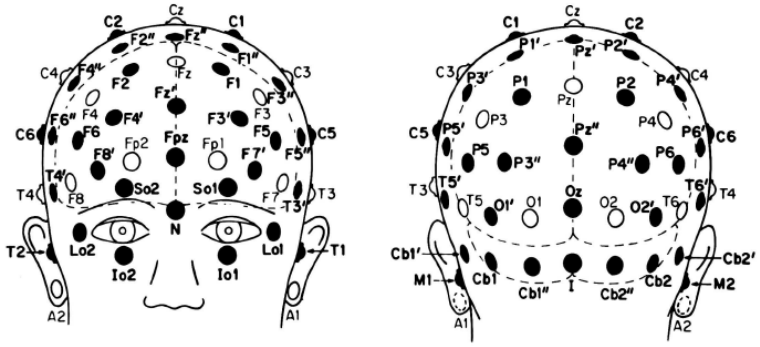


Figure 5.5. The auxiliary markers, 'Fpz' and 'Oz', were identified by a red marker, to ensure correct optode placement. Markers were identified using the 10/20 system (Chatrian et al., 1985).

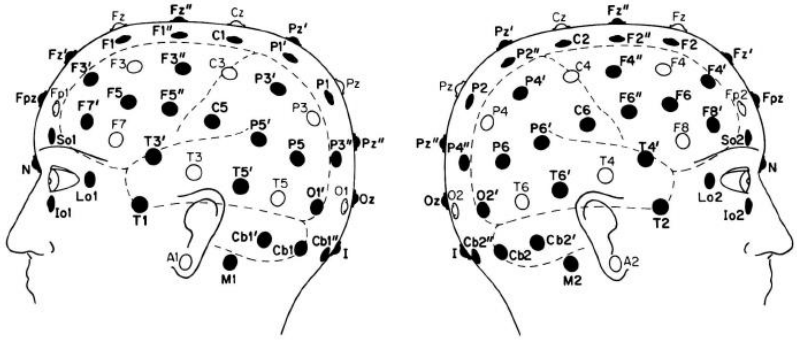


Figure 5.6. The auxiliary markers, 'T3' and 'T4', were identified by a red marker, to ensure correct optode placement. Markers were identified using the 10/20 system (Chatrian et al., 1985).

Step 2 Placement of fNIRS Cap

- Once fiducial points were established, participants were fitted the fNIRS cap (see Figure 5.7), tightly fixed with a dark shower overlay.
- To prevent external light affecting the fNIRS signal, room lights were deemed or turned off.
- fNIRS recording then commenced using Aurora Data Acquisition Software (NIRx, Germany), as indicated in Steps 3 to Step 11.

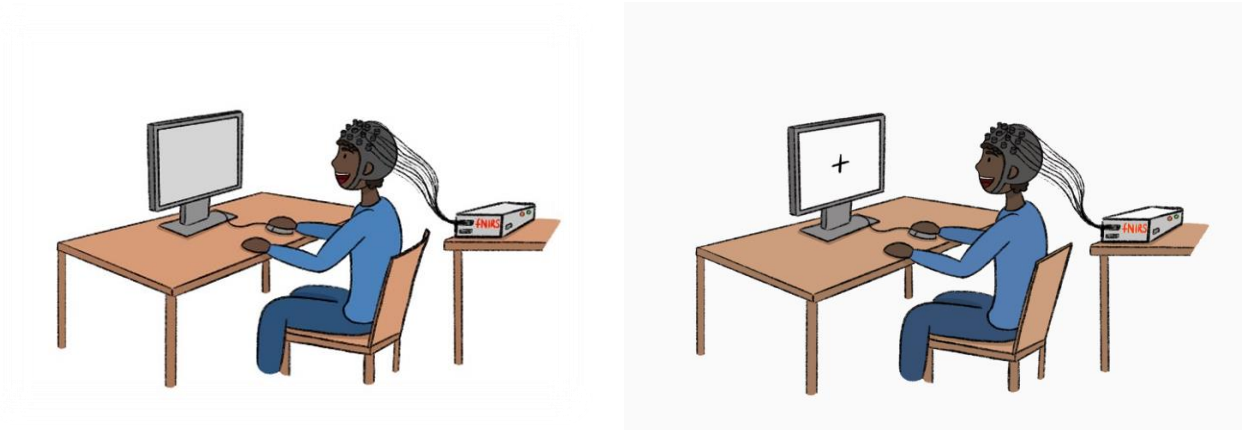


Figure 5.7. Participant with fNIRS cap in seating position the completing the SCWT. Copyright: Laura Bell & Sizwe Zondo

Step 3: Aurora fNIRS Data Acquisition

- Open the Aurora Software and go to Configurations (blue arrow) (Figure 5.8).
- Choose the Headband 8 X 8 montage (orange arrow). The configuration for the Headband_8 X 8 headband, is inbuilt within Aurora, and should reflect eight sources, and eight detectors, as indicated in the bottom righthand of the caption.
- Please note the above configuration can be used with seven detectors as indicated in the 'Configuration details', in Figure 5.8.

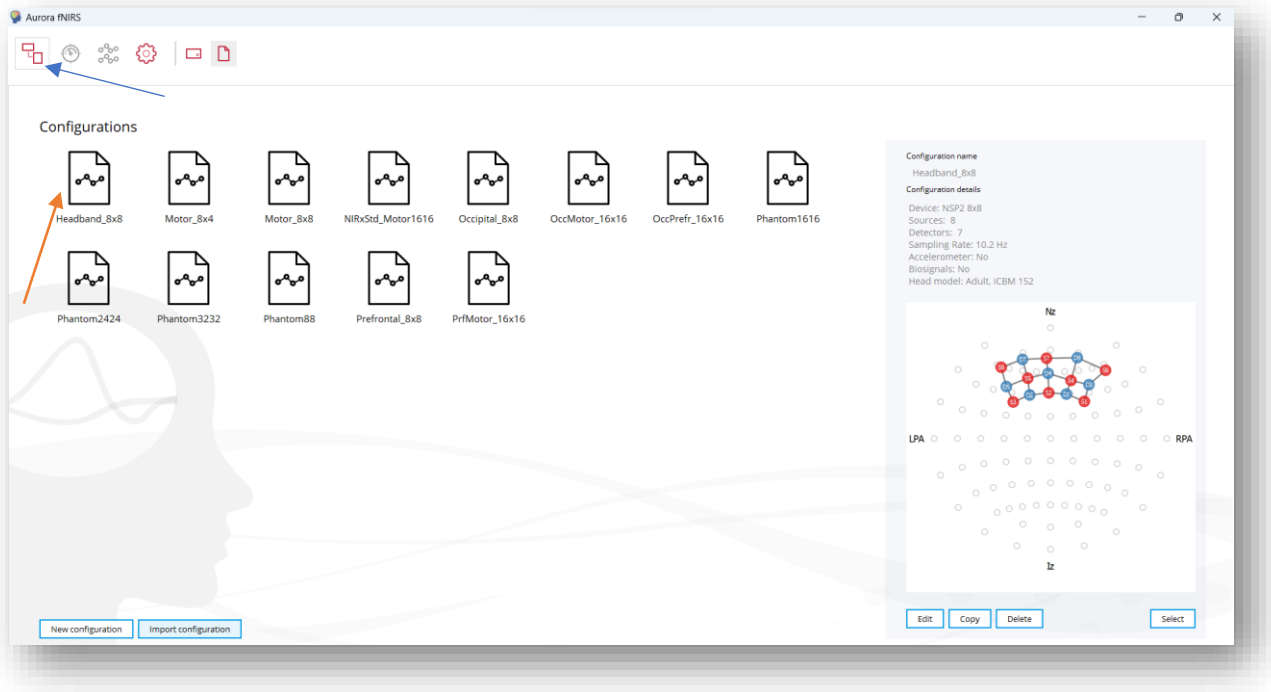


Figure 5.8. The Aurora montage used for the study protocol.

Step 4: Connect Aurora Acquisition Software to NIRxSport2

- Insert Wi-Fi password which can be found on the NIRXSport2 (if conducting research in places with limited internet, it is recommended you choose Option 2 below).
- Connect Aurora to the NIRxSport2 using a cable linked to your laptop (Option 2; Figure 5.9).

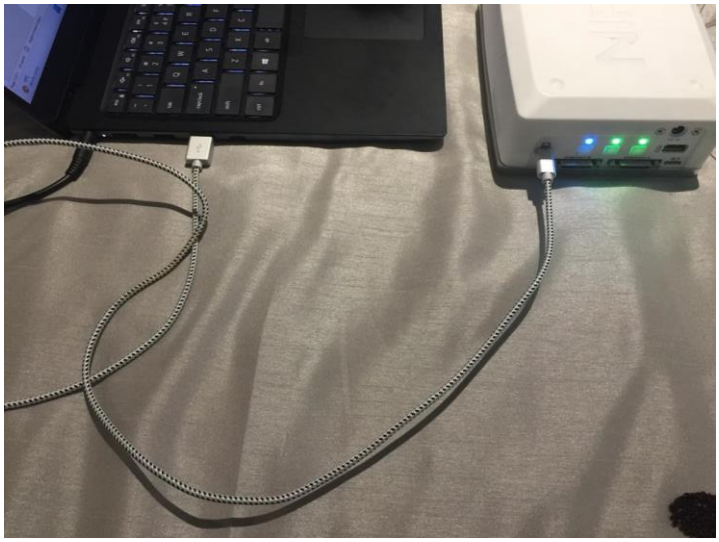


Figure 5.9. Cable Link of Aurora to the NIRxSport2.

Step 5: Connect Aurora to NIRxSport2

➢ The below caption indicates a successful connection between Aurora and the NIRxSport2 fNIRS device.

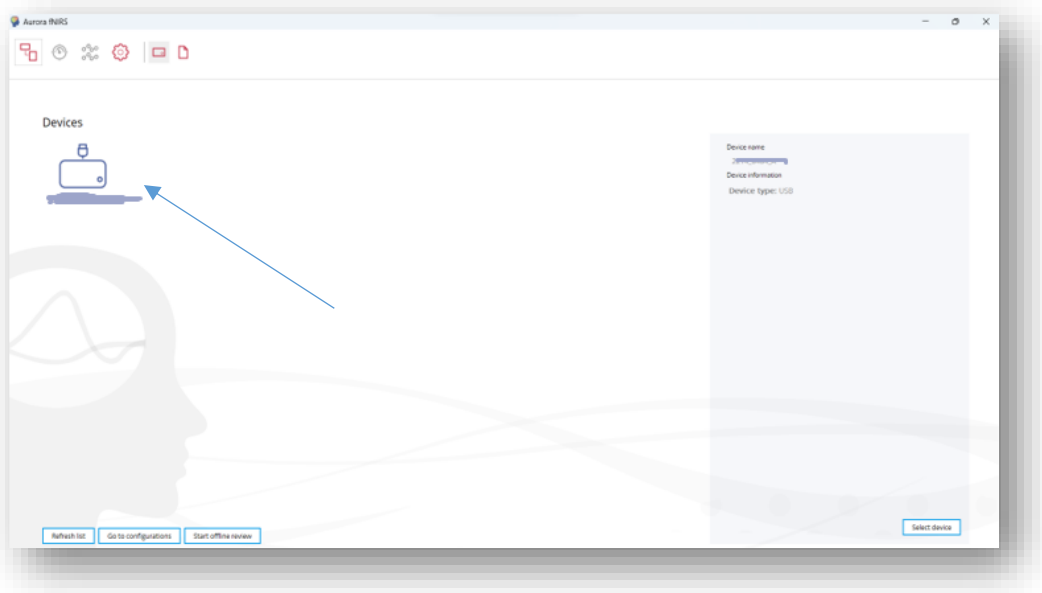


Figure 5.10. An example of a successful linkage.

Step 6: Sources and Detector on NIRxSport2

- Detectors (8) are marked in blue and must be fitted on the left side of the NIRxSport2 fNIRS device (Figure 5.11)

- Sources (8) are marked in red and must be fitted on the right side of the NIRxSport2 fNIRS device.

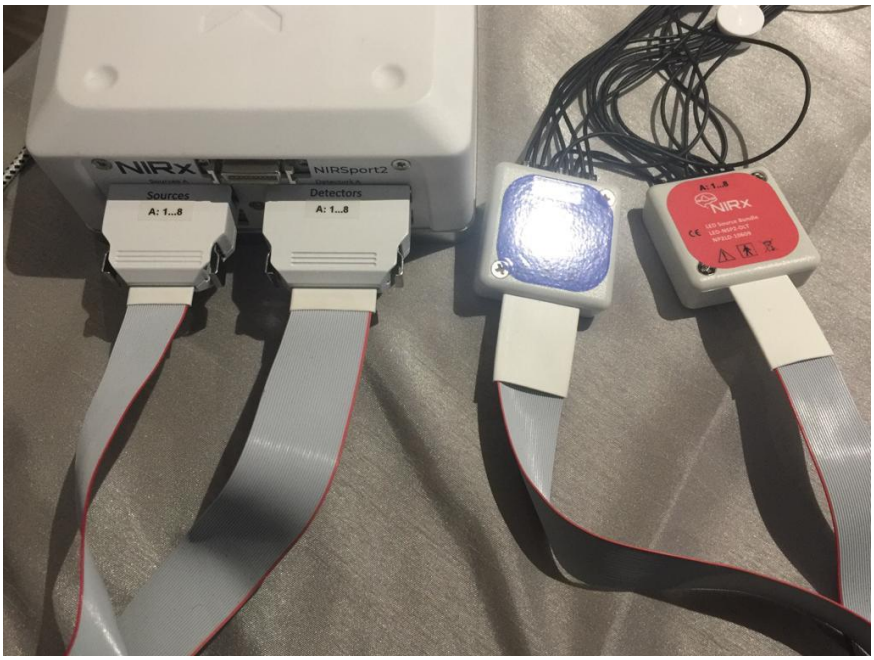


Figure 5.11. NIRxSport2 correct source (red) and detector (blue) placement.

Step 7: Aurora Signal Optimization

- Run signal optimizations until 'excellent' green signals are obtained to ensure no signal saturation.

- To limit saturation, dim all lights in the experimental room, and ensure that a headcap (overlay) is worn over the optodes.

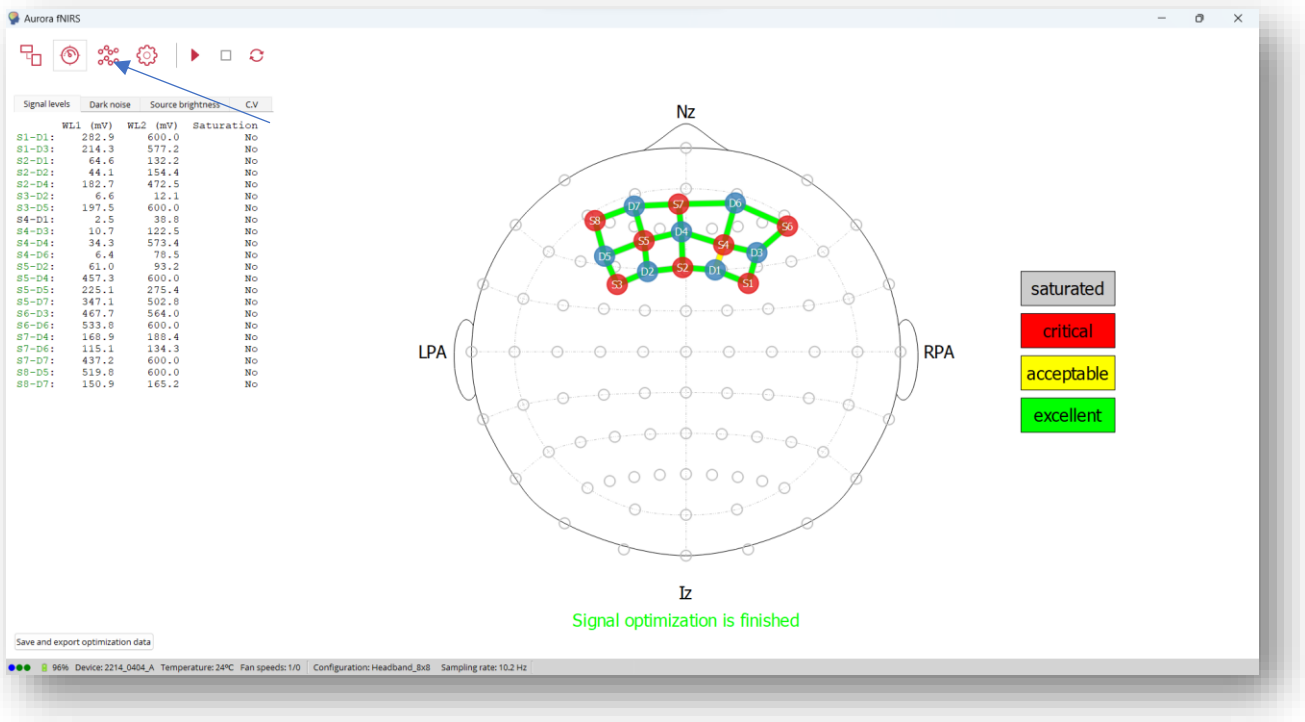


Figure 5.12. Screen shot of Aurora signal optimization.

Step 8: Connect PsychoPy SCWT to NIRxSport2

➢ The SCWT (created on PsychoPy), must now be connected to Aurora, using Lab Stream Layering (LSL) as requested by the below PsychoPy caption.

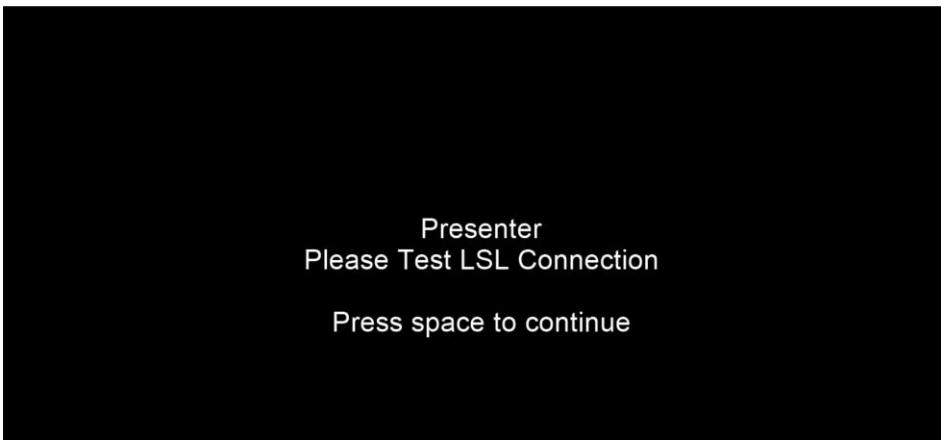


Figure 5.13. An example of an LSL connection request on PsychoPy.

Step 9: Enabling LSL on PsychoPy for the fNIRS SCWT

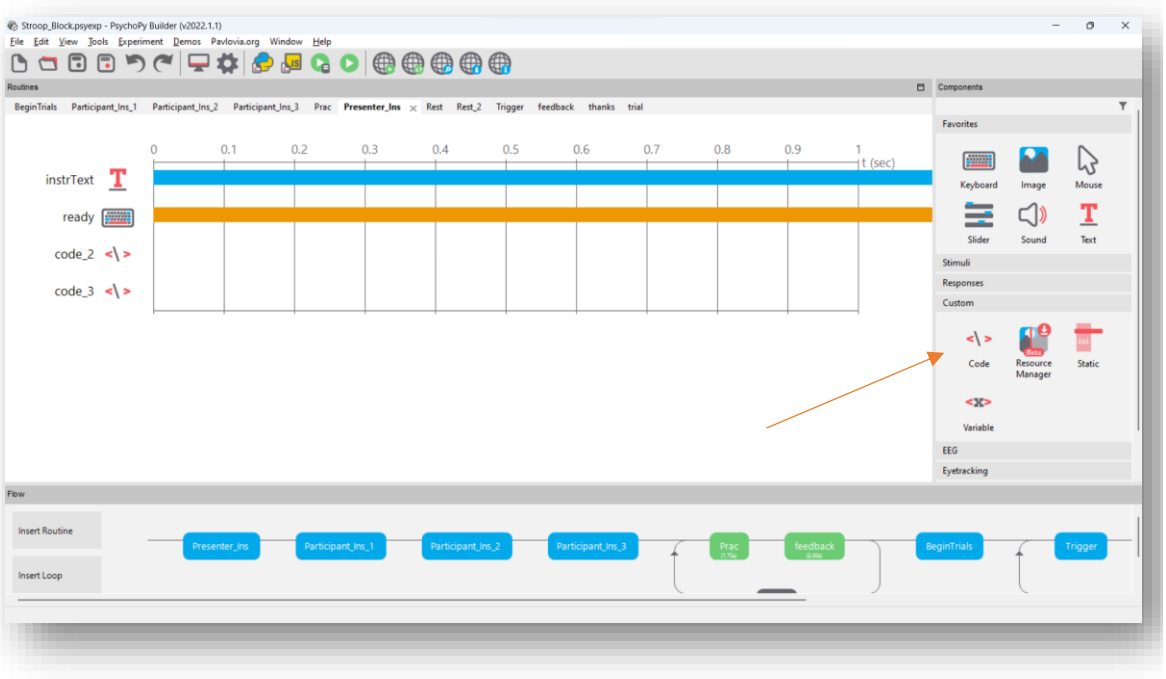


Figure 5.14. Code optimization on PsychoPy for the SCWT

➢ Under the *Custom Tab* (yellow arrow), insert the below code, within the *Begin Experiment* tab when prompted.

```
from pylsl import StreamInfo, StreamOutlet # import required classes
info = StreamInfo(name='Trigger', type='Markers', channel_count=1, channel_format='int32', source_id='Example') # sets variables for object info
outlet = StreamOutlet(info) # initialize stream.
outlet.push_sample(x=[marker]) outlet.push_sample(x=[congruent])
```

Step 10: Commence recording of fNIRS signal

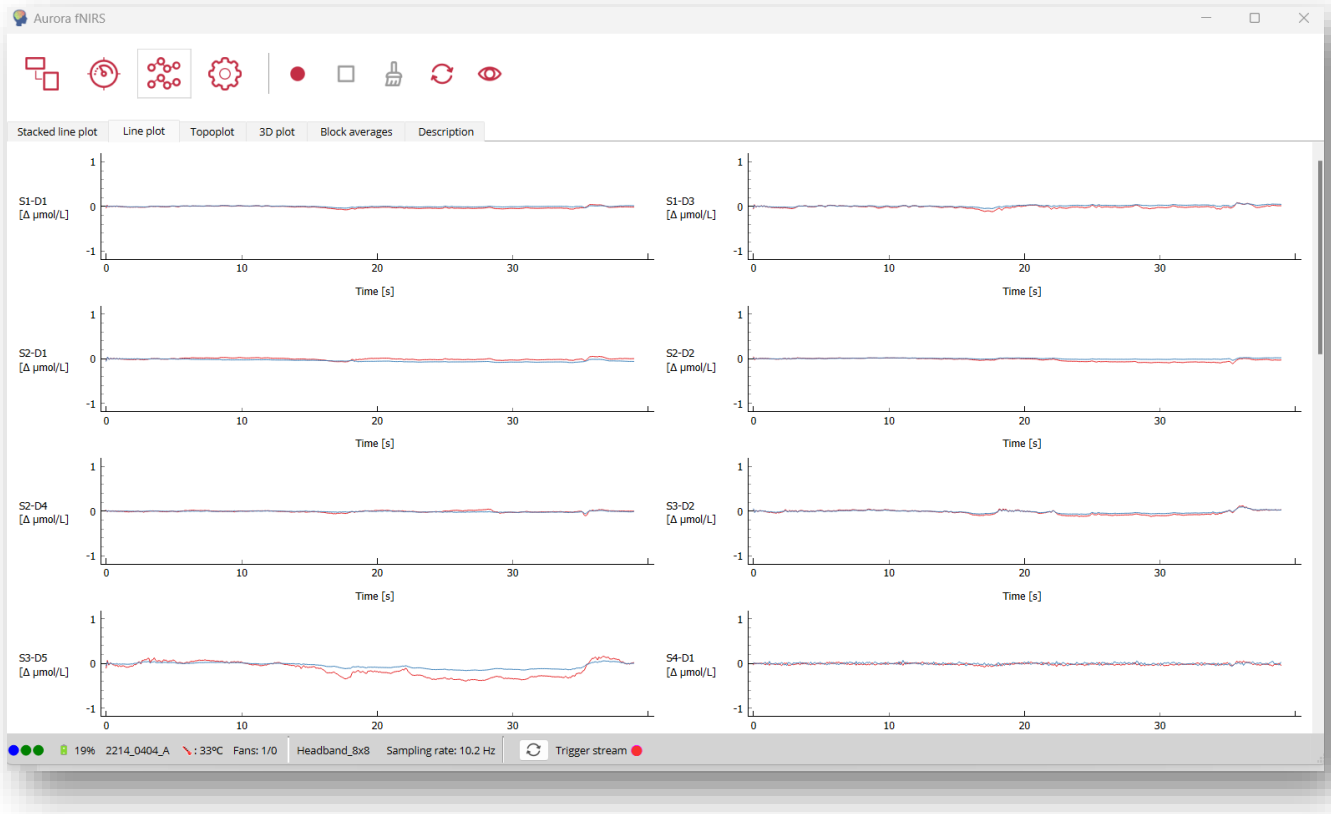


Figure 5.15. Screen shot of an fNIRS signal recording (line plot) on Aurora

5.3.8 **Data File and Data Pre-processing**

Once fNIRS data was collected, the analysis of changes in hemodynamic responses, was executed on Satori fNIRS (Lührs & Goebel, 2017) using oxygenated hemoglobin data (HbO). Supplementary Figure S1 provides an example of a Satori fNIRS analysis file, indicating the channels, and properties of the nirs file used for the analysis. The pre-processing steps are detailed in Figure S2. Channel rejections were applied using the Scalp Coupling Index (SCI) = 0.75 (Pollonini et al., 2014). Motion artefacts, including head movement, were corrected by applying spike removal parameters based on monotonic interpolations (van Brakel, 2014). Spike removal corrections were followed by temporal derivative distribution repair (TDDR) to remove baseline shifts and spike artefacts in the data (Fishburn et al., 2019). Low-frequency band-pass filtering was applied to eliminate baseline drift on the data. Physiological fluctuations related to blood pressure fluctuations (1~1.5Hz) and respiration

(0.2~0.5Hz) were removed using low-pass (LP) and high-pass Butterworth filtering method. Summarily, the LP filter (0.1-0.2 Hz) enabled further removal of high-frequency noise within the data that was not accounted for by brain activity (Huppert et al., 2009). The high pass filter (0.01 Hz) was applied to attenuate low-frequency signals by removing baseline drift that may have affected the hemodynamic signal. Once data was pre-processed, changes in light intensity were converted into concentration changes in HbO, using the Modified Beer-Lambert Law (MBLL).

5.4 Intervention

HIV-CRT attention training was conducted using ACTIVATE^{TM} (Wexler et al., 2021b). The computerized brain training program consists of six brain training exercises focusing on sustained attention, working memory, inhibitory control, and cognitive flexibility. The program was installed on computers at the children's shelters, and participants completed the cognitive tasks during after school hours. The cognitive tasks included various attention exercises such as memorizing sequences of stimuli presentations, completing pattern designs, task-switching, and categorizing objects. All training activities were implemented to enhance 'top-down cognitive processes', which foster cognitive control, and maintaining vigilance, thus enhancing task readiness and attention skills (Wexler et al., 2021a). The program automatically scheduled cognitive tasks based on varying levels of complexity levels, with every new level of difficulty, dynamically customised for each individual participant based on feedback mechanisms incorporated within ACTIVATE^{TM} (Wexler et al., 2021a). In total, participants underwent three cognitive training sessions weekly for a period of 25-30 sessions. Each session lasted approximately 30 minutes, and the intervention was carried out over a 12-week period, spanning six months. Additional information about ACTIVATE^{TM} can be found on the C8 sciences website (http://www.c8sciences.com/about/games/).

5.5 Statistical Analysis

Statistical analysis was performed using JASP (Version 0.18). Pre and post differences on cognitive and fNIRS performance were calculated to compare estimated mean differences between the groups. Planned comparison differences were executed by controlling for pretest scores and group interaction, using analysis of covariance (ANCOVA). All assumptions, including independence of the covariate (*pretest scores*), and homogeneity of regression slopes were undertaken for the analysis. Further statistical imputations were conducted to investigate fNIRS seed-based correlation functional connectivity as detailed below.

5.5.1 Seed-based correlation functional connectivity (FC) analysis

Seed-based correlation FC was executed within Satori fNIRS. Based on priori evidence, we selected the left dorsolateral prefrontal cortex (L-DLPFC), as the seed region for the cross-correlation. The L-DLPFC is pliable to neuronal plasticity, following HIV brain training (Chang et al., 2017), and following deep brain stimulation, to improve HIV neurocognition (Ownby & Acevedo, 2016; Ownby & Kim, 2021). With reference to our study, this seed represented Channel 6 (Seed S3-D2), with MNI coordinates, x = - 31, y = 39, z = 41 (Table 1). This seed indicated a specificity index of 92%, as determined by fOLD. Seed-based correlation FC analyses were performed by computing the temporal correlations between the seed (S3-D2), and *each of the channels* indicated in Table 1, for all participants. Once correlations were computed, these were transposed to create an average correlation, for each of the channels (See Supplementary Figure S3 for an example).

Similar to (Ji et al., 2020), to increase the normality of the distribution of the individual correlation values, Fisher's r-to-z transformations, were applied to each correlation coefficient. Summarily, Fisher's transformed bivariate correlation coefficients, were calculated between the seed hemodynamic time series, and each of the individual channel time series (Silver &

Dunlap, 1987), which enabled Fisher's r-to-z normalizations, to be transformed to correlation maps (r). These maps were generated on Satori, at the individual and group level. The above transformation enabled planned comparisons between the groups to be computed controlling for pretest scores (average correlations), and group interaction, using Analysis of Covariance (ANCOVAs).

5.5.2 **Hemispheric Interaction and Threshold Survival**

Since average correlations were derived as described above, we were able to derive data to compare the average hemodynamic response effect, between the left and right hemisphere, (HbO), between the groups (please see Supplementary Figure S4 for an example). To further explore FC, and to identify regions (channels), with the greatest connectivity with the seed region (S3-D2), at post training, (in the treatment group), we computed threshold 'survival' analysis. This additional analysis enabled us to examine the percentage of 'surviving' channels in each hemisphere, with increased correlation thresholding. Surviving channels / voxels would be indicative of the strongest correlations with the priori seed. Importantly, there is a lack of consensus on optimal threshold parameters for functional connectivity analysis. Garrison et al (Garrison et al., 2015), for example, applied threshold surviving parameters based on increments ranging from 5% to 95%, while, Jia et al (Jia et al., 2023) employed increments of 20% to 70% to study link density survival edges in adult HIV brain training. Our study employed threshold increments of $r = 0.2$ to $r = 0.8$, investigate 'surviving' channels with the largest correlation to the seed (S3-D2).

5.6 Discussion

South Africa, where the protocol was implemented, has the highest rates of HIV infection in pediatric and adolescent populations (UNAIDS, 2019). The protocol answers an urgent 'call to action' (Weber et al., 2013) for the implementation of longitudinal studies to investigate non-

pharmaceutical measures to reverse cognitive decline in neuroHIV, especially in African populations. By undertaking the study, and pairing behavioural gains (or lack thereof), emanating from the brain training, with neuroimaging data, the study provides invaluable insights into the nature of neuroplasticity and adolescent neuroHIV. Importantly, the protocol addresses a social justice issue, to apportion mental health services to the least served regions, in South Africa, including 'townships', and rural areas (Lund et al., 2012).

Notwithstanding the above, it is important to note that the execution of neuroimaging research in African contexts, is attendant to logistical challenges. For example, execution of neuroimaging commands, particularly Lab-Streaming Layer (LSL) requires constant electricity, and internet connectivity, which may be in short supply in our context. Moreover, due to the nature of the population (children living with HIV), copious levels of clinical research are undertaken with the population which may lead to participants experiencing research fatigue, resulting in increased attrition rates, as experienced in our study. We thus recommend future researchers adapting the present protocol, to consider pursuing Single Case Experimental Designs (SCED), were possible.

5.7 Study Progress

The data collection for the study has since been completed, and data analysis is underway. Given ongoing analysis, no research outputs exist from the protocol. This protocol study has a distinct scientific contribution in detailing the step-by-step fNIRS neuroimaging procedures and the behavioural assessments used to investigate neuroHIV cognition in adolescent populations, especially in the domain of attention. As the first study detailing the joint investigation of hemodynamic responses paired with behavioural changes, to investigate HIV-CRT, in the context of adolescent HIV, the study contributes to uncovering potential biomarkers for the cognitive rehabilitation of adolescent neuroHIV, in Sub-Saharan Africa.

5.7.1 **Protocol validation**

Data analysis for the protocol is currently underway. An example of a JASP data file for the analysis can be found under the Supplementary section. The data analysis includes ANCOVA and mixed methods models.

5.8 Limitations

For successful replication of the above study, it is important that optodes are correctly placed, using the details provided in the protocol. Moreover, it is advised that children practise the pencil and paper Colour Stroop Word Test (Table S2), before completing the fNIRS-SCWT. Lastly, it is advised that, to minimize ambient light affecting the optodes, the experimental room setting should be dimly lit, and a black cap should be placed over the optodes.

5.9 Acknowledgments

The authors would like to thank the Directors of the children's shelters, the children, and their guardians for participating in the study. The authors also thank Dr Armin Heinecke, at NIRx, Germany, for his assistance with the Satori fNIRS data protocols that will be used in the data analysis stage. The corresponding acknowledges the Centre for Africa Studies, at Harvard University, and Professor Leah Somerville at the Affective Neuroscience & Development Lab, (Harvard University), for hosting the corresponding during his Fellowship at Harvard University. This work was supported by funding from the South African National Research Foundation, [grant number TTK200408511634]; the Rhodes University Research Grant [grant number PGSD05/2022]

5.10 Conflict of Interest

There are no conflicts of interest to declare. Copyright permission for the use of all images, has been obtained from the appropriate publishing house.

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CHAPTER 6

A Feasibility Study on the Efficacy of Functional Near-Infrared Spectrometry (fNIRS) to Measure Prefrontal Activation in Pediatric HIV

Reprinted with permission from Zondo S, Ferreira, Correia A, Cockcroft, A. (2024). A feasibility study on the efficacy of Functional Near-Infrared Spectrometry (fNIRS) to measure prefrontal activation in Pediatric HIV. Journal of Sensors, vol. 2024, Article ID 4970794, 14 pages, 2024. https://doi.org/10.1155/2024/4970794

Abstract: HIV infection is associated with disturbed neurotransmission and aberrant cortical networks. Although advances in the imaging of brain microarchitecture following neuroHIV has added to our knowledge of structural and functional changes associated with HIV, no data exists on paediatric HIV using optical neuroimaging techniques. This study investigated the feasibility of optical neuroimaging in paediatric HIV using functional near-infrared spectrometry (fNIRS). We measured prefrontal brain activation while participants executed a sustained attention task. We specifically tested whether patients living with HIV and study controls could perform the study protocol and whether we could measure the typical fNIRS hemodynamic response associated with neuronal activity. Eighteen participants (10 HIV participants, mean age: 13.9, *SD* =1.66 years; 8 controls, mean age: 14.8, *SD* =1.28 years), matched for sex, Grade, and socioeconomic status, were included in the study. All participants completed the Stroop Colour Word Test (SCWT). Oxygenated hemoglobin concentration (HbO) and the deoxygenated hemoglobin (deoxy-Hb) signal were recorded from the dorsolateral prefrontal cortex (DLPFC) and the frontopolar area (FA) using fNIRS. The control group performed significantly better in terms of reaction time, on the congruent and incongruent condition (congruent: t (16) = −3.36, $p < 0.05$: incongruent: $p < 0.05$). A pooled group analysis of the sample indicated significant activation in the DLPFC and FA to the congruent condition of the SCWT ($p < 0.05$). Although there was noted cortical activation in

the DLPFC and the FA in each of the groups when analysed independently, this neural activation did not reach statistical significance. The results show promise that fNIRS techniques are feasible for assessing prefrontal cortical activity in paediatric HIV. Future studies should seek to reduce the signal to noise ratio and consider inter-individual variability when measuring prefrontal activation in paediatric samples.

Keywords: pediatric HIV, Stroop, fNIRS, hemodynamic response, dorsolateral prefrontal.

6.1 Background

The Human immunodeficiency virus (HIV) continues to be a significant global pandemic, despite medical advances, such as haematopoietic stem cell transplantation (Gupta et al. 2019; Gupta et al., 2020) and 'shock and kill' gene transcription strategies (Chandrasekar & Badley 2022; Kim, et al., Lewin 2018) to cure the disease. UNAIDS (2021) figures indicate that by the end of 2022, approximately 38.4 million people were living with the virus, with 1.3 million newly reported cases of HIV in 2022 alone (Poltronieri, et al., 2015). HIV is an ribonucleic acid (RNA), positive sense, enveloped, and single-stranded retrovirus (Poltronieri, et al., 2015). The virus targets T cells that have differentiated into CD8 (cytokine) or CD4 (helper cell) cells. HIV primarily targets CD4+ T cells by binding to the protein gp120 that is found in its envelope. The gp120 protein further binds to either CXCR4 co-receptors or CCR5 co-receptors. HIV then injects its single strand of RNA into T cells and uses the enzyme reverse transcriptase to transcribe a complementary strand of proviral DNA.

Consequently, HIV infects the DNA of the host and replicates itself into the genetic material of its host. Over time, HIV further depletes CD4 cells, leading to HIV / AIDS (Ellero, et al., 2017). Through a mechanism yet to be understood, HIV is able to, almost immediately, permeate the blood brain barrier (BBB) and enters the brain, through the differentiation of monocytes into macrophages (Wilmshurst et al. 2018). Research suggests that macrophages infect other cells in the CNS, such as microglia and astrocytes (Filipowicz et al. 2016; Sillman et al. 2018). Thus, microglia and macrophages are thought to be cellular reservoirs for HIV, allowing the virus to further replicate within the CNS, eventually affecting the integrity of nerve cells associated with neurocognition (Brew 2018; Churchill et al. 2016; Ellero, et al., 2017).

Although neurons do not express CD4 cells, HIV is believed to influence neural transmission in the nervous system (Gonzalez et al. 2020; Nolan & Gaskill 2019a). The impact of HIV on neural transmission is important, as neuronal networks are the basic foundations of cognitive processes within the cerebral cortex. Neuropathogenic studies, for example, reveal that HIV affects catecholaminergic neurotransmission. Catecholamines are derived from the amino acid tyrosine and include the neurotransmitters dopamine, norepinephrine, and epinephrine. Collectively, catecholamines are thought to be responsible for cognition, in particular higher order abilities such as executive functions and sustained attention (Chandler, et al., 2014; Logue & Gould 2014; Thiele & Bellgrove 2018), and their dysregulation in the CNS, through HIV infection, is thought to affect these cognitive functions. Collectively, cognitive deficits consequent HIV infection are referred to as HIV Associated Neurocognitive Disorder (HAND) (Nolan & Gaskill 2019b).

6.1.1 **The Neuroimaging of neuroHIV**

Given the above neuronal dysregulation, quantifying the effect of the virus within the cerebral cortex is integral, both for nosology and therapeutic objectives. Hitherto, neuroimaging studies, including functional magnetic resonance imaging (fMRI) (19,20), positron emission tomography (PET) (Vera et al. 2017), diffusion tensor imaging (DTI) (Hoare et al. 2012), proton magnetic resonance spectroscopy (MRS) (23) and magneto-electroencephalography (MEG) (Arif et al. 2020), have provided valuable biomarker data into the structural and functional pursuance of HIV in the cerebral cortex. For example, fMRI neuroimaging has evidenced brain atrophy and cortical thinning in the frontal cortices of HIV+ participants, which is associated with dysexecutive functions in people living with HIV (du Plessis et al. 2016). Similarly, PET studies using brain radioligands have indicated chronic activation of microglia cells, leading to neuroinflammation in cortical regions such as the frontal and parietal

cortices, and basal ganglia, which are thought to contribute to neurocognitive disorders observed in HAND (Vera et al. 2016, 2017).

Similarly, MRS neuroimaging studies have indicated increased metabolite concentrations of membrane markers (Cho, Mi) whose elevation in HIV reflects inflammation and demyelination in microglia, which in turn are associated with the neurocognitive decline observed in neuroHIV (Chaganti & Brew 2021). Analogously, DTI indicates that compared to healthy controls, HIV-positive children (HAART-naïve and slow progressors) display lower fractional anisotropy (FA), indicative of lower white matter integrity in the corpus callosum, internal capsule, and superior longitudinal fasciculus. Demyelination in these cortical regions is associated with poor performance in various neuropsychological assessments, including executive functions, attention, and processing speed (Hoare et al. 2012).

Although neuroimaging techniques provide invaluable insight into cortical macroarchitecture sequent HIV neuroinvasion, these techniques tend to be inaccessible and less practical in low-resource settings due to the elevated and operational costs associated with their implementation (Deoni et al. 2021; Ogbole et al. 2018). Secondarily, PET, fMRI, and MEG techniques have intrinsic limitations. For example, PET requires using radioisotopes, which have perceived radiation hazards (Conti & Eriksson 2016). Magnetic resonance imaging (MRI) and magneto-electroencephalography (MEG) require participants to remain restrained whilst completing neuropsychological assessments, making them unsuitable for use with children (Deoni et al. 2021). Given these limitations, advances in neuroimaging technology allow the investigation of neurocognition using optical neuroimaging in the form of functional near-infrared spectrometry (fNIRS). The latter are portable neuroimaging devices which provide a high measure of spatial specificity into cortical function at a relatively low cost (Blasi et al. 2019; Katus et al. 2019; Pinti et al. 2020).

6.1.2 **Functional Near Infrared Spectrometry Neuroimaging**

fNIRS brain imaging techniques use light to collect data related to superficial cortical hemodynamic activity (Ferrari & Quaresima 2012). Contextually, light is fragmented into multiple wavelength spectra[19] that represent color. fNIRS neuroimaging uses light in the near-infrared (IN) spectrum range (650-950 nanometers) (red light) to detect the concentration of oxygenated hemoglobin (HbO) and deoxygenated hemoglobin (deoxy-Hb), activated within the cortex in response to neuronal activation (Ferrari & Quaresima 2012)[20]. As a biosensor, fNIRS measures the interaction between light and matter and how much of the light is absorbed by hemoglobin - a metalloprotein that transports oxygen from the alveolus to the rest of the body via red blood cells (Pauling & Coryell 1936). Within the cerebral cortex, neuronal cells carry oxygenated hemoglobin or deoxygenated hemoglobin.

fNIRS neuroimaging, therefore, seeks to gather brain activity by measuring changes in hemodynamic responses, as indicated by changes in the concentration of hemoglobin protein in neuronal cells (Pinti et al. 2020). In their application, fNIRS elicit cortical activation by emitting near-infrared light through sources and detectors attached to fNIRS neuroimaging devices (Pinti et al. 2020). Correspondingly, increased cortical activity within neuronal cells increases metabolic demand for oxygenated blood (greater hemoglobin) juxtaposed with a decrease in deoxygenated blood. Summarily, optical neuroimaging techniques, in the form of fNIRS, use optical properties of light to capture the amount of hemoglobin present within neuronal cells, which indicates the brain's response to cognitive and cortical activity.

[19] The wavelength spectrum includes gamma rays, x-ray ultraviolet, infrared, microwave, short radiowave and long-radio wave.

[20] Light in the near-infra range spectrum (650-950 nanometers) passes human tissue at relatively high intensity and is more likely to be detected by light detectors. An additional property of near-infrared light is that it is less absorbed by other body tissues in the body, other than hemoglobin (Pinti et al. 2020; Scholkmann et al. 2014).

A recent systematic review (Musielak & Fine 2016) indicates a paucity of neuroimaging studies in paediatric HIV. This is due to multiple factors, not limited to, but including the limited availability of appropriate imaging techniques for this population and the cost limitations previously noted. Given the above limitations, this pilot study sought to explore the feasibility of using fNIRS neuroimaging to investigate cortical activation in paediatric HIV. Our study specifically focused on assessing prefrontal activation during the execution of a sustained attention task, the Stroop Colour Word Test (SCWT).

Firstly, to answer the question of fNIRS feasibility, we explored participants' reported comfortability and ease of completing the study protocol whilst wearing the fNIRS neuroimaging device. Secondly, we measured various primary indexes related to fNIRS signal quality, including (a) scalp coupling index (SCI) (Pollonini et al., 2016), (b) wavelength synchrony (Pollonini et al., 2016), (c) spike removal (van Brakel, 2014), (d) typical hemodynamic response (i.e., an increase in HbO, and a decrease in deoxy-Hb) (Ferrari & Quaresima 2012; Scholkmann et al. 2014), and (e) task-dependent vascular coupling due to completing the SCWT.

The SCI measures the quality of the light transmission and light detection of the optodes (sources and detectors) as they are coupled to the skin, namely the scalp. It is based on the cross-correlation across measurement of the fNIRS signal (760 and 690nm) in relation to the frequency range of the cardiac signal (Pollonini, et al., 2016). Significantly, the SCI can be affected by multiple factors, including coarse hair, skin pigmentation, and optode pressure - the former factors are important to be aware of when working with African participants, as in our study (Pollonini et al., 2016). Results from the SCI are interpreted in that the higher the correlation coefficient, the better the optode-scalp coupling within a particular channel of interest. Channels below a threshold of (SCI < 0.75) indicate a greater signal-to-noise ratio and

are consequently excluded from further processing in the fNIRS general linear model (GLM) (Pollonini, et al., 2016).

We chose to limit our feasibility study to the prefrontal lobes since HIV predominantly affects the Central Executive Network (CEN; anterior frontal lobes, DLPFC, inferior parietal, and temporal regions; (Hoare et al. 2012; Ipser et al. 2015; Israel et al. 2019; du Plessis et al. 2016; Wang et al. 2017), leading to executive dysfunction and impairments in attention and working memory (among the areas of interest in our main study). Our pilot focused on key nodes within the CEN, namely the anterior frontal lobes and DLPFC, whilst participants completed the SCWT. The SCWT has previously been used to study attention and executive functions in paediatric HIV (Chandra et al., 2019; Haase et al. 2014; Ruiz-Saez et al. 2021; Zhao et al. 2015) and neural activation of the DLPFC [Brodmann's area (BA) 9, 46] in healthy subjects (e.g., 45). The SCWT has successfully been paired with fNIRS neuroimaging to investigate, for example, (a) the effect of attention workload (46), (b) the effects of meditation on sustained attention (Izzetoglu et al. 2020); (c) the effects of Traumatic Brain Injury (TBI) on selective attention and response inhibition (Plenger et al. 2016); and (d) the effects of caffeine on sustained attention (Yuan et al. 2020). Given the previous indications to evoke the hemodynamic response in the prefrontal and DLPFC, we selected the SCWT as the assessment choice for our feasibility study.

6.2 Methods

6.2.1 Participants

Purposive sampling was used to recruit eighteen participants from a shelter caring for children living with HIV. Ten of the research participants were children living with HIV, whereas the

remaining eight were HIV-negative. All participants were indigenous right-handed Africans[21], aged between 12 and 16 years of age (M = 14.28, SD = 1.53) and were attending either primary or secondary schooling at the time of the study. Participants living with HIV were enrolled into the study if they were on a course of HAART therapy. Participants were excluded from the study if they presented with (a) auditory deficits, (b) visual impairments, (c) TBI, and (d) other CNS related ailments (e.g., cerebral palsy, meningitis, or other neurological diseases). Written informed consent was obtained from the Directors of the shelter and, where possible, from the children's guardians. Assent was obtained from all participants. Ethical approval for this study was granted by the University of the Witwatersrand's Human Ethics Committee (M211073). Equator reporting standards for conducting and reporting neuroimaging research were followed as suggested by (Poldrack et al. 2008) (Supplementary Materials, File1).

6.2.2 Demographic Questionnaire

A *Demographic Questionnaire* completed by the Director/guardian collected data concerning age, gender, education, HIV status, and other relevant information related to the inclusion and exclusion criteria.

6.2.3 Behavioural Assessment

Participants completed a computerised version of the SCWT, built using PsychoPy (Peirce & MacAskill 2018), to measure sustained attention. Our SCWT took the form of an fNIRS block design[22] adapted from Schroeter et al. (2002). In the classical SCWT, a color word, such as blue, is written in an ink color, which may or may not be the same as the colour word. First,

[21] In this context 'indigenous African' refers to Black Africans of Sub-Saharan Africa descent, with brown/dark skin pigmentation and dark, curlier hair (Agyemang, Bhopal, and Bruijnzeels 2005; Kwasa et al. 2022b).
[22] We adopted the block design procedure as opposed to the event-related designs. The former has been indicated to show stronger statistical power and elucidate greater hemodynamic responses (Friston et al. 1999; Scholkmann et al. 2014).

the participant must name the colour of the word, while ignoring the actual word. Then, the participant must read the word and ignore the colour (Stroop 1935; Treisman & Fearnley 1969). The Stroop interference effect occurs when reading the word interferes with naming the color (incongruent condition). Generally, the interference effect requires greater attentional capacity. It has been correlated with slower responses, less accuracy, and greater cortical activation of the central executive network attuned to higher cognitive functions, including executive functions and attention (Schroeter et al. 2002, 2004).

In the SCWT used in our study, participants were required to answer the following question: "Does the colour ink of the top word match the meaning of the bottom word?". As indicated in Figure 6.1, two conditions were implemented to answer this question, namely, Condition 1, which was a Congruent Block (the colour of the top word was the same as the meaning of the bottom word), and Condition 2, which was an Incongruent Block (colour of the top word differed from the meaning of the bottom word).

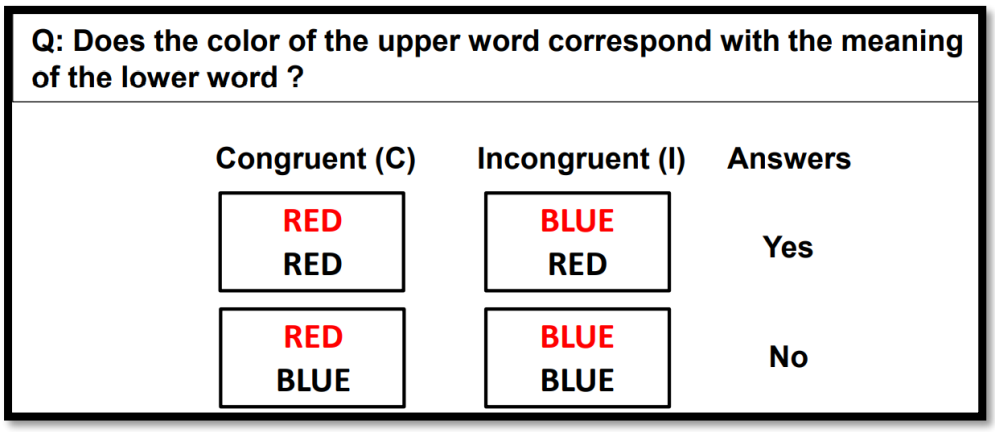


Figure 6.1. The Stroop Colour Word Test **(**SCWT) adapted from Schroeter et al. (2002).

As indicated in Figure 6.2, each block (Congruent, Incongruent) was presented five times for a maximum of ten blocks. Each block was interspaced with 15 seconds of rest, during which participants had to stare at a '+' sign before responding to the block condition. Event markers (triggers) built on PsychoPy required participants to press *q* on the computer keyboard

in response to congruent stimuli and *p* in response to incongruent stimuli. Participants were first presented with a paper version of the SCWT for practice purposes before completing the test version for neuroimaging purposes (Supplementary File 1). In total, the SCWT took 8 minutes to complete.

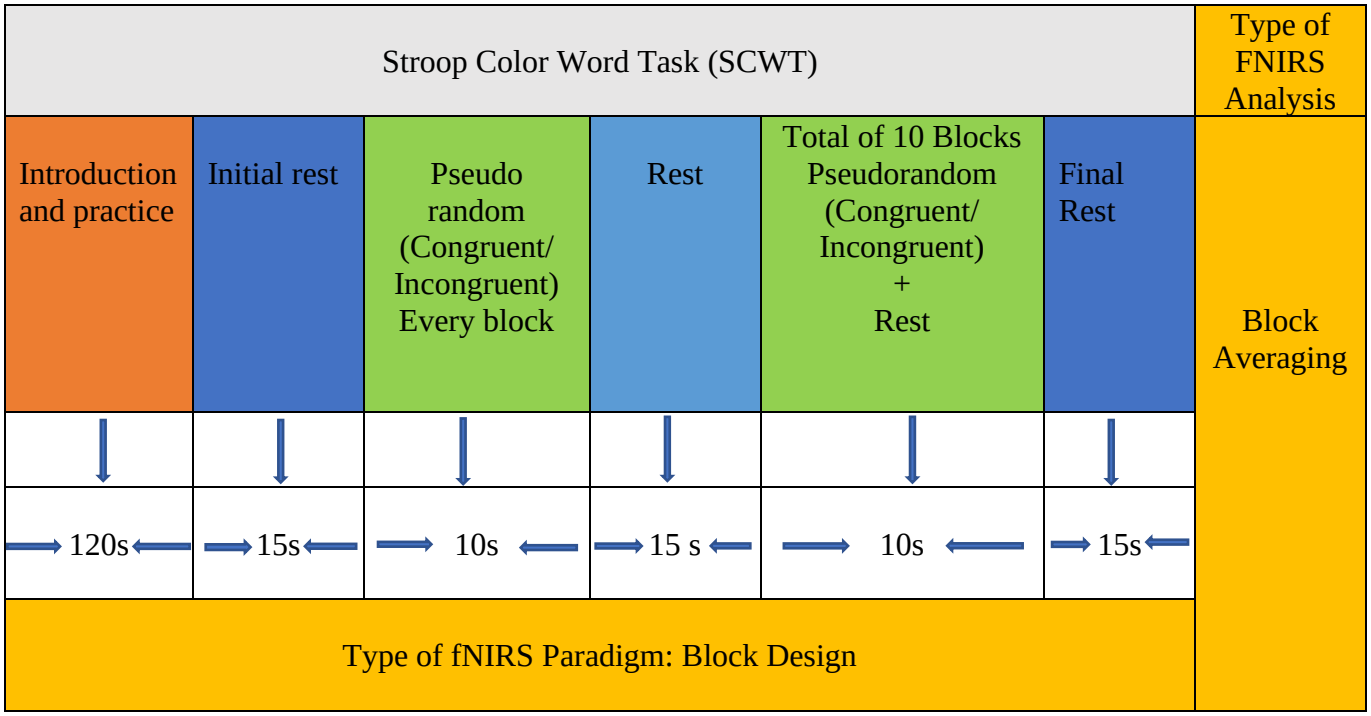


Figure 6.2. The fNIRS SCWT Block Design*:* An fNIRS block average design was applied to analyse the SCWT. In total, 10 blocks (five congruent and five incongruent) lasting ten seconds each were interspaced with 15 seconds of rest.

6.2.4 **Functional Near-Infrared Spectrometry**

Data Acquisition

The NIRxSport2 (NIRx, Medical Technologies, Berlin), a portable, wearable, multichannel fNIRS system, measured concentration changes in HbO and deoxy-Hb while participants completed the SCWT. As indicated in Figure 6.3, we used 8 X 7 optode arrays covering the prefrontal cortex for our study. Eight LED emitters consisting of two near-infrared (NIR) light sources, with 760 and 850 nm wavelengths, were placed on positions AF3, AF7, Fz, F3, AF4,

AF8, FpZ, and F4. LED emitters were paired with seven photodiode detectors to capture LED light placed on positions F1, Fp1, F5, F6, AFz, Fp2, and F2 of the fNIRS cap. The placement of sources and detectors corresponded with underlying cortical regions concentrated in Brodmann Areas 9, 10, 45, and 46. The Broadman areas, covering the frontopolar prefrontal cortex and dorsolateral prefrontal cortex, have been implicated in the cortical activation of executive functions and sustained attention (Esterman & Rothlein 2019; Rosenberg et al. 2016; Sarter, et al., 2001a).

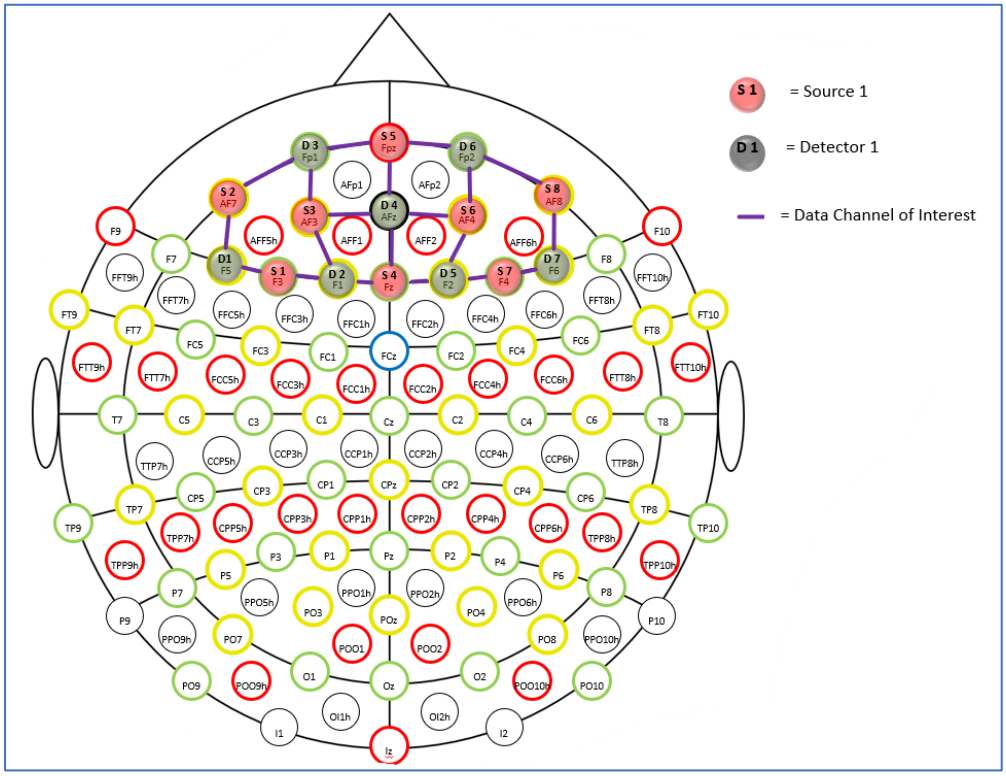


Figure 6.3. Regions of Interest (ROI) for Optode Placement: ROI for our study covered the frontopolar and dorsolateral prefrontal cortex (DLPFC).

Probe placement (sources and detectors) to identify the location of the above-predefined regions was determined using the 'fNIRS Optodes Location Decider' (fOLD) software (Zimeo Morais, et al., 2018) (Please see Supplementary Material File 3). In total, we investigated twenty-two channels covering the prefrontal cortex. The distance between sources and detectors was 2.5 cm, following guidelines for data acquisition with paediatric samples (Pinti

et al. 2019). Signal calibration and recording of fNIRS data was done using Aurora 1.4. Acquisition Software (v2021.9, Medical Technologies, Berlin). Data were recorded at a sampling frequency rate of 7.85 Hz, based on two wavelengths, 760 and 850 nm.

6.2.5 **Borg Rating of Perceived Exertion - Feasibility Assessment**

To judge the feasibility of the protocol, participants were asked to complete two measures. In the first task, the participant completed the Borg Rating of Perceived Exertion Scale (RPE; 60). The BORG scale has been used in other fNIRS feasibility studies (Nieuwhof et al. 2016) to measure the perceived exertion of any physical task on a scale from 1 (really easy) to 10 (Really Really Hard). Participants also completed a 5-point Likert-Scale questionnaire based on their experience with the fNIRS system. The questionnaire included two primary questions: "Did the fNIRS system (NIRXSport2) burden you while completing the cognitive activity?" (1 = "No, not at all" and 5 = "Yes, a lot") and "Could you complete the cognitive activity?" (1 = "Yes, very easily do-able" and 5 = "No, undoable"). All questions were asked in either, isiXhosa, or isiZulu, two indigenous languages spoken in South Africa, or in English.

6.2.6 Procedure

All participants were tested independently in a secure research laboratory in the Department of Psychology at Rhodes University. The laboratory was equipped with a desk, computer, and chair. Upon arrival, participants were first seated at a desk equipped with a computer (screen diameter: 22 centimetres; height: 33.2 centimetres) and were requested to complete an assay of protocols. Firstly, to confirm information gathered during the recruitment phase of the study, participants were asked to verify their demographic details. Thereafter, the Participant Information Sheet was read to participants, which was proceeded by participants reading and signing the informed assent sheet. Once these assays were complete, participants completed the fNIRS protocol as detailed below.

fNIRS Cap Placement

A red marker was first used to note the 'Fpz' optode position to assist with placing the fNIRS cap. The location of the 'Fpz' was followed by cranial measurements, using a measuring tape, to establish the pre-auricular points and the distance from the nasion to the inion. Once these fiducial points were established, the researcher (SZ) fitted the fNIRS cap onto the research participants (see Figure 6.4). The fNIRS neoprene head cap with optodes was then covered with an overlayer cap to prevent external light from affecting the fNIRS signal. When all signals and channels were deemed acceptable, as indicated by Aurora Software, administration of the SCWT commenced. In total, the entire protocol took 25 - 30 minutes to complete.



Figure 6.4. Seating Position of Research Participant while completing the SCWT coupled with fNIRS neuroimaging. Copyright: Laura Bell & Sizwe Zondo

6.2.7 **Data Signal Preprocessing**

The analysis of fNIRS data was executed on Satori fNIRS (NIRX Software, Brain Innovation, BV, Netherlands). Channel rejections were applied based on the SCI = 0.75 (62). Motion artefacts, including head movement, were corrected by applying spike removal parameters based on monotonic interpolations (van Brakel 2014). Spike removal corrections were followed by temporal derivative distribution repair (TDDR) to remove baseline shifts and spike

artefacts in the data (Fishburn et al., 2019). Low-frequency band-pass filtering was applied to eliminate baseline drift on the data. Physiological fluctuations related to blood pressure fluctuations (1~1.5Hz) and respiration (0.2~0.5Hz) were removed using low-pass (LP) and High-pass Butterworth filtering. In this manner, the LP filter (0.1-0.2 Hz) enabled further removal of high-frequency noise within the data that was not accounted for by brain activity (Huppert et al., 2009). The high pass filter (0.01 Hz) was applied to attenuate low-frequency signals by removing baseline drift that may have affected the hemodynamic signal. Once data was preprocessed, changes in light intensity were converted into concentration changes in Oxy-Hb and deoxy-Hb, using the Modified Beer-Lambert Law (MBLL).

6.3 Results

6.3.1 Demographic Data

Table 6.1 summarises the demographic characteristics of the sample. Chi-Squared tests revealed no significant differences in sex ratio, χ^2 = 0. 22, p = 0.63, and schooling level, χ^2 = 2.00, p = 0.16. There were, however, significant differences in the sample based on the age index, χ^2 = 13.6, p = 0.004.

Table 6.1. Demographics Characteristics (*N* = 18)

Sample Characteristics	HIV Group		Control Group		Full Sample	
	n	%	n	%	n	%
Sex						
Male	5	27.8	3	16.7	8	44
Female	5	27.8	5	27.8	10	56
Age Range (years)						
10 -12	2	11.1	0	0	2	11
12-14	2	11.1	2	11.1	4	22
14-16	6	33.3	5	27.8	11	61
16-18	0	0	1	5.6	1	6
Ethnicity						
isiXhosa	9	50	8	44	17	94
Other languages	1	5.6	0	0	1	6
School						
Primary	2	11.1	4	22.2	4	22
Secondary	8	44	4	22.2	14	78

Feasibility Measures

6.3.2 **Borg Ratings**

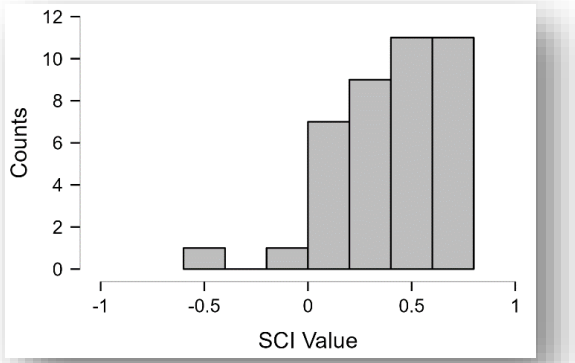
Most participants (83.3%) reported that they could complete the study protocol. On average, participants' scores (*M* = 3.83, *SD* = 1.34) on the Borg CR10, corresponded to a fairly light physical exertion for all study protocols. Concerning completing the SCWT whilst fitted with the NIRXSport2, participants reported that the device did not burden them whilst undertaking the SCWT (*M* = 2.28, *SD* = 1.02). Participants further indicated that the cognitive task (SCWT) was *easily doable* (*M* =2.61, *SD* = 1.29).

6.3.3 **fNIRS measures**

Scalp Coupling Index

Results of the SCI analysis (Figure 6.5) indicated that when we set a threshold of SCI < 0.75, 80% of channels in our study were rejected, and 20% were retained. The average SCI for the combined sample (HIV participants and Controls) of our study was SCI = 0.45.

A: Scalp Coupling Index (0.75)



B: Scalp Coupling Index (0.75)

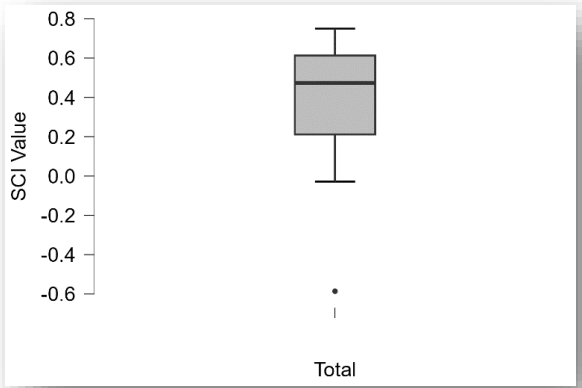


Figure 5 | SCI for all participants in the study was = 0.45.
A indicates the distribution of scores.
B indicates the Boxplot of all SCI scores, with one outlier in the data.

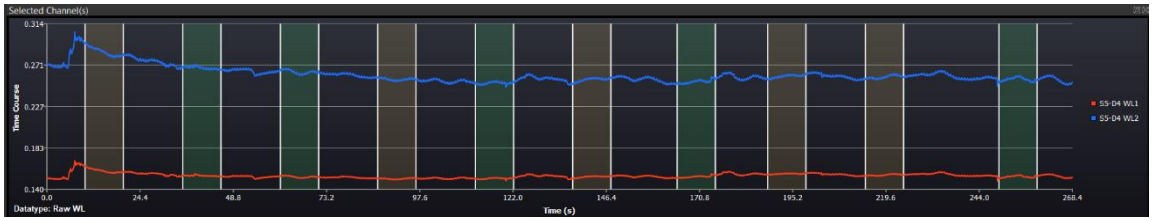
Figure 6.5. Scalp Coupling Index.

Wavelength data

Figure 6.6 represents raw wavelength data. Raw wavelength explorations analyse the time course of the two fNIRS wavelengths, 760 and 850 nm. Within the fNIRS data, synchronous behaviour should be noted between the wavelengths which corresponds with the SCI measure (Pollonini, Bortfeld, and Oghalai 2016). For feasibility purposes, we indicate the sufficiency of this criterion by representing synchrony in channels S5 - D4 and S8 - D5 of Participant 1. Importantly, we noted synchrony in all raw wavelength analyses (760 and 850 nm) for each of our participants in our feasibility study (n=18).

Wavelength

S5 - D4



S8 - D5

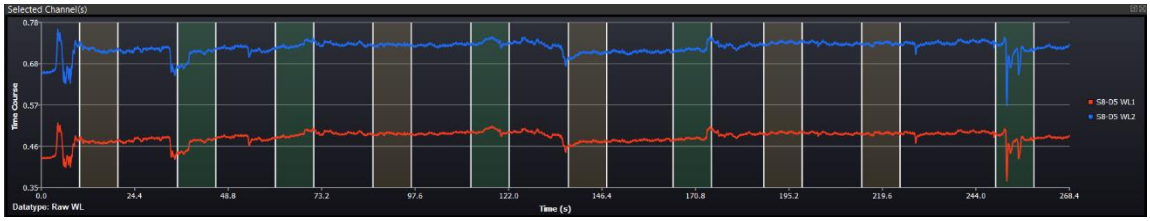


Figure 6.6. Wavelength Synchrony for Participant 1 at two wavelengths, 760 and 850.

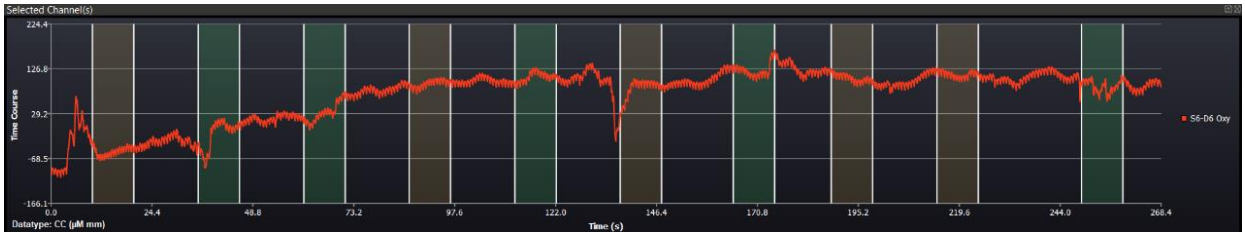
Spike Removal

We further analysed feasibility by measuring motion artefact corrections by applying the spike removal method, which is applied before TDDR algorithm corrections to process signal data.

As indicated in Figure 6.7, we were able to identify and remove several “spikes” within our data channels (e.g., S6-D6) using z-score spike detection methods, as suggested by van Brakel (2014). This finding illustrates that for our sample of interest, we were able to correct motion artefacts without exacerbating baseline shifts within our data, thus allowing for more robust statistical analysis to be carried out using general linear modelling.

Spike Removal

Before



After

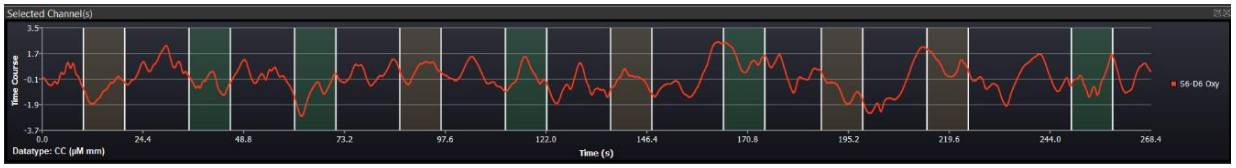
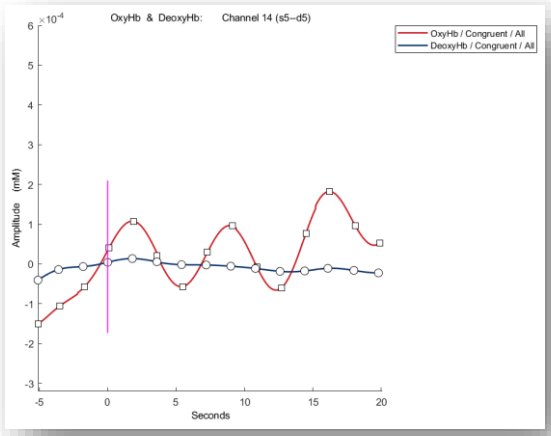
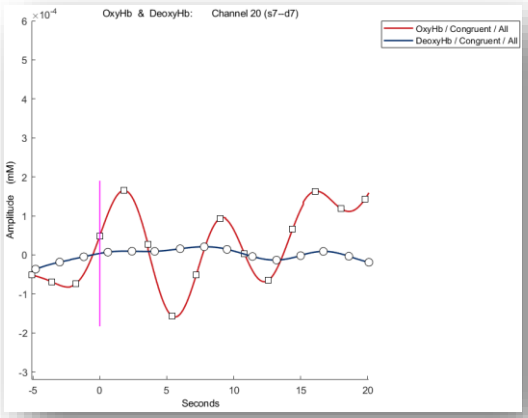
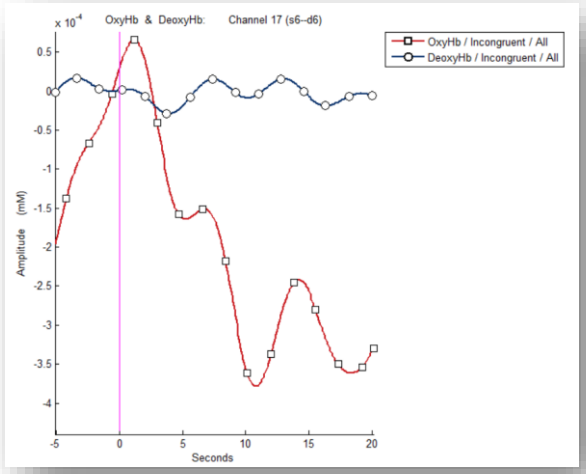
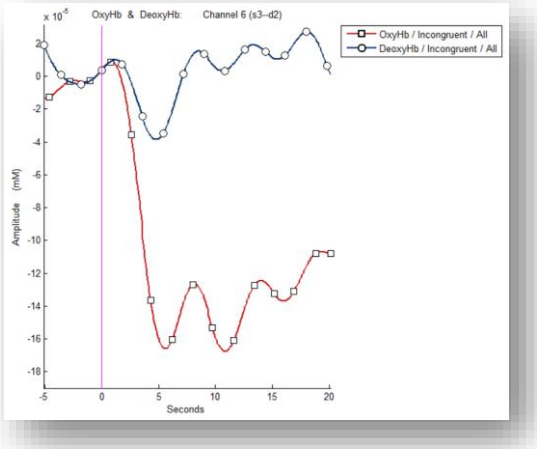


Figure 6.7. Effect of Spike Removal Indicating Motion Artefact Corrections.

Event Related Averages

Lastly, we undertook feasibility measures by analysing event-related averages due to cortical activation whilst completing the SCWT. Several channels in the feasibility study indicated expected task-dependent relative increases of oxygenated hemoglobin relative to a decrease or stable level of deoxygenated hemoglobin (Ferrari & Quaresima 2012). For example, Figures 6.8A and 6.8B (Participant 1), indicate the expected relative increases in HbO relative to a decrease in HbO during the congruent vs baseline task (channels, S5-D5, S7-D7). Nonetheless,

our feasibility study indicated atypical hemodynamic responses in the incongruent versus baseline condition (e.g., Figure 6.8C and 6.8D), in several participants.

<table>
<tr><td>A: Event Related Average (Congruent)

</td><td>B: Event Related (Congruent)

</td></tr>
<tr><td>C: Event Related Average (Incongruent)

</td><td>C: Event Related Average (Incongruent)

</td></tr>
<tr><td colspan="2">A and B indicate the typical hemodynamic response in the congruent condition (increase in HbO relative to a decrease in deoxy-HbO).

The typical hemodynamic response was not always evident in the incongruent vs baseline condition (C and D).</td></tr>
</table>

Figure 6.8. Event Related Averages for Congruent vs Baseline and Incongruent vs Baseline.

6.3.4 **fNIRS Results**

PFC Brain Activation (Group analysis)

Brain activation is indicated using T-statistics maps for HbO. T-maps were conducted at three levels, (1) for the entire sample, (2) for the HIV group, and (3) for the control group. We compared brain activation for congruent versus baseline and incongruent versus baseline activation. The combined sample demonstrated significantly greater HbO increases in the congruent versus baseline condition. Brain activation was noted in the bilateral DLPFC and VLPFC, with greater activation in the right hemisphere (Figure 6.9A). The latency peak of HbO activity in this condition indicated brain activation on several channels (4, 7, 8, and 12), resulting in significant t-map activations ($p < 0.05$) in this condition. Although brain activation was noted in the right hemisphere for the incongruent versus baseline condition, the latency to peak of HbO activity did not reach significance ($p > 0.05$; Figure 6.9B).

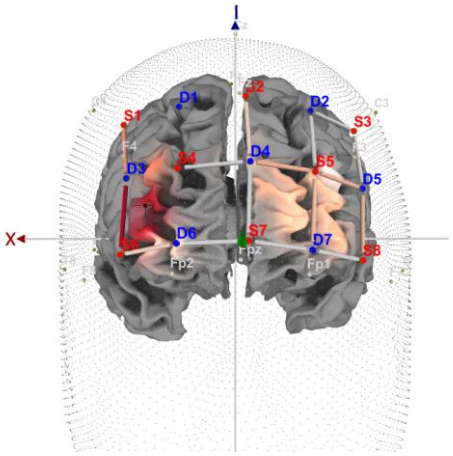
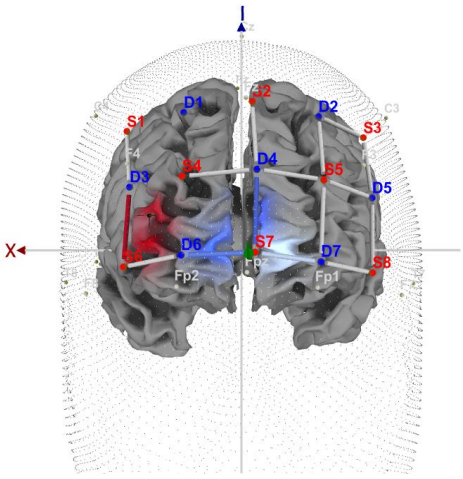
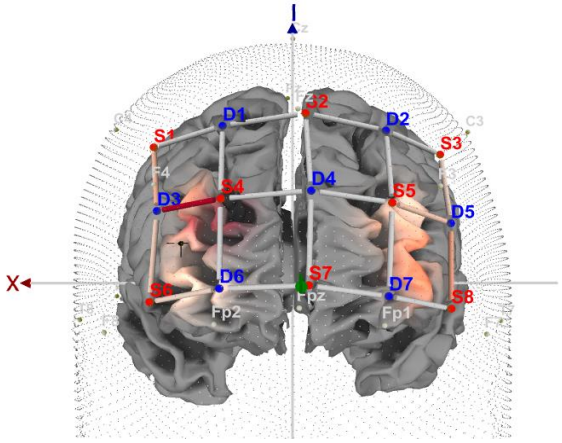
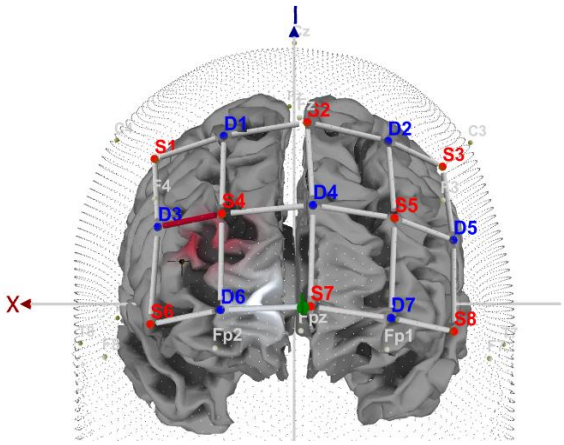
A: Congruent vs Baseline	B: Incongruent vs Baseline
	
A. Statistically significant differences ($p < 0.05$) were noted for the congruent vs baseline condition in the prefrontal cortex. **B**. Although there was activation in the incongruent vs baseline comparison, this was not significant ($p > 0.05$)	

Figure 6.9. Task versus Baseline Measures T Maps (Entire Sample)

PFC Brain Activation: HIV Group

During the congruent condition, the HIV group demonstrated bilateral brain activation in the DLPFC and VLPFC for the congruent versus baseline condition. The latency to peak of HbO activity during this condition did not reach statistical significance ($p > 0.05$; Figure 6.10 A). As indicated in Figure 6.10 B, there was markedly diminished cortical activation for the incongruent versus baseline condition in most channels within the HIV group.

A: Congruent vs Baseline (HIV Group)	B: Incongruent vs Baseline (HIV Group)
	

A. The prefrontal region showed strong activation in the congruent vs baseline condition for the HIV group, this activation did not reach statistical significance ($p > 0.05$). B.
B. There was markedly diminished cortical activation in the incongruent vs baseline ($p > 0.05$) for the HIV group.

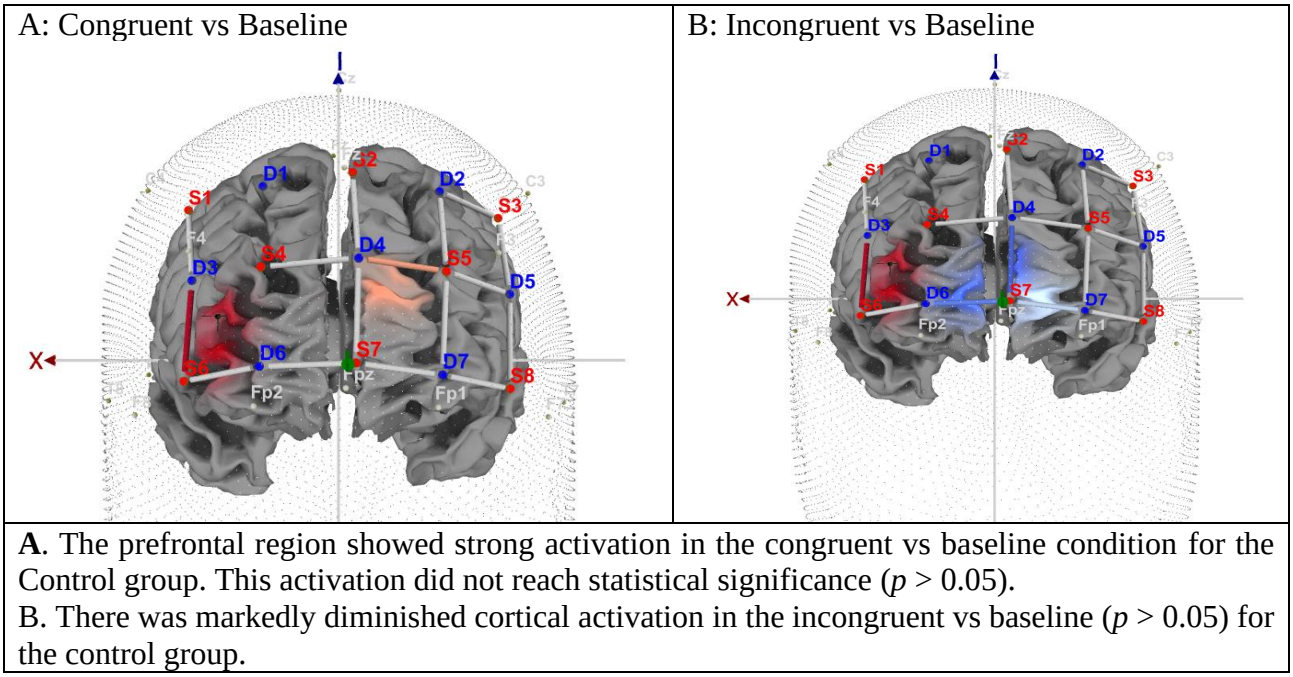
Figure 6.10. Task versus Baseline Measures T Maps (HIV Group).

PFC Brain Activation: Control Group

During the congruent condition, the control group demonstrated bilateral brain activation in the VLPFC for the congruent versus baseline condition. The latency to peak of HbO activity during this condition did not reach statistical significance ($p > 0.05$; Fig. 6.11 A). Diminished cortical activation was noted for the incongruent vs baseline condition in most channels, resulting in insignificant t-map activations ($p > 0.05$; Figure 6.11 B).

PFC Brain Activation: HIV Group compared to Control Group

In addition to the above, we compared the two groups on the latency to peak of HbO on the congruent vs baseline and incongruent vs baseline condition. No significant latency to peak differences were noted between the HIV and control groups on any of the conditions (p > 0.05).



A. The prefrontal region showed strong activation in the congruent vs baseline condition for the Control group. This activation did not reach statistical significance ($p > 0.05$).
B. There was markedly diminished cortical activation in the incongruent vs baseline ($p > 0.05$) for the control group.

Figure 6.11. Task vs Baseline Measures T Maps (Control Group)

6.3.5 **Behavioural Results**

Results of the SCWT task are indicated in Table 6.2. During the congruent condition, the HIV group was significantly slower at responding (*M*=3585.48; *SD*=932.38), compared to the control group (*M*=2321.48; *SD*=565.49) (*t* (16) = −3.36. *p* < 0.05). Similarly, the HIV group made significantly more errors (*M*=0.826, SD=0.062) compared to the control group (*M*=0.936, SD=0.049) (*t* (16) = −4.11, *p* < 0.05) for this condition. During the incongruent condition, the HIV group was also significantly slower (*M*=4336.10, *SD*=1038.76) compared to the control group (*M*=3029.83, *SD*=625.011) (*t* (14) =−3.77, *p* <0.05). Additionally, the HIV group also made significantly more errors on this condition (*M*=0.601; *SD*=0.189) compared to the control group (*M*=0.870; *SD*=0.07) (*t* (16) = −3.12, *p* <0.05).

Table 6.2. Stroop Colour Word Test Behavioural Performance

Condition	Response Time (ms)				Accuracy (%)			
	Congruent		Incongruent		Congruent		Incongruent	
	M	SD	M	SD	M	SD	M	SD
HIV	3585.48	932.38	4336.10	1038.76	0.826	0.062	0.601	0.189
Control	2321.48	565.49	3029.83	625.011	0.936	0.049	0.870	0.075

Note. Significant differences were noted in congruent and incongruent responses between the two groups.

6.4 Discussion

Research indicates frontostriatal and central executive network (CEN) aberrations due to HIV, subsequently leading to HAND (Arentoft et al. 2015; Hoare et al. 2012; du Plessis et al. 2016). There is a paucity of neuroimaging research investigating the effects of HIV on the cerebral cortex (Musielak and Fine 2016). Cognisant of the dearth of neuroimaging studies in paediatric HIV, our study investigated the feasibility of fNIRS neuroimaging to measure prefrontal cortical activation in children and adolescents living with HIV. Findings suggest that optical imaging captured cortical activation in this population. Primarily, participants reported experiencing a low burden of the fNIRS devices whilst performing the SCWT cognitive task.

Significantly, visual inspection of the fNIRS signal indicated feasibility as indicated by acceptable, though low SCI measures, coupled with synchronous wavelength behaviour. Pointedly, fNIRS data indicated typical cortical activity patterns of increased oxygenated (HbO) and stable deoxygenated hemoglobin (deoxy-Hb) concentrations in several channels during the congruent vs baseline condition. Although our study did not detect significant group differences between the HIV and control group, fNIRS neuroimaging was able to detect task-dependent changes in HbO (congruent vs baseline, incongruent vs baseline) within the HIV and control group as a cohort. These findings support the feasibility of using fNIRS

neuroimaging techniques to measure sustained attention in the PFC, which is compromised in HIV (Chang & Shukla 2018; Sanford et al. 2017).

Although we could not detect significant neuronal differences between controls and HIV participants, at a cortical level, behavioural findings indicated significant differences between the groups on the SCWT. This is in line with previous studies (Chan et al., 2019; Hinkin et al., 1999; Zhao et al., 2015). Interestingly, although there were significant differences in the Stroop interference task between the groups, fNIRS neuroimaging indicated diminished cortical activation in both groups when completing the Stroop interference task relative to the congruent vs baseline task. The interference tasks require greater neuronal workload, leading to greater activation of the central executive network (Banich, 2019; Banich et al., 2009). Given expected neuronal activation due to the interference task, diminished cortical activation during the SCWT interference task may be indicative of SES-dependent prefrontal hypoactivation (Moriguchi & Shinohara 2019) with data suggesting that living in low SES environments may be linked with reduced cognitive stimulation (Farah, 2017; Finn et al., 2017; Moriguchi & Shinohara 2019), thus leading to diminished prefrontal activation.

Notwithstanding the above, although our feasibility study sought to control for the influence of hair density on the fNIRS signal by employing spring grommets, we did not control for superficial (e.g., skin) hemodynamics using short separation channels (Gagnon et al. 2012; Pinti et al. 2019). There is evidence that epidermal pigments can potentially affect photon transmission in fNIRS in dark-skinned subjects, similar to our participants, leading to difficulty in detecting neuronal depolarisation when completing cognitive tasks (Kwasa et al. 2022a; Quaresima, Scholkmann, and Ferrari 2023).

Sequel to the above, it is recommended that future fNIRS studies improve on our preliminary findings by applying various measures to study the hemodynamic response in the

context of paediatric HIV. For example, although the placement of the fNIRS cap procedure was identical for all participants, as it was based on relative distances from external landmarks, namely, the nasion and inion, there is a small chance that cap placement might have targeted slightly different cortical regions due to morphological differences between participants. Future protocols could improve signal detection, and subsequent SCI, between tasks by adjusting the fNIRS device and using crochet hooks to gently adjust coarse hair until task-related cortical activity is observed and before commencing cortical measurement.

In addition to the above, research indicates inter-individual differences in the neuropsychological and neurobiological sequelae of HIV (Brahmbhatt et al. 2017) based on divergent factors such as adverse childhood experiences (ACE), HIV genotype and phenotype, and commencement of HAART. It is recommended that future fNIRS studies investigating the effects of neuroHIV on cognition could benefit from larger samples. Although our sample size (n =18), was sufficient to meet the primary objectives of conducting a feasibility study, the small sample was a limitation and prevented the implementation of robust statistical procedures to analyse the multiple variables that may affect the fNIRS hemodynamic response. Nonetheless, based on the mean difference in HbO concentrations between congruent and incongruent conditions in the present study, it was deemed that at least 42 participants would be needed to find significant differences in HbO concentrations between the cognitive tasks (power = 0.80, alpha = 0.05, one-tailed testing).

6.5 Conclusion

To the researchers' knowledge, this is the first study to investigate the efficacy of fNIRS neuroimaging for a paediatric HIV sample, inclusive of participants of African descent. Findings suggest the feasibility of fNIRS to study frontal activation in both clinical and healthy children with dark pigmentation and curly hair who are under-represented in fNIRS research

(Kwasa et al. 2022a). Most significantly, our findings imply that fNIRS may be used as a marker for frontal lobe in/efficiency in a cognitive rehabilitation setting at a relatively inexpensive cost.

6.6 Acknowledgements

The authors would like to thank the Director of the children's shelter and the children's guardians for admitting their child/ward into the study. The authors would further like to extend their gratitude to the 'elderly children' at the shelter who assisted in accompanying research participants to the research site and enabling rapport with the participants during the execution of the study.

6.7 Conflict of Interest

There are no conflicts of interest to declare. Copyright permission for the use of all images, has been obtained from the appropriate publishing house.

6.8 References

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CHAPTER 7

Shining Light into Adolescent HIV Neuroplasticity: A Behavioural and Neuroimaging Study of the Prefrontal Cortex Using Functional Near Infrared Spectrometry (fNIRS)

Manuscript under review (Neuroimage): Zondo, S, Cockcroft, K, da Silva Ferreira Barreto & Ferreira-Correia, A.

Abstract: HIV crosses the blood-brain barrier, causing aberrant cortical networks and compromises cognition. Current neuropharmacological intervention in the form of combination antiretroviral therapy (cART) does not reverse cognitive decline in pediatric and adolescent HIV, sequent HIV neuroinvasion. We evaluated the effectiveness of attention training to enhance neurocognition in adolescents living with HIV by pairing cognitive outcomes on the Stroop Colour Word Test (SCWT), to brain hemodynamic responses measured by functional near-infrared spectrometry (fNIRS). We compared changes in oxygenated hemoglobin (ΔHbO) in the prefrontal cortex in 15 HIV+ children who received attention training, with 13 HIV+ children not receiving the intervention. Repeated and between group analysis were undertaken, to investigate changes in oxygenated haemoglobin (ΔHbO), complemented by the SCWT, to determine the efficacy of the intervention. Intragroup analysis showed differences in HbO levels between congruent and incongruent conditions only for children who received intervention training. A decrease in HbO was found in the dorsolateral prefrontal cortex, and frontopolar areas, when comparing incongruent and congruent conditions. These results suggest that customised cognitive training maybe an effective complementary adjunct to cARTs, in pediatric and adolescent HIV.

Keywords: Adolescent HIV, cARTs, oxygenated hemoglobin, attention, dorsolateral prefrontal cortex, fNIRS

7.1 Background

Despite recent medical advances such as ‘shock and kill’ gene transcription (Chandrasekar & Badley, 2022; Kim et al., 2018) and haematopoietic stem cell transplantation (Gupta et al., 2019; Gupta et al., 2020), the Human Immunodeficiency Virus (HIV) continues to be a significant global pandemic. Most recent UNAIDS (2023) estimates indicate approximately 39 million people living with the virus, with Sub-Saharan Africa accounting for 20.8 million of these estimates. Globally, South Africa continues to have the highest burden of HIV, with approximately 14% of the population, equivalent to approximately 7.9 million people living with the virus (UNAIDS, 2023). With reference to children (0-9 years old) and adolescents (10-19 years old), UNICEF statistics indicate that 1.8 million children and adolescents were living with HIV in Sub-Saharan Africa by the end of 2022 (UNICEF, 2023).

Virologically, HIV is a ribonucleic acid (RNA), single-stranded retrovirus that uses the enzyme reverse transcriptase to transcribe its RNA genome into a complementary strand of proviral DNA within the cell host genome (Poltronieri et al., 2015). Once in the genome, proviral DNA replicates and targets T cells that have differentiated into CD8 (cytokine) or CD4 (helper cell) cells. After its integration in the host genome, the proviral DNA may remain latent or become actively transcribed, depleting CD4 cells, which results in HIV/AIDS (Ellero et al., 2017; Poltronieri et al., 2015). Significantly, HIV permeates the blood-brain barrier (BBB), and enters the cerebral cortex, where it results in the differentiation of monocytes into macrophages, which act as cellular reservoirs for HIV (Wilmshurst et al., 2018).

Once in the cortex, HIV initiates pathogenetic processes, particularly neuroinflammation, resulting in aberrant neural transmission (Brew 2018; Churchill et al. 2016; Ellero et al. 2017), white matter loss (Jensen et al., 2019), neuronal apoptosis (Das et al., 2016; Smail & Brew, 2018), and the dysregulation of catecholamines, namely, dopamine and

tryptophan, a precursor to serotonin (Elbirt et al. 2015; Nolan & Gaskill 2019). Consequently, HIV's neuroinvasion has been associated with compromised neurocognitive and behavioural outcomes in children (Boivin et al., 2018; Wilmshurst et al., 2018) and adults alike (Cody & Vance, 2016).

7.1.1 **Effect of neuroHIV on Child and Adolescent Neurocognition**

With reference to children and adolescents, neuroHIV is concomitant with neurodevelopmental delay (Debeaudrap et al., 2018), delays in scholastic development (Abubakar, 2014; Anabwani et al., 2016; Cockcroft & Cassimjee, 2020), and poorer academic outcomes (Pufall et al. 2014). It is plausible that poorer outcomes in scholastic ability are resultant from compromised higher-order cognitive functions in this population. For example, compared to HIV-negative controls, children living with HIV indicate difficulties regulating working memory (Boivin et al., 2020; Milligan & Cockcroft, 2017), performing optimally on executive function tasks (Nichols et al., 2015; Walker & Brown, 2018), as well as difficulty monitoring and self-regulating behaviour (Debeaudrap et al., 2018). Importantly, children and adolescents diagnosed with HIV often indicate difficulty in sustaining and shifting attention compared to healthy controls (Cohen et al., 2014; Rice et al., 2014; Walker et al., 2013).

Emerging research indicates that combination antiretroviral therapy (cARTs), due to their toxicity, inadvertently play a role in poorer cognitive outcomes observed in children and adolescents living with HIV, which aggravates the cognitive profile associated with pediatric and adolescent neuroHIV (Alford & Vera, 2018; Lanman et al., 2019; Yuan & Kaul, 2019). Research further indicates that HIV-caused cognitive decline may be irreversible. For example, children in a South African study (median age = 8.4 years) showed no cognitive gains after receiving efavirenz, a non-nucleoside reverse transcriptase inhibitor (NNRT) (Hammond et al., 2019). Correspondingly, no association was evident between early viral suppression and

improved neurocognitive outcomes amongst Thai and Cambodian children (median age = 9 years; n =139) after a three-year initiation of cARTs (Puthanakit et al., 2013).

7.1.2 **Neuroimaging of Attention Performance in neuroHIV**

Neuroimaging studies indicate that neuroHIV causes predilection to neuronal networks, associated with attention and executive functions, both in adolescents (e.g., Yu et al., 2019) and adult populations (e.g., Ortega et al., 2015; du Plessis et al. 2017; Wang et al. 2017). Relevant to the purposes of our study, attention is mediated by a dual neural network system comprising the (a) Central Executive Network (CEN) and the (b) Default Mode Network (DMN) (Esterman & Rothlein, 2019; Rosenberg et al., 2016; Martin Sarter et al., 2001a). These networks work in a complementary manner, in that the CEN is responsible for 'top-down attention processing', whilst the DMN is involved in 'bottom-up processing'. 'Top down' processes are task-orientated cognitive processes and involve voluntary control of cognition, in an effort to maintain task vigilance and to suppress and filter out task-irrelevant distractions (Clark & Noudoost 2014; Treisman & Gelade 1980). 'Bottom-up' processes, on the other hand, rely on automatic salient sensory properties of a stimuli, such as colour, orientation or pitch, to easily discriminate objects or stimuli (Sarter et al. 2001).

Anatomically, the CEN is regulated by cortical nodes located in the dorsolateral (DLPFC) (bilaterally), ventrolateral prefrontal (VLPFC), anterior cingulate cortex, and those in the parietal cortices (bilaterally). Conversely, the DMN is regulated by nodes in the medial prefrontal and inferior parietal lobes (Denkova et al., 2019). Relevant to HIV and attention, the CEN is connected to the striatum (basal ganglia) through the frontostriatal network, modulated by the dopaminergic and noradrenergic system (Leh et al., 2010; Morris et al., 2016). NeuroHIV, leads to cortical thinning of the frontostriatal network (du Plessis et al., 2017; Ipser et al., 2015a), consequently disrupting frontostriatal connectivity (Ortega et al., 2015) and

dopaminergic integrity. Due to reduced frontostriatal integrity, patients living with HIV have been indicated to require a higher demand for blood oxygenation to execute cognitive tasks associated with attention and working memory. Moreover, due to compromised fronto-striatal circuity, patients are indicated to recruit adjacent cortical regions, adjacent the CEN, to solve cognitive tasks (Chang et al., 2017; Chang & Shukla, 2018; du Plessis et al., 2016; Ernst et al. 2009)**.**

7.1.3 **Blood Oxygen Level Dependency (BOLD), Attention and neuroHIV**

Chang et al. (2001) investigated blood oxygen level dependency (BOLD) of HIV+ (n =11; mean age = 41; SD = 4.8) and HIV-negative controls (n=11; mean age = 38; SD = 4.8) using functional magnetic resonance imaging (fMRI) during the execution of simple and complex attention tasks. In the simple attention reaction task, a number was flashed at random intervals on a screen for 500 milliseconds. Participants had to press a button in response to the number stimuli. In the complex attention task, numbers were sequentially displayed on the screen, and participants were instructed to respond only when the number was twice as high as the preceding number. The second attention task thus required greater cognitive load[23], and increased neural resources, tapping into inhibitory control and working memory (Chang et al., 2001).

Chang et al. (2001) found that for the simple attention task, the HIV group indicated greater BOLD activation in the parietal regions compared to controls. Interestingly, no significant differences were noted in the frontal cortex between the groups. For the latter task, the HIV+ group, showed greater BOLD activation in the inferior lateral prefrontal cortex, and parietal lobes, compared to controls. The authors conclude that increased neural activation in both the frontal and parietal regions while executing simple cognitive processes within the

[23] Cognitive load refers to the total amount of mental effort being utilised to solve a mental task.

HIV+ group maybe reflective of the brain's compensatory response to neuroHIV. The authors add that increased BOLD activation within the prefrontal cortex is indicative of greater requirement for 'top-down' neuronal resources to manipulate and maintain working memory resources in order to perform cognitively demanding tasks.

Similarly, Chang et al. (2004) investigated BOLD responses in the visual attention network system[24], between HIV+ (n =18; mean age = 38.2; SD =1.7) and HIV-negative controls (n=18; mean age = 38; SD = 2.1). Participants were required to mentally track two, three, or four balls with a radius of ten moving balls. Findings indicated that, compared to controls, participants in the HIV group indicated greater neural activation in the right prefrontal and right parietal regions, with increasing mental load, compared to seronegative controls. Similarly, the authors concluded that increased BOLD activation in the frontal, parietal, and adjacent regions, was associated with increased cognitive load, requiring greater compensatory recruitment, indicative of neuronal inefficiency, sequent neuroHIV (Chang et al., 2004, 2013). In light of findings indicating limitations of cART, increased cognitive load and neuronal inefficiency in neuroHIV, the exploration of non-pharmaceutical interventions has become imperative.

7.1.4 **Brain Plasticity in neuroHIV**

To this end, Weber et al. (2013, p.17) champion an urgent call for empirical research investigating non-pharmaceutical therapies, such as brain training and cognitive rehabilitation therapy (CRT), to reverse cognitive decline in neuroHIV. The clarion call for experimental brain training research, sequent HIV neuroinvasion, is based on the premises of cortical neuroplasticity, which emphasizes the nervous system's inherent ability to adapt and modify itself through adaptive learning, which may translate to functional changes within the cerebral cortex (Crosson et al., 2017; Luria, 1970; Monday et al., 2018). Although there has been a

[24] This network comprises the bilateral parietal and dorsolateral prefrontal cortex, the thalamus, anterior cingulate, and occipital lobes.

steady growth of studies indicating the efficacy of CRT to remediate attention (Basterfield & Zondo 2022; Ikekwere et al. 2021), working memory (Fraser & Cockcroft 2020), executive functions (Boivin et al. 2010; Boivin, Nakasujja, et al. 2019), and processing speed (Giordani et al., 2015), in pediatric and adolescent HIV, there is a dearth of studies, pairing behavioural changes with objective brain measures, to study the efficacy of cognitive rehabilitation in pediatric and adolescent HIV.

The literature indicates that the sole study (at the time of writing) to study brain plasticity in neuroHIV, pairing behavioural outcomes with neuroimaging data, is the study by Chang et al. (2017). They investigated working memory training (CogMed), paired with fMRI. Participants were inclusive of HIV+ (n=54; mean age = 50; SD = 1.9), and matched HIV negative controls (n=54; mean age = 52; SD = 2.3), who underwent working memory training. Results indicated that, after a one-month follow-up, participants (HIV+, n = 34; HIV-, n = 43), who underwent 25 sessions of working memory training indicated decreased BOLD activation when completing cognitive tasks after the intervention. The HIV group indicated decreased BOLD activation in the right middle prefrontal gyrus when completing the *n*-back (2 back) working memory task, post the intervention. Moreover, reduction in BOLD activation correlated with improved scores on untrained tasks such as the Digit-Span Backward and the Spatial Span Forward, suggesting some transfer of skills.

Follow-up at six months indicated that both the HIV+ and control group showed BOLD, deactivation in the right medial prefrontal gyrus, and Brodmann Area 6 (Primary Motor Area), when completing the *n*-back (1-back). BOLD deactivation was correlated with significant improvement on the Digit-Span Forward, compared to pre-testing. The authors posit that decreased BOLD-fMRI activation within the groups is indicative of cortical reorganization, associated with improved neural efficiency when completing tasks with increased cognitive load.

These findings (Chang et al., 2017) are similar to those noted by Vartanian et al. (2013), who found decreased BOLD activation in the right ventrolateral prefrontal (BA 47) and DLPFC (BA 46) among healthy participants (n=17; mean age = 31; SD = 7.6), who received three sessions (20 minutes) of working memory training. Decreased BOLD activation in the experimental group was correlated with greater performance on the Alternate Uses Task (AUT), a divergent thinking task that requires participants to generate as many possible uses for a given object.

7.2 The Present Study

There is a dearth of empirical research corroborating cognitive rehabilitation gains with brain data for children and adolescents living with HIV in Sub-Saharan Africa (Benki-Nugent & Boivin, 2019; Boivin et al., 2017; Hoare et al., 2014; Musielak & Fine, 2016). To address this, the study investigated the effect of sustained attention training on behavioural outcomes using the SCWT and brain hemodynamic response outcomes, using optical neuroimaging techniques in the form of functional near-infrared spectrometry (fNIRS). Although the reviewed literature seems to indicate improved cognitive efficiency and decreased brain activation in regions of interest following brain training in neuroHIV, we did not propose any directional hypothesis to our study since no empirical studies have been undertaken to investigate brain plasticity outcomes paired with hemodynamic responses, in adolescents living with HIV in the Sub-Saharan Africa context.

7.3 Research Questions

Compared to controls, do HIV-positive participants receiving sustained attention training indicate improved cognitive behavioural scores on the SCWT?

Do improvements on cognitive measures on the SCWT correlate with decreased hemodynamic responses in the prefrontal cortex post-attention training?

7.4 Methods

This study followed recommendations for best practices in fNIRS research (Yücel et al., 2021). Importantly, there is a slight overlap in the application of fNIRS neuroimaging procedures reported in the current study to those previously described in a feasibility study we previously executed (Zondo et al., 2024). In some cases, the same text is used in the current study, similar to our previous study, for clarity.

7.4.1 Participants

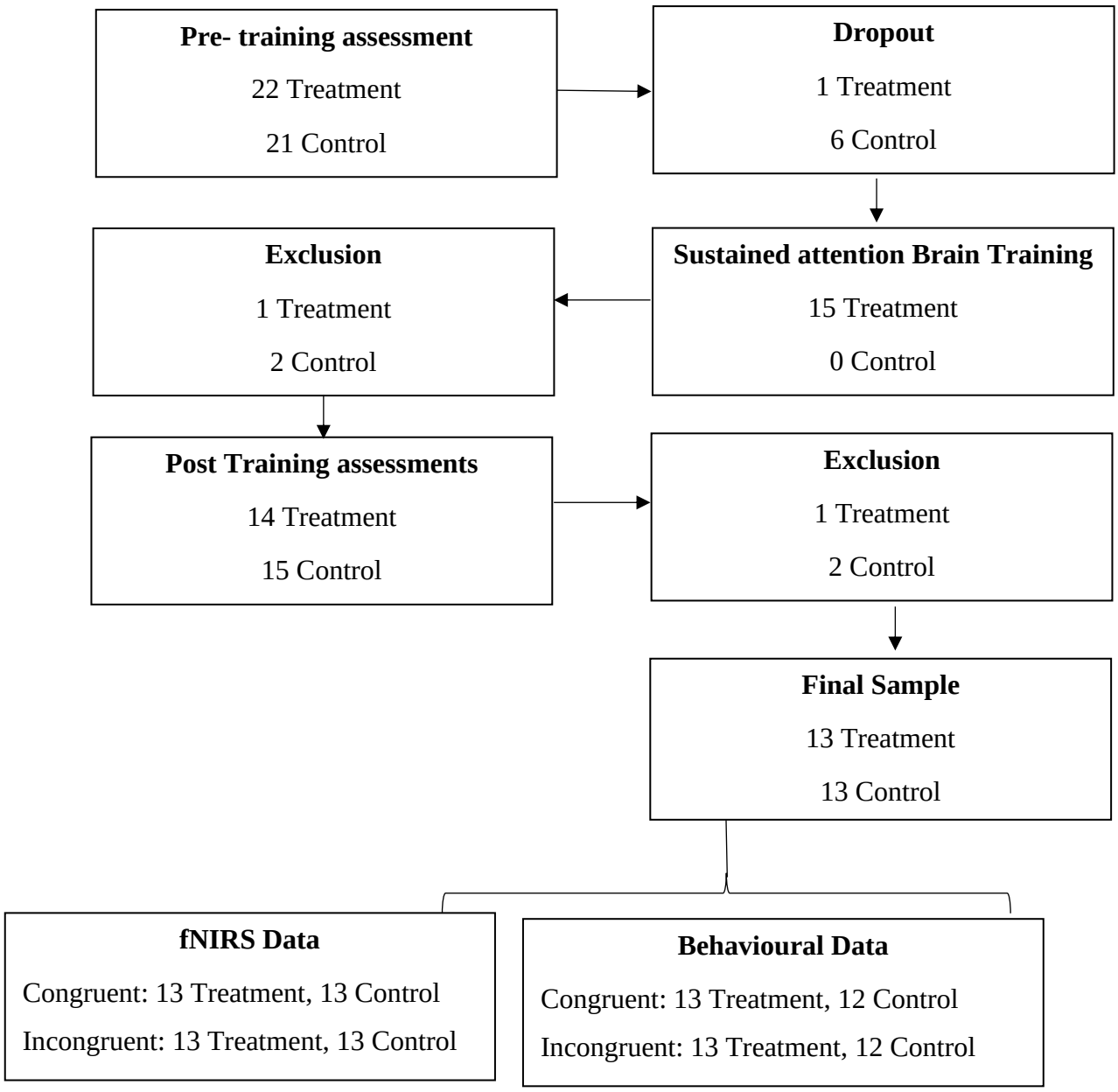
Purposive sampling was used to recruit 26 participants from three shelters caring for children living with HIV. For our study only children diagnosed with HIV-1[25] participated in the study. Participants constituted indigenous Africans[26], coloured[27] and white participants, aged between 14 and 18 years of age (M = 17.28, SD =1.94). All participants were on a course of cART and were either attending primary or secondary schooling at the time of the study. Participants were excluded if they presented with (a) TBI, (b) CNS-related ailments (e.g., cerebral palsy, meningitis), or (c) learning difficulties. Written informed consent was obtained from the Directors of the shelters and, where possible, from guardians of the children. Assent was obtained from all participants aged 14 and older. Ethical approval for this study was granted by the Ethics Committee of the University of the Witwatersrand, South Africa [M211073].

Participants were first randomly assigned to either the experimental or control group using the Research Randomizer Software (Urbaniak & Plous, 2013). Figure 7.1 shows the flowchart of the study. Forty-three participants were initially recruited for the study (Experimental, n=22; Control, n=21), with 15 participants in the experimental and 15

[25] HIV diagnosis status was attained from participant medical records, and confirmed by the attending nurse, or the Director of the shelter.
[26] 'Indigenous African' refers to Black Africans of Sub-Saharan Africa descent, with brown/dark skin pigmentation and dark, curlier hair (Agyemang et al., 2005; Kwasa et al., 2022).
[27] In South Africa, 'Coloured' refers to descendants of indigenous Africans, with a multiracial identity (Dooms & Chutel 2023; Nilsson 2016).

participants in the control group, completing all pre-assessments. Pre-assessments included completing the Stroop Colour Word Test (SCWT), Developmental Neuropsychological Assessment (NEPSY II), and neuroimaging measures obtained using fNIRS. Sequent baseline assessment: one participant in the experimental group withdrew from the study, citing a lack of interest. A further six participants in the control group dropped out, citing clashes of the study time with their school timetable (n = 2), a lack of interest (n = 2), no longer residing at the care shelter (n = 1), or illness (n = 1). After post-training (experimental group = brain training; control group = placebo), and when all post-training assessments were obtained, we deleted data from a further three participants from the final analysis, due to low fNIRS signal data (n = 1), or corrupted imaging data due to internet or electricity loss (n = 2). The final study sample consisted of 13 HIV+ participants in the treatment group and 13 HIV+ participants in the active control group. For our behavioural analysis, we deleted data from one participant in the control group, as they did not respond to more than 38% of the trials and appeared to have pressed the same response key (*q*) for both congruent and incongruent trials on the SCWT, at post-assessment.

Figure 7.1. Flowchart of the Study



7.4.2 **Experimental Procedure**

Design

The study used a repeated measures design. This design enabled us to collect behavioural and neuroimaging data, pre- and post-treatment to allow for the investigation of the active ingredient on the dependent measures, namely performance on congruent and incongruent measures on the SCWT and on fNIRS imaging, to investigate changes in oxygenated (HbO) and deoxygenated hemoglobin (Hb) concentration, pre- and post-in the intervention.

Assessment before and after Sustained Attention Training: SCWT Tasks

For the behavioural assessments, we used the SCWT, described in our previous study, Zondo et al. (2024). Participants completed a computerised version of the SCWT at pre - and post-assessment. The SCWT was built using PsychoPy (Peirce & MacAskill, 2018). Before completing the computerised version of the SCWT, participants completed the pencil and paper version of the SCWT and received feedback on their performance (Supplementary Material File 1). The SCWT took the form of an fNIRS block design[28] adapted from Schroeter et al. (2002). In the classical SCWT, a colour word, such as blue, is written in an ink colour, which may or may not be the same as the colour word. First, the participant must name the colour of the word while ignoring the actual word. Then, the participant must read the word and ignore the colour (Stroop, 1935; Treisman & Fearnley, 1969). The Stroop interference effect occurs when reading the word interferes with naming the colour (incongruent condition). Generally, the interference effect requires greater attentional capacity. Responses on the incongruent task

[28] We adopted the block design procedure as opposed to the event-related design. The former has been indicated to show stronger statistical power and elucidate greater hemodynamic responses (Friston et al., 1999; Scholkmann et al., 2014).

have been associated with slower responses, less accuracy, and greater cortical activation in the central executive network (Schroeter et al., 2002, 2004).

For the SCWT, participants answered the following question: "*Does the colour ink of the top word match the meaning of the bottom word*?". As indicated in Figure 7.2, two conditions were implemented to answer this question, namely, Condition 1, which was a Congruent Block (the colour of the top word was the same as the meaning of the bottom word), and Condition 2, which was an Incongruent Block (colour of the top word differed from the meaning of the bottom word).

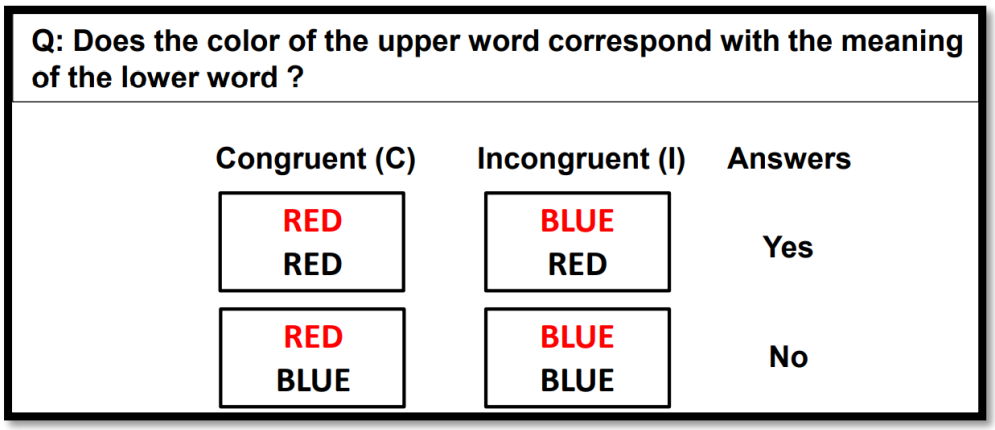


Figure 7.2. The SCWT adapted from Schroeter et al. (2002).

As indicated in Figure 7.3, blocks (Congruent, Incongruent) were randomly assigned, with each block presented for 10 seconds, interspaced with 15 seconds of rest, were participants had to stare at a '+' sign before responding to the block condition. Each block condition was presented five times for a maximum of ten blocks, during which participants were required to press *q* on the computer keyboard in response to congruent stimuli and *p* in response to incongruent stimuli. All event markers (triggers) were programmed on PsychoPy and sent to the Aurora Acquisition Software (NIRx, Medical Technologies, LLC, Berlin, Germany), via lab streaming layer (LSL).

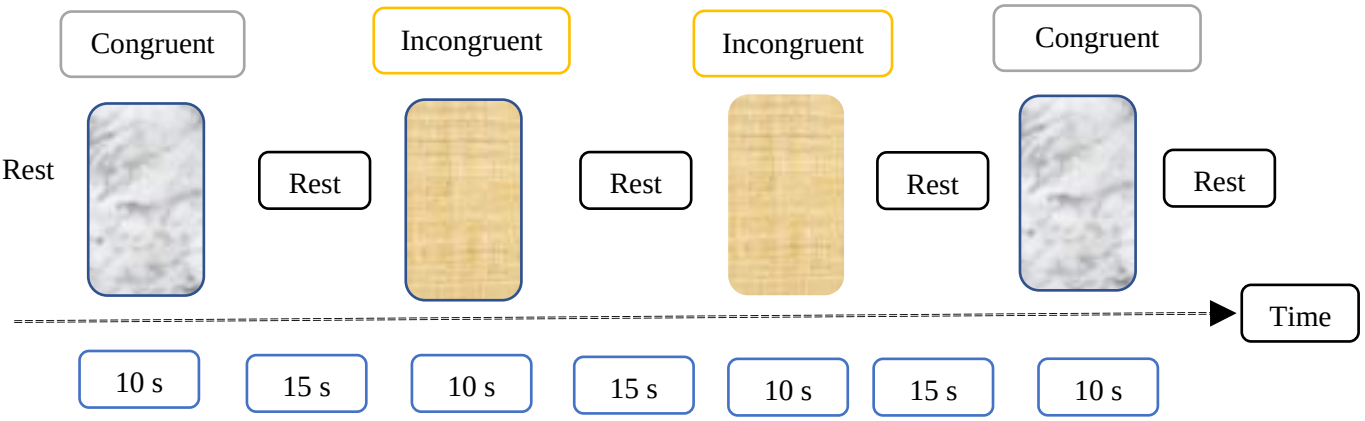


Figure 7.3. The SCTW Block Design: In total, 10 blocks (five congruent and five incongruent) lasting ten seconds each were interspaced with 15 seconds of rest.

7.4.3 **Cognitive Intervention: ACTIVATE**

Attention training was administered using ACTIVATE™ (Wexler et al., 2021b), a computerized training program comprising six games targeting sustained attention, working memory, inhibitory control, and cognitive flexibility. The program was installed onto the computers of the respective children's shelters, and participants completed the tasks after school hours. Cognitive tasks included multiple attention tasks such as memorizing sequences of stimuli presentations, completing pattern design, task-switching and assigning objects to categories. Training tasks were deployed to recruit 'top-down processes', requiring wilful control of cognitive processes to maintain vigilance and enhance task alertness (Wexler, 2013). The program automatically staggered cognitive tasks based on levels of complexity. Each new level of complexity was uniquely customized for each participant, using customized dynamic feedback automations built within ACTIVATE™ (Wexler et al., 2021a). The program was specifically useful for the purposes of the research as it contains proven adaptive titration features, that ensure tasks automatically adjust in difficulty, based on the participant's performance and mastery, thus maintaining an optimal level of cognitive engagement during the cognitive rehabilitation, ensuring long-term cognitive improvements (Wexler, 2013). Lastly, ACTIVATE™ has been scientifically validated to improve cognition in developmental

disorders, namely ADHD (e.g., Bikic et al., 2018), and has been demonstrated to show improved neurocognition, when paired with neuroimaging techniques, such as EEGs (e.g., Smith et al., 2019).

In total, participants completed three cognitive training sessions per week. All sessions were conducted individually and were supervised by a research assistant, *not* blinded to the experimental conditions. Each session lasted approximately 25-30 minutes in length, with the intervention spanning a period of six months. Further details regarding ACTIVATE™ can be found on the C8 sciences website (http://www.c8sciences.com/about/games/).

7.4.4 **Control Group**

We initially utilized an active control group; however, due to high attrition, the control group took the form of a treatment-as-usual (TAU) control. The TAU group continued with regular psychosocial and/or neuropharmacological therapy (cART), without receiving the active ingredient inherent in the intervention. At study entry, two participants in the TAU group were receiving intermittent psychosocial care from the attending nurse(s), three were receiving one-to-one school assistance, and one was receiving speech therapy service.

7.4.5 **Functional Near-Infrared Spectrometry**

Data Acquisition and montage

We measured cerebral activity based on concentration changes in oxygenated (HbO) and deoxygenated hemoglobin (Hb). There is an overlap of fNIRS neuroimaging procedures in the current study, to those described in our previous study (Zondo et al., 2024). Data were collected using the NIRxSport2 (NIRx, Medical Technologies, LLC, Berlin, Germany), a portable continuous wave fNIRS device, while participants completed the SCWT. As indicated in Figure 7.4, we used eight LED emitters (sources), paired with seven photodiode detectors, covering the prefrontal cortex. The optodes were placed according to the 10-20 system (Jasper,

1958), using a standardized prefrontal fNIRS Headband (EasyCap, NIRx, Medical Technologies, LLC, Berlin, Germany).

Probe placement (sources and detectors) to identify the most sensitive placement for each optode location was determined using the 'fNIRS Optodes Location Decider' (fOLD) software (Zimeo Morais et al., 2018) (Supplementary Information 1), paired with relevant Montreal Neurological Institute (MNI), coordinates (Table 1). Please note that the Optode Placement, and reporting of MNI coordinates differs from our previous methods section (Zondo et al., 2024). The placement of sources and detectors corresponded with cortical regions implicated in attention, and working memory within the central executive network (CEN), namely the frontopolar, orbitofrontal, and dorsolateral prefrontal cortices (Esterman & Rothlein, 2019; Rosenberg et al., 2016; Martin Sarter et al., 2001).

In total, signals were captured from twenty-two channels covering the prefrontal cortex. The distance between sources and detectors was set at 2.5 cm, following guidelines for data acquisition with paediatric and adolescent samples (Pinti et al., 2019). Data were recorded at a sampling frequency rate of 10.2 Hz, based on two wavelengths, 760 and 850 nm.

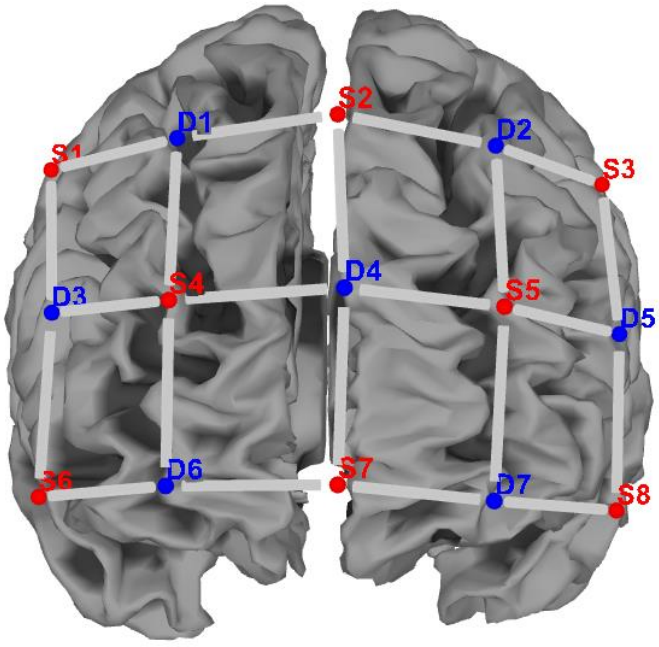


Figure 7.4. Optode Placement Montage: Regions of interest for our study covered the frontopolar area, and DLPFC. Optode placements followed the 10-20 system.

Table 7.1 fNIRS Optodes and corresponding brain regions

Channel	Optode name	MNI Position			BA	Anatomical Location (Specificity %)
		x	***y***	***z***		
CH 1	S1- D1	30	40	41	9	Right dorsolateral prefrontal cortex (69)
					46	Right dorsolateral prefrontal cortex (22)
CH 2	S1 - D3	46	38	24	45	Right pars triangularis Broca's Area (71)
					46	Right dorsolateral prefrontal cortex (24)
CH 3	S2- D1	10	41	50	9	Right dorsolateral prefrontal cortex (68)
					8	Right includes frontal eye fields (29)
CH 4	S2 - D2	-9	41	50	9	Left dorsolateral prefrontal cortex (63)
					8	Left includes frontal eye fields (35)
CH 5	S2 - D4	2	50	39	9	Medial dorsolateral prefrontal cortex (62)
					10	Medial Frontopolar Area (20)
CH 6	S3 - D2	-31	39	41	9	Left dorsolateral prefrontal cortex (67)
					46	Left dorsolateral prefrontal cortex (25)
CH 7	S3 - D5	-46	39	26	45	Left pars triangularis Broca's Area (73)
					46	Left dorsolateral prefrontal cortex (22)
CH 8	S4 - D3	40	50	16	46	Right dorsolateral prefrontal cortex (47)
					45	Right pars triangularis Broca's Area (30)
					10	Right frontopolar area (19)
CH 9	S4 - D4	13	61	24	10	Right frontopolar area (72)
					11	Right orbitofrontal area 17)
CH 10	S4 - D6	22	52	33	9	Right dorsolateral prefrontal cortex (51)
					46	Right dorsolateral prefrontal cortex (26)
CH 11	S6 - D5	-39	50	17	46	Left dorsolateral prefrontal cortex (49)
					45	Left pars triangularis Broca's area (32)
CH 12	S5 - D4	-12	62	23	10	Left frontopolar area (76)
					9	Left dorsolateral prefrontal cortex (15)
CH 13	S5 - D7	-24	63	9	10	Left frontopolar Area (70)
					11	Left orbitofrontal area (20)
					46	Left dorsolateral (9)
CH 14	S6 - D3	48	46	5	45	Right pars triangularis Broca's Area (44)
					46	Right dorsolateral prefrontal cortex (43)
CH 15	S6 - D6	25	63	9	10	Right frontopolar area (69)
					11	Right orbitofrontal area (22)
CH 16	S7 - D4	1	64	14	10	Medial frontopolar area (88)
CH 17	S7 - D6	13	67	0	10	Right frontopolar area (53)
					11	Right orbitofrontal area (45)
CH 18	S7 - D7	-12	67	0	10	Left Frontopolar area (54)
					11	Left orbitofrontal area (45)
CH 19	S8 - D5	-47	46	6	45	Left pars triangularis Broca's area (49)
					46	Left dorsolateral prefrontal cortex (43)
CH 20	S8 - D7	-23	62	23	9	Left dorsolateral prefrontal cortex (48)
					46	Left dorsolateral prefrontal cortex (32)
					10	Left Frontopolar Area (17)

Note: fNIRS, functional near infrared spectrometry, MNI, Montreal Neurological Institute, BA, Brodman Area, Specificity %, anatomical overlap with cortical region.

Procedure

All participants were tested individually in a quiet room, with a desk, computer, and chair, at the children's shelter. Upon arrival, participants were first seated at a desk equipped with a computer (screen diameter: 22 centimetres; height: 33.2 centimetres) and were requested to complete a series of assessments. Firstly, participants were requested to verify their demographic data collected during the recruitment phase of the study. Thereafter, participants read and signed the Study Information Sheet and completed the fNIRS protocol as detailed below.

fNIRS Cap Placement

Detection optodes (Table 7.1), were placed 25-30 mm, above the midpoint of the eyebrow of participants, in accordance with the 10-20 electrode system. To ensure consistency of optode placement, a red marker was used to note the 'Fpz' position. Location of the 'Fpz' was followed by cranial measurements, using a measuring tape, to establish the pre-auricular points and the distance from the nasion to the inion. Once the above fiducials were established, participants were then fitted the fNIRS cap (see Figure 7.5), which was tightly fixed with a dark shower cap to prevent external light from affecting the fNIRS signal. Once all signals and channels were deemed acceptable, as indicated by Aurora Acquisition Software, participants were administered the SCWT. The entire data collection protocol took approximately 25 minutes to complete.



Figure 7.5. Participant seating position while completing the SCWT coupled with fNIRS neuroimaging. Copyright: Laura Bell & Sizwe Zondo.

Data Preprocessing

The analysis of fNIRS data was executed on Satori fNIRS (NIRX Software, Brain Innovation, BV, Netherlands). Please note, there is an overlap of pre-processing procedures in the current protocol similar to our previous study (Zondo et al., 2024). Channel rejections were applied based on the Scalp Coupling Index (SCI) = 0.75 (Pollonini et al., 2014). Motion artefacts, including head movement, were corrected by applying spike removal parameters based on monotonic interpolations (van Brakel, 2014). Spike removal corrections were followed by temporal derivative distribution repair (TDDR) to remove baseline shifts and spike artefacts in the data (Fishburn et al., 2019). Low-frequency band-pass filtering was applied to eliminate baseline drift on the data. Physiological fluctuations related to blood pressure fluctuations (1~1.5Hz) and respiration (0.2~0.5Hz) were removed using low-pass (LP) and High-pass Butterworth filtering. In this manner, the LP filter (0.1-0.2 Hz) enabled further removal of high-frequency noise within the data that was not accounted for by brain activity (Huppert et al., 2009). The high pass filter (0.01 Hz) was applied to attenuate low-frequency signals by removing baseline drift that may have affected the hemodynamic signal. Once data was

preprocessed, changes in light intensity were converted into concentration changes in HbO and Hb, using the Modified Beer-Lambert Law (MBLL). An example of a pre-processing pipeline can be found under Supplementary Materials 1.

7.4.6 **Statistical Analysis**

7.4.7 **Behavioural Performance**

Statistical analysis was performed using SPSS Statistics Version 27. First, we evaluated the normality of the behavioural data using the Shapiro-Wilk test. The reaction time (in milliseconds), and accuracy (in total correct scores, %) data of the SCWT, were then subjected to repeated measures, paired t-tests, with group (Treatment vs Control), the between subjects' factor. Cohen's *d* was used to report the effects size, where results were statistically significant. Mean reaction times (RTs) of correctly identified responses were calculated for each participant for each condition.

7.4.8 **fNIRS**

We implemented guidelines for the analysis of repeated measures in fNIRS (NIRX Software, Brain Innovation, BV, Netherlands). Standardized beta coefficients were first derived using Satori. For each channel, we applied pre-processing filters as previously described, this was followed by convolving each stimulus (congruent, incongruent) to a hemodynamic response model. General Linear Models were then applied with the measured fNIRS (oxyHb and Hb) signals as dependent variables, and the convolved functions as independent variables. The beta values of these models were used as estimates for hemodynamic responses for the brain regions, as represented by respective channels. The sign and magnitude of each beta coefficient provided an indicator of the direction (positive/negative) and intensity of concentration changes in HbO (i.e., cortical activity) for each condition. Once all beta values were estimated, we then pattened our analysis similar to that described in Khoe et al. (2020). As such, beta values

representing HbO responses activation were recorded at pre-intervention, and these served as a baseline for post-intervention hemodynamic response comparison. Primary outcomes for HbO activation were, therefore, changes in HbO, at post-intervention, minus those at pre-intervention (ΔHbO = (Post-intervention HbO) − (Pre-intervention HbO). Concentration changes (ΔHbO) were calculated for congruent and incongruent trials for both groups. Figure 7.6 provides an example of an event marker used to calculate ΔHbO at pre and post-test within Satori fNIRS.



Figure 7.6. Event Marker Evaluating Changes in Oxygenated Hemoglobin (ΔHbO), at Pre and Post Testing: Green Bars under Parameter Weights, indicate Congruent Trials. Red bars indicate incongruent Trials. Within the 'Conditions' panel, *run1* indicates pretest HbO levels; *run2*, indicates post intervention HbO levels. For the above example, the Congruent stimuli time course is indicated in green within the *Intervals* (seconds) panel.

Changes in HbO (ΔHbO) within the Experimental and Control group, were then represented by topographical maps of regions of the prefrontal cortex. Increase in brain hemodynamic response was represented by red colors. Increased oxygenated hemoglobin levels correlated with increased hemodynamic activation and cognitive effort. Light or dark blue colors represented hemodynamic deactivation and decreased brain activity. The Shapiro-Wilk Test was used to test normality for changes in oxygenated hemoglobin (ΔHbO), pre and post the

intervention. Differences in pre- and post-measures within the group were calculated using paired samples t-test. Between-group differences in ΔHbO were evaluated using an independent samples t-test. The Benjamini-Yekutieli method (Benjamini & Yekutieli, 2001) was used to adjust for multiple comparisons.

7.5 Results

7.5.1 Demographic Data

Table 7.2 summarises the sample characteristics at baseline. Chi-squared tests revealed no significant differences between the groups, by ethnicity $\chi^2 = 0.38$, $p = 0.827$, and schooling, $\chi^2 = 0.195$, $p = 0.658$. There were, however, differences by sex, $\chi^2 = 3.86$, $p = 0.05$, and age group, $\chi^2 = 3.94$, $p = 0.05$. Although all participants were on a course of cART (n = 26), significant differences were noted in terms of medication between the groups, $\chi^2 = 6.01$, $p = 0.01$, with three participants in the treatment group on a course of cART and psychotropic medication (n = 2), coupled with ADHD medication (n = 1).

Table 7.2. Demographics Characteristics of Participants and Their Comparisons

Sample Characteristics	Treatment Group n=13	Control Group n=13	χ^2	p Value
Sex (F/M)[a]	5/8	9/4	3.86	0.05
Age Range[b] (0-13 years / 14-18 years)	3 / 10	8 / 5	3.93	0.05
Ethnicity (African, Coloured, White)	11 /1 /1	10 / 1/ 2	0.38	0.82
Medication (Mood[c] / ADHD)	2/1	0 / 0	6.19	0.01
School (Primary / Secondary)	3/10	4 / 9	0.195	0.658

Note: [a] Female and Male categories for sex. [b] Age categories were based on WHO age range suggestions for children and adolescents. [c] Participants were receiving either Risperidol or Citalopram at low dosages.

7.5.2 **Behavioural Data: *Repeated Measures***

The reaction time and accuracy scores of the SCWT, pre and post the intervention, for both the experimental and control group are indicated in Table 7.3. For the treatment group, within-subject analysis indicated no significant differences, in reaction time, in response to correctly identifying *congruent* trials (M=-0.01; SD =0.43), t (170) = - 0.45, p = 0.469, d =0.43. Notably, although not significant, participants' accuracy rates improved from 52% at baseline to 61% post the intervention (p >0.05). Results further indicated that at pre-intervention participants accurately identified 54.9% of incongruent trials, to a minimal improvement of 57%, post the intervention (p > 0.05). Notably, although there were increases in accuracy rates (%) post the

intervention, participant reaction times was significantly slower, post the intervention (*M* =1.24), compared to baseline (*M* =1.09), *p* = 0.001, *d* =0.6.

Within-subject analysis of the control group indicated an accuracy rate of 48% for congruent trials at baseline and 39% at post-intervention. On average, participants indicated slower reaction times (millisecond), post the intervention (*M* = 1.37; SD = 0.81), compared to pre-intervention (*M* = 0.97), to correctly identify congruent trials, (*M* = -0.33; *SD* =0.91), *t* (108) = -3.85, *p* = 0.011, *d* =0.91. At baseline, participants accurately identified 45.1% of incongruent trials and 43.4%, post the intervention (p>0.05). On average, participants' reaction time was significantly slower post the intervention (*M* = 1.17; *SD* = 0.6) in response to identifying incongruent trials (*M* = 0.11; *SD* =0.47), *t* (134) = -2.85, *p* = 0.05, *d* =0.47

7.5.3 **Between subject analysis**

Between subject analysis indicated no significant differences between the experimental and control group reaction times, pre and post the intervention, in response to correctly identifying congruent trials (*U* =1175, *p* = 0.76). Similarly, no significant differences were found pre and post the intervention, between the groups in terms of reaction times, to accurately identifying incongruent trials (*U* =1200, *p* = 0.065).

Table 7.3. Reaction Time and Accuracy % on the SCWT

	Treatment Group				Control Group			
	Pre		Post		Pre		Post	
	C	I	C	I	C	I	C	I
RT (sec)	1.09 (0.3)	1.24 (0.4)	1.03 (0.2)	1.27 (0.5)	0.97 (0.02)	1.03 (0.2)	1.17 (0.07)	1.15 (0.03)
ACC (%)	52%	54%	61.4%	57%	47.8%	45.1%	39.1%	43.4%

Note: For reaction time, data are presented as the M (SD). C = Congruent, I = Incongruent. RT = reaction time. ACC = Accuracy.

7.6 fNIRS Results

PFC Brain Activation: Pre & Post Intervention: Congruent Trial

Differences in brain activation are indicated by contrast t-statistics maps for HbO. We compared brain activation in the prefrontal cortex, pre- and post-intervention, in connection to (a) congruent and (b) incongruent tasks. Figure 7.7 indicates neuronal differences in ΔHbO, between the Treatment and Control group during the congruent task. Although the control group indicated greater differences in HbO activation (ΔHbO), Independent samples t-test analyses revealed no significant differences ($p > 0.05$) between the treatment and control group on any of the optodes in our regions of interest (ROI).

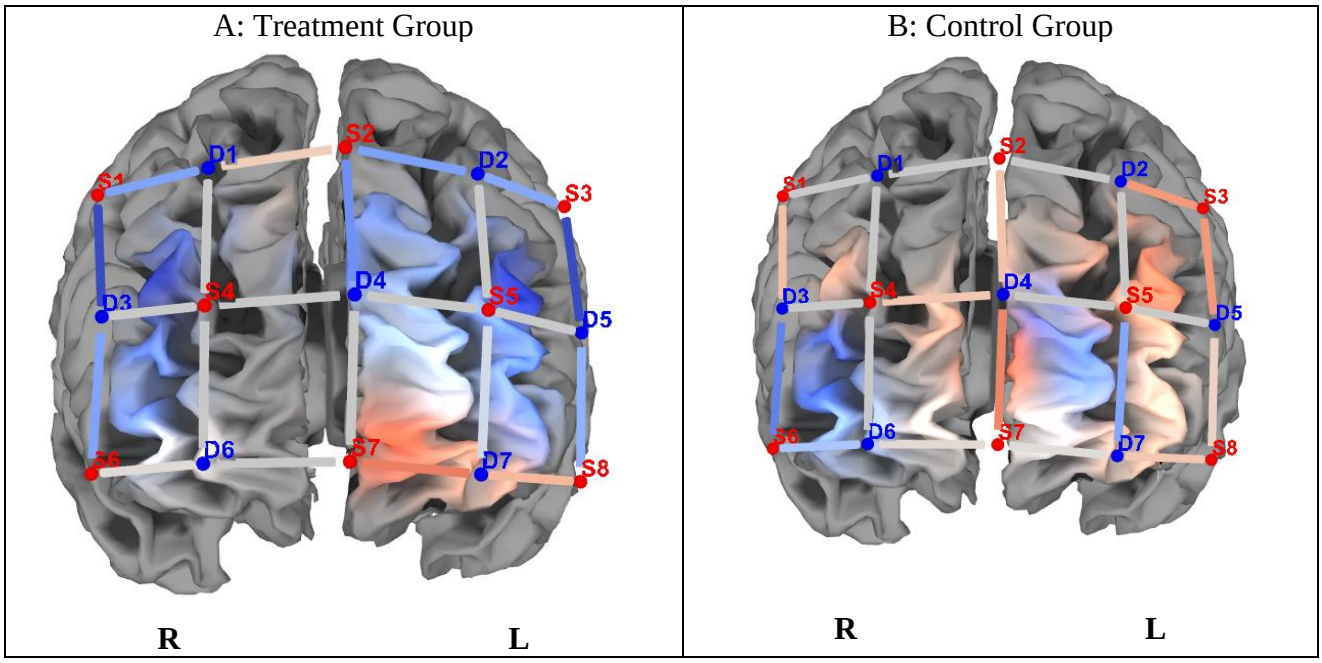


Figure 7.7. Changes in PFCA (ΔHbO), Between the Treatment and Control Group on Congruent Trials: **A**. The Treatment Group indicated lesser hemodynamic changes Pre and Post intervention (ΔHbO). **B**. The Control group seems to indicate greater hemodynamic changes on Pre and Post congruent trials (ΔHbO). No significant differences were found between the groups ($p > 0.05$). Warmer to red colours indicate greater cortical activation.

PFC Brain Activation: Pre & Post Intervention: Incongruent Trials

Figure 7.8 indicates differences in ΔHbO between the Treatment and Control group. Independent sample t-test analyses revealed that completing incongruent trials, resulted in significantly lower hemodynamic responses in the left and right DLPF (BA 9) and left frontopolar Area (BA 10)[29], within the experimental group, compared to the control group ($p < 0.05$). Table 7.4 summarises significant areas of lower activation in the experimental group compared to the control group.

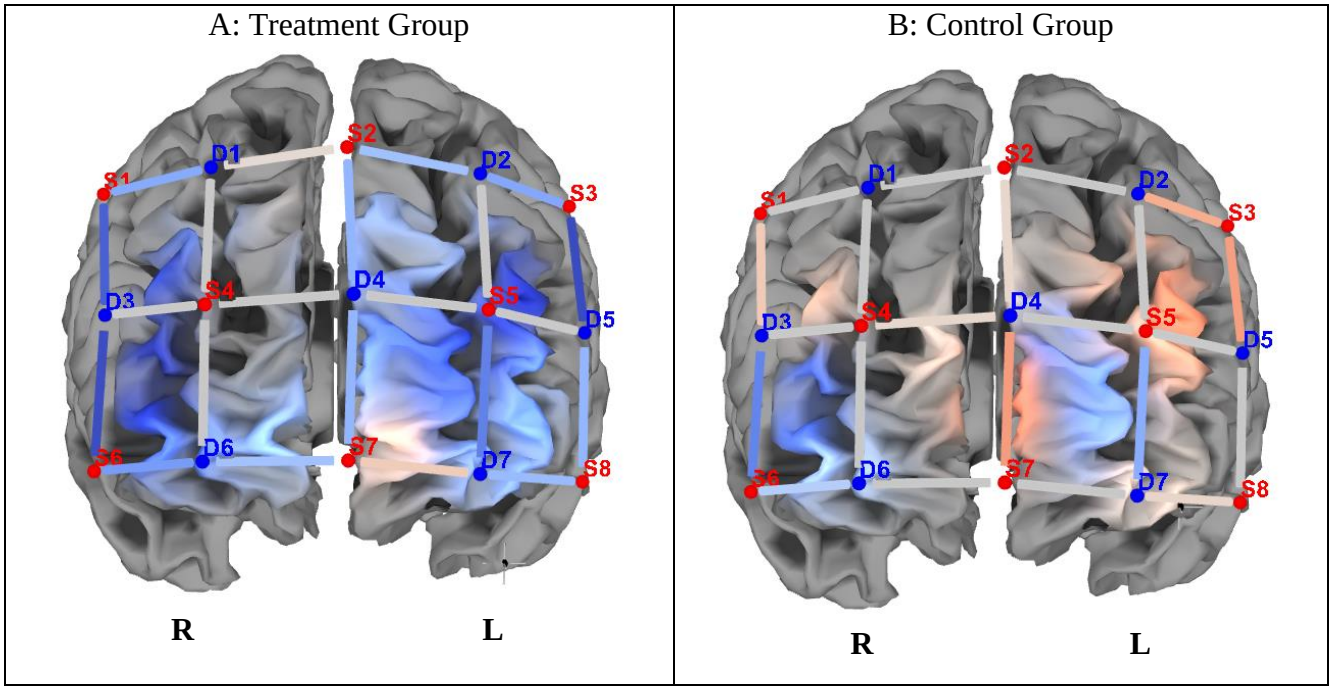


Figure 7.8. Changes in PFCA (ΔHbO), Between the Treatment and Control Group on Incongruent Trials: **A**. The Treatment Group indicated lesser hemodynamic changes Pre and Post intervention (ΔHbO). **B**. The Control group indicated greater hemodynamic changes in Pre and Post Incongruent Trials (ΔHbO). Significant differences were noted between the groups with reference to ΔHbO ($p < 0.05$). Warmer to red colours indicate greater cortical activation.

[29] Some studies include the medial prefrontal cortex (MPFC), as part of Broadman Area 10 (Passingham, 2021). The terms Frontopolar and anterior prefrontal cortex are used simultaneously in the neuroscience literature. Both anatomical regions, including the MPFC, constitute Broadman Area 10 (Passingham, 2021).

Table 7.4 Areas of Significantly Lower Activation in the HIV Treatment group in Relation to Completing Incongruent Trials

Channel	Optode name	MNI Position			BA	Anatomical Region
		x	***y***	***z***		
CH 2	S1 - D3	46	38	24	45	Right pars triangularis Broca's Area
					46	Right dorsolateral prefrontal cortex
CH 7	S3 - D5	-46	39	26	45	Left pars triangularis Broca's Area
					46	Left dorsolateral prefrontal cortex
CH 14	S6 - D3	48	46	5	45	Right pars triangularis Broca's Area
					46	Right dorsolateral prefrontal cortex
CH 18	S7 - D7	-12	67	0	10	Left frontopolar area
					11	Left Orbitofrontal area
CH 19	S8 - D5	-47	46	6	45	Left pars triangularis Broca's area
					46	Left dorsolateral prefrontal cortex
CH 20	S8 - D7	-23	62	23	9	Left dorsolateral prefrontal cortex
					46	Left dorsolateral prefrontal cortex
					10	Left frontopolar Area

Note: S = Source, D = Detector; MNI Montreal Neurological Institute; BA = Brodman Area.

7.7 Discussion

HIV crosses the BBB, causing aberrant neural transmission in the prefrontal cortex, and frontostriatal network (Ipser et al., 2015). Disturbance in neural cytoarchitecture is associated with decreased cognitive function, in attention, working memory and executive functions (Brew, 2018; Hammond et al., 2019). Significantly, cART cannot reverse cognitive decline due to their toxicity and impermeability within the BBB (Chaganti & Brew, 2021; Gonzalez et al., 2020). Functional neuroimaging indicates that individuals living with HIV typically indicate lower task-induced BOLD activation in the central executive networks (CEN), but greater BOLD activation in both the CEN and compensatory brain regions (i.e., the parietal regions), with increased attention and working memory load (Chang et al., 2004, 2013; Chang & Shukla, 2018b; Ernst et al., 2009; O'Connor et al., 2023). In neuroHIV, typically, increased BOLD activation is a marker of neuronal inefficiency, as the cortex overcompensates and

recruits associative neural networks in response to resolving cognitive demands consigned to it (Chang et al., 2004, 2013; Ernst et al., 2009).

Working memory training, in adult HIV (Chang et al., 2017b), however, indicates that prolonged brain training may lead to cognitive proficiency in working memory tasks, which is associated with decreased BOLD activation, symbolic of neural efficiency, and task proficiency. Notwithstanding these findings, no empirical studies exist investigating changes in BOLD or hemodynamic responses in pediatric and adolescent HIV in Sub-Saharan Africa, which continues to bear the brunt of neuroHIV. Given this dearth, our study investigated brain training, and whether attention remediation increased cognitive scores, and whether cognitive outcomes corroborate with decreased hemodynamic responses activation within the prefrontal cortex. Contrary to Chang et al. (2017), who employed fMRI, we investigated brain plasticity in pediatric and adolescent HIV, using optical neuroimaging techniques in the form of fNIRS.

Firstly, we investigated whether HIV positive participants receiving sustained attention training, indicate improved cognitive outcomes on the SCWT, compared to controls, sequent brain training. Although not significant, within-subject analysis indicated gains in congruent trial accuracy on the SCWT, pre- and post-intervention (52% vs 61%) for the experimental group. This accuracy gain was not evident in the control group (48% vs 39%), who indicated a decline in performance on the task from pre- to post-test. Despite gains in congruency trial accuracy, within the experimental group, attention remediation had minimal impact on accuracy outcomes on incongruent trials (54% vs 57%). Similar to congruent outcomes, the control group indicated a decline in performance on incongruent trials and maintained increased hemodynamic responses levels when solving lower task congruent trials. Although no significant between-group differences were observed on the behavioural measures, particularly on reaction times for correctly identifying congruent and incongruent stimuli, our

study found significant differences on hemodynamic responses, between the groups in reaction to completing incongruent stimuli.

Secondary to the above, we investigated whether improvements on cognitive measures correlate with decreased hemodynamic responses in the prefrontal cortex post attention training. With reference to congruent trials, our findings indicated that although the control group showed increased hemodynamic responses activation on ΔHbO, compared to the experimental group, these changes were statistically insignificant. Concerning incongruent trials, we found significant differences in ΔHbO between the experimental and control group, with the control group showing increased hemodynamic responses, and the experimental group indicating attenuation in hemodynamic responses, suggesting greater neural efficiency in dedicated areas. Defined cortical regions of hemodynamic attenuation were localised to the frontopolar/anterior prefrontal area (BA 10; unilateral), dorsolateral PFC (BA 9/46; bilateral), the orbitofrontal region (BA 11; bilateral), and the pars triangularis Broca's Area (BA 45; bilateral), in relation to the interference task (incongruent) of the SCWT.

The SCWT interference task typically places significant cognitive load on cortical processes, resulting in hyperactivation of cortical regions, including the dorsal, orbitofrontal, medial prefrontal and ventrolateral prefrontal cortex (Banich, 2019; Zysset et al., 2001). Findings from our study that attention training in neuroHIV seems to induce decreased hemodynamic responses in the central executive network are particularly noteworthy. Since the dorsolateral prefrontal network is connected to the orbitofrontal cortex (OFC) (Area 11) through association fibres (Passingham, 2021), the concomitant decrease in hemodynamic responses in these regions may be suggestive of brain training to enhance participants' ability to inhibit automatic responses and to better monitor and adjust their response strategies, to improve their accuracy on incongruent trials on the SCWT (Spielberg et al., 2015).

The findings from our study are similar to those reported by Chang et al. (2017), who observed decreased BOLD activation in the dorsal and lateral cortices, following working memory intervention. In their study, decreased BOLD activation was accompanied by improved performance on the *n*-back-2, a working memory task. Similarly, Vartanian et al. (2013), observed decreased BOLD activation and increased cognitive performance amongst neurotypical individuals undertaking five sessions of working memory training. Contrary to Chang et al. and Vartanian et al. (2013), who observed an association between decreased BOLD activation, and increased cognitive performance, sequent brain training, our study primarily observed decreased hemodynamic response (on incongruent trials), not concomitant with increased cognitive outcomes on the SCWT.

Notwithstanding the absence of significant cognitive improvements following brain training, decreased cortical activation in Area 10, as observed in the experimental group is a noteworthy finding. The frontopolar area (Area 10) is implicated in maintaining alertness and subsequent retrieval of stored information to solve mental activities (Hogeveen et al., 2022). Due to projections of the frontopolar region to the anterior cingulate cortex (ACC), which is implicated in neuroHIV (Israel et al., 2019; Toich et al., 2017), decreased hemodynamic activation in Area 10 may be suggestive of improved neural efficiency and cortical proficiency. Moreover, attenuation in hemodynamic responses may be indicative of reduced requirement of the 'top-down attention network' to solve cognitive tasks such as the SCWT, which place greater cognitive load, on 'top-down attention' networks (Banich, 2019).

Markedly, decreased hemodynamic responses in the left pars triangularis Broca's Area and the orbitofrontal area are notable findings. Broca's area is activated during the completion of the SCWT, especially in incongruent trials (Wallentin et al., 2015). To this end, the interference trial of the SCWT places significant cognitive load on language processes, that require identifying the ink colour of the SCWT, while inhibiting the conflict that may arise

when identifying the colour of the word (Wallentin et al., 2015). In our study, in addition to correctly identifying incongruent stimuli, participants had to manipulate visual data (colour word) and employ cognitive flexibility, so as not associate a colour with a word, thus engaging the orbitofrontal cortex (Li et al., 2019; Rolls et al., 1996). Thus, a decrease in this region may suggest less requirement for 'top-down' attention processing sequent the intervention.

Pertaining our study, despite observed hemodynamic attenuation in the cortical regions identified above, participants in the experimental group did not show significant increase in accuracy rates (%), pre- and post-intervention, and neither did they indicate improved reaction time rates, compared to the control group, in identifying congruent and incongruent trials. As such, it may appear that improvements due to the intervention were primarily noted at the cortical level, and these improvements did not explicitly transfer to a behavioural level. Findings from our study, indicating neural changes, independent of observed cognitive gains, are not unique. A comprehensive systematic review analysing findings of brain imaging studies related to working memory training found that, although for the most part, decreased BOLD activation is associated with improved neurocognition in brain training, neural changes (BOLD activation) often precede observable cognitive gains (Brooks et al., 2020).

The review further indicated that gains in neural attenuation and increased functional connectivity, are often observed relatively earlier than cognitive gains, indicative of the malleability of the cerebral cortex. The authors highlight that the timing of cognitive changes following brain training are dependent on multiple variables, including duration of the training, individual differences in neural plasticity, and the intensity of the brain training. Nonetheless, observed changes in hemodynamic attenuation, preceding cognitive efficiency, maybe suggestive of neuronal plasticity and synaptic connectivity, with cognitive gains being more apparent after longer brain training duration. Indeed, other empirical studies (e.g., Powell &

Redish, 2016; Tremblay et al., 1998) have indicated that neuronal changes may precede observable cognitive behavioural change in brain training interventions.

7.7.1 **Limitations and Future Directions**

To the best of our knowledge, this if the first study investigating hemodynamic responses related to brain training in pediatric neuroHIV. Although our findings indicate the value of brain training, as an adjunct to cART, our study has several limitations. Firstly, due to the nature of the sample (vulnerable children and adolescents living with HIV), the study experienced high attrition rates, leading to a small sample size, decreasing the statistical power of the study. Future studies could benefit from large sample sizes to expand on the early findings of our study.

Secondly, although we followed randomization procedures, in group allocation, there were age and sex differences between the groups at baseline. Future studies could benefit from equally matched experimental and control group, in terms of baseline characteristics inclusive of neurocognition, sex, age, and schooling level. Moreover, from a design perspective, the neuroscience literature indicates that several factors influence cognitive outcomes in pediatric and adolescent HIV, including, inter-individual differences in the neurobiological sequelae of HIV (Brahmbhatt et al., 2017; Brew & Garber, 2018), HIV genotype, and the commencement of cART. Our study did not investigate the effect of these latent variables on hemodynamic responses and behavioural outcomes, pre and post the intervention. Future studies could expand their scope and investigate the influence of latent variables on brain plasticity and neuronal activation.

Moreover, outcomes in brain training protocols are influenced by multiple moderator variables, such as the *type* of control group (s) employed, blinding of subjects to condition, minimizing participant expectation, personality and the duration of the intervention (Shawn

Green et al., 2019; Simons et al., 2016). It is recommended that future studies employ *active control group* instead of a treatment as usual controls (Simons et al., 2016), as active controls better ascertain the active ingredient in brain training protocols, compared to passive controls.

Additionally, we only investigated neural changes one month after the cognitive training. There has been a clarion call within the brain plasticity literature for experimental studies, such as the current study, to conduct follow ups at post-intervention and after a prolonged period (i.e., six-month), to investigate the long-term efficacy of brain training (Simons et al., 2016). Our study conducted a single follow up, at one-month post brain training. It is suggested future studies conduct more follow ups, to investigate brain training efficacy, and whether hemodynamic attenuations are sustained with cognitive correlates.

Lastly, the fNIRS protocol used in our study covered a limited region of interest (Table 1), to investigate neuroHIV and neuroplasticity. Although the PFC is a key cortical region implicated in neuroHIV, it is recommended that future studies use optodes that cover the fronto-parietal network (FPN) in order to extensively investigate neural acreage, sequent brain training. It is also recommended that future fNIRS studies implement short separation channels to mitigate the effect of systemic physiological noise on neuronal data (Pfeifer et al., 2018).

7.8 Conclusions

Cortical perturbations in neuroHIV result in increased BOLD activation when undertaking cognitive tasks due to neuronal overcompensation (Chang & Shukla, 2018b; Ernst et al., 2009; O'Connor et al., 2023). We employed functional near-infrared spectrometry (fNIRS) neuroimaging as a marker to study cortical efficiency following attention training. Our study indicates the promise of brain training to induce brain plasticity in adolescent HIV, as indicated by decreased hemodynamic responses in the prefrontal cortex, post the intervention within the treatment group. Markedly, our study found that attenuation in hemodynamic responses is

associated with improved neurocognition, albeit at a minimal level, on incongruent trials of the SCWT, a sustained attention, and inhibitory control task. In conclusion, attention remediation holds promise as an adjunct to cARTs, for adolescent and pediatric populations who continue to bear the consequences of maladaptive neurocognitive outcomes, sequent neuroHIV.

7.9 Acknowledgements

The authors would like to thank the Directors of the children's shelters, the children, and their guardians for participating in the study. The authors would like to acknowledge Professor Rickson Mesquita for his assistance with fNIRS data analysis. Lastly, the corresponding, acknowledges the Centre for African Studies (CAS), at Harvard University, for hosting him during his Fellowship at the University.

7.10 Conflict of Interest

There are no conflicts of interest to declare. Copyright permission for the use of all images, has been obtained from the appropriate publishing house.

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CHAPTER 8

Cortical Neuroplasticity and Seed Based Functional Connectivity in Adolescent neuroHIV: An fNIRS Investigation

Manuscript Under Preparation. Zondo, S (2024). Target Journal: *Behavioural Brain Research*

Abstract: HIV neuroinvasion results in neuronal dysregulation and compromised neurocognition. Neuroplasticity measures, such as HIV cognitive rehabilitation, have shown potential in partially reversing cognitive deficits sequent HIV invasion. Previous functional NIRS (fNIRS) studies demonstrate that customised attention brain training (ABT) has the potential to alter brain activity in adolescents with HIV. Nonetheless, the effects of ABT on brain functional connectivity in adolescent HIV remains unclear. Instead of focusing on averaged hemodynamic responses related to brain plasticity, the current investigation undertook a functional connectivity analysis, paired with behavioural data, to investigate brain plasticity among participants receiving either 12 weeks of ABT, compared to Treatment as Usual (TAU) controls. Twenty-six adolescents living with HIV were recruited and randomly assigned to either the ABT treatment group ($N = 13$) or the TAU group ($N = 13$). Participants completed NEPSY-II and functional near-infrared spectrometry (fNIRS) measures before and after the training. Functional connectivity (FC) measures were evaluated using seed-based correlation analysis in the central executive network (CEN) and across the hemispheres. No significant behavioural differences were noted on the NEPSY-II and BRIEF scores. However, functional connectivity measures indicated that the ABT group exhibited significantly increased FCs in the left hemisphere ($p < 0.05$) following brain training. Significantly, thresholding analysis measures indicated the dorsolateral prefrontal cortex may be a potential marker for brain training in adolescent neuroHIV.

Keywords: Adolescent HIV, brain training, Central Executive Network, seed-based correlation fNIRS, functional connectivity.

8.1 Background

The Human Immunodeficiency Virus (HIV) not only interferes with the body's immune system but also has a deleterious effect on the body's central nervous system (Morgello, 2018). Markedly, when HIV permeates the blood-brain barrier (BBB) and enters the cerebral cortex, 15%–60% of people affected by neuroHIV are indicated to experience progressive cognitive and motor decline (Alford & Vera, 2018; Elbirt et al., 2015). Cognitive decline is noted explicitly in multiple domains, including working memory (WM) (Fraser & Cockcroft, 2020), attention and processing speed (Rice et al., 2014; Wang et al., 2017), executive functions (Bugarski Ignjatovic et al., 2018) and response inhibition (Du Plessis et al., 2019). Collectively, cognitive deficits arising from neuroHIV are referred to as HIV-associated neurocognitive disorders (HAND) (Nightingale et al., 2023).

Despite the development of highly active antiretroviral drugs (ARTs), the cerebral cortex continues to be a cellular reservoir for HIV, primarily due to the inflammation of macrophages and the production of neurotoxins within the cortex (Morgello, 2018; Wilmshurst et al., 2018). Once in the cerebral cortex, HIV-initiated pathogenetic neuroinflammation is indicated to result in aberrant neural transmission (Brew 2018), white and grey matter loss (Jensen et al., 2019), neuronal apoptosis (Das et al., 2016), and catecholaminergic dysregulation (Nolan & Gaskill, 2019a), resulting to in the persistence of HAND, both in adults (Cody & Vance, 2016) and adolescents HIV populations (Hoare et al., 2016).

Given the effects of HIV in the cortex (e.g., Morgello, 2018; Nightingale et al., 2023), HIV brain training[30] protocols have taken an added pre-eminence to reverse cognitive impairment sequent neuroHIV. For example, concerning adolescent HIV, brain training

[30] The neuroscience literature uses the terms, HIV brain training, HIV adaptive training, HIV cognitive rehabilitation, HIV cognitive remediation, HIV cognitive intervention, and HIV computerised cognitive training, interchangeably. In the article, the terms HIV brain training and HIV cognitive training will be preferred.

protocols have been applied to remediate attention (Basterfield & Zondo, 2022), working memory (Fraser & Cockcroft, 2020), and executive functions (Boivin et al., 2010; Boivin et al., 2019). Notwithstanding the above, there continues to be a dearth of research pairing behavioural outcomes sequent HIV brain training with neuroimaging measures to investigate the efficacy of brain training protocols at a neuronal level, especially in children and adolescents living with HIV, in Sub-Saharan Africa (Benki-Nugent & Boivin, 2019; Musielak & Fine, 2016).

At the time of writing, the literature indicates that the sole published study pairing behavioural outcomes with neuroimaging outcomes to investigate HIV brain training is the study by Chang et al. (2017). They used functional MRI (fMRI) to investigate the effects of working memory training (WMT) on near and far transfer cognitive gains, coupled with blood oxygen level dependency (BOLD) changes, before and after brain training. Findings indicated that WMT was associated with significantly reduced BOLD activation in the frontal and parietal regions of HIV+ patients (n=11; mean age = 41; SD = 4.8) and HIV-negative controls (n=11; mean age = 38; SD = 4.8) receiving WMT. As noted by the authors, reduced BOLD activation and increased performance on untrained near tasks (Digit Span and Spatial-Span) following WMT were suggestive of improved intrinsic functional connectivity and reduced neuronal demand to complete working memory tasks (Chang et al., 2017).

In a similar study using functional near-infrared spectrometry (fNIRS), Zondo et al. 2024b, (*under review*) investigated neuronal changes among HIV+ adolescents (n = 13; mean age = 16; SD = 1.2), receiving brain training to remediate attention skills, and HIV+ controls (n=13; mean age = 17; SD = 1.3). Findings indicated decreased BOLD activation in the dorsolateral prefrontal (DLPF) and frontopolar network when completing incongruent trials on the Stroop Colour Word Test (SCWT) following HIV brain training. Although decreased

BOLD activation was indicative of improved neural efficiency in the SCWT, behavioural improvements did not reach statistical significance post-brain training.

Although Zondo et al. (2024b, under review) showed that brain plasticity is associated with decreased BOLD activation, sequent HIV brain training, the study did not report on functional connectivity analysis related to brain plasticity in neuroHIV. The current study seeks to cover this lacuna in the brain plasticity and neuroHIV field. Accordingly, the neuroscience literature indicates that neuronal adaptation is best investigated through functional connectivity analysis (Lang et al., 2012; Shahhosseini & Miranda, 2022). Functional connectivity (FC) is defined as the 'temporal correlations between spatially remote brain events' (Friston, 1994, p. 58). The precedence of FC analysis, as opposed to functional segregation, is that FC enables the study of distributed processing and functional interaction across and within brain regions. FC analysis, therefore, allows for the determination and analysis of cortical synchrony and temporal dependency (time) of neuronal activation within the cortex. As previously noted, there is a paucity of research investigating the relationship between cortical brain plasticity and neuroHIV. Notwithstanding this limitation, there is an even more significant shortage of research investigating functional brain connectivity following HIV cognitive rehabilitation using fNIRS.

8.1.1 **Functional Connectivity and HIV Brain Training**

A literature review indicates that the sole study investigating FC following HIV brain training is the study by Jia et al. (2023). They investigated FC, sequent working memory training (WMT), in adult HIV using resting-state fMRI (rsfMRI). rsfMRI, investigates changes in intrinsic functional networks during states of rest when subjects are not performing a specific cognitive task or receiving any cognitive stimulation (Biswal et al., 1995). From a clinical perspective, the advantage of resting state analysis is that it enables the identification of

intrinsic brain connectivity and biomarkers for brain health and brain injury (Bijsterbosch et al., 2017). In its application, rsfMRI uses spontaneous BOLD signals to study FC in spatially distinct and near brain regions.

Regarding HIV brain training, Jia et al. (2023) investigated FC as estimated by independent component analysis (ICA) and graph theory. Concerning graph theory, they investigated whether WMT (CogMed) resulted in 'network normalization' within resting state networks (RSNs), as determined by eigenvector centrality and local efficacy measures. Summarily, eigenvector centrality measures the contribution of a node *within* a cortical network (e.g., default mode network). Specifically, nodes with higher eigenvector centrality represent nodes that are not only well-connected within a network but also connected to other highly central nodes. Consequently, highly connected nodes act as hubs for information flow, enabling efficient communication between nodes within a network. Similarly, local efficiency measures how efficiently information is exchanged within a *local* neighbourhood of a node within a network.

Jia et al. (2023) investigated 'network normalization', pre and post-WMT, in the default mode network (DMN), cognitive control network (CON)[31], visual network (VIS), auditory network (AUN) and subcortical network (SC). The authors defined 'network normalization' as restoring or optimizing the functional connectivity patterns within the cortex to typical neuronal network patterns. Summarily, Jia et al. (2023) investigated whether HIV+ participants would indicate similar network organisation to HIV-negative controls post WMT, as determined by eigenvector centrality and local efficiency analysis.

[31] The CEN is referred to as the Cognitive Control Network (CON) in the study. A growing body of research seems to suggest that the CON and CEN may share the same anatomical correlates (Breukelaar et al., 2017; Menon & D'Esposito, 2021).

The samples included HIV+ (n=53; mean age = 50; SD = 1.5) and HIV seronegative controls (n=48; mean age = 49; SD = 1.6) matched for sex, race, and socioeconomic status. At preintervention, findings indicated abnormalities in RSNs in the HIV+ group, as indicated by eigenvector centrality and local efficiency measures. Post-intervention (one month) measures indicated that 'the eigenvector centrality of the ventral DMN in PWL (people with HIV), become more like that of SNs (seronegative)' (Jia et al., 2023, p. 1560). The authors conclude that changes in eigenvector centrality 'may suggest that the vDMN with high eigenvector centrality might be a key neural substrate leading to normalization of brain function within WMT' (Jia et al., 2023, p. 1560). Significantly, findings indicated that eigenvector centrality normalization (in the HIV+ group) was associated with improved memory outcomes at post-assessment. Notwithstanding this finding, the study did not provide levels of significance measures (*p-value*) for post-assessment measures (attention, executive functions), except detailing improved cognitive outcomes in memory function.

8.1.2 **The Present Study**

In the previous study (Zondo et al., 2024a), the study illustrated the feasibility of functional near-infrared spectrometry (fNIRS) to investigate regional hemodynamic activity in paediatric and adolescent HIV. In a follow-up study (Zondo et al., 2024a), we investigated the effect of attention training on BOLD activation within the CEN in adolescent HIV. Subsequent findings (Zondo et al., 2024b, *Under Review*) indicated that brain attention training (12 weeks) in adolescent HIV leads to decreased BOLD activation in the dorsolateral prefrontal cortex (DLPF) and frontopolar network in response to completing incongruent trials on the Stroop Colour Word Test (SCWT). The previous study (Zondo et al., 2024b, *Under Review*) investigated block-averaged hemodynamic activation (HbO) in response to cognitive stimuli following brain training. In the current study, the aim was to investigate task-based functional connectivity, pre and post-attention brain training, using seed-based functional connectivity.

In contrast to Jia et al. (2023), who investigated FC using rsfMRI in adults, the current study investigated FC within an adolescent HIV population. The decision to pursue fNIRS optical imaging techniques was based on cost limitations associated with fMRI in Sub-Saharan Africa (Ogbole et al., 2018). Additionally, instead of studying FC using graph theory (eigenvector centrality and local efficiency), analysis was conducted using fNIRS task-related seed-based correlation. Seed-based correlation connectivity is based on selecting an a priori 'seed' or 'seed region' based on a priori relevance to the field of study (Joel et al., 2011; Toich et al., 2017). The technique examines the temporal correlation of hemodynamic activity between the seed and distant nodes/voxels within a cortical network of interest (Joel et al., 2011; Thomason et al., 2013). Seed-based connectivity analysis has provided insights into cortical synchrony in neuroHIV (Toich et al., 2017). It has helped establish biomarkers for neurological disorders (Ji et al., 2020) and psychological treatment (Shen et al., 2020).

In addition to studying FC, the study investigated near and far cognitive transfer associated with attention-brain training. Due to the scarcity of published research on seed-based correlation analysis to investigate FC using fNIRS, sequent brain training in adolescent neuroHIV, the study did not propose any hypothesis but explored the study questions below.

8.2 Materials

The study used the ACTIVATE^{TM} intervention program (Wexler et al., 2021b). Behavioural data was gathered using the NEPSY-II, whilst imaging data was collected using fNIRS optical imaging. The same participants were used, as detailed in a previously published article (Zondo et al., 2024a).

8.2.1 Study Research Questions

1. Compared to controls, do HIV+ participants receiving attention training show improved cognitive outcomes on behavioural measures post-intervention?

2. Compared to controls, do HIV+ participants receiving attention training indicate greater functional connectivity in either of the hemispheres (left or right) in the CEN post-intervention?

8.3 Results

8.3.1 Demographic Data

Table 8.1 summarises the sample characteristics at baseline. Chi-squared tests revealed no significant differences between the groups by ethnicity ($\chi^2 = 0.38$, $p = 0.827$) and schooling ($\chi^2 = 0.195$, $p = 0.658$). There were significant differences by sex ($\chi^2 = 3.86$, $p = 0.05$) and age group ($\chi^2 = 3.94$, $p = 0.05$), with more females (n=14), and participants aged 14-18 years of age (n=15). Although all participants were on a course of cART (n = 26), significant differences were noted in terms of medication between the groups ($\chi^2 = 6.01$, $p = 0.01$), with three participants in the treatment group on an additional course of psychotropic medication for mood regulation (n = 2), and one for the management of ADHD (n = 1).

Table 8.1. Demographics Characteristics of Participants and their Comparisons (Mean/SD)

Sample Characteristics	Treatment Group n=13	Control Group n=13	χ^2	p Value
Sex (F/M)[a]	5/8	9/4	3.86	0.05*
Age Range[b] (0-13 years / 14-18 years)	3 / 10	8 / 5	3.93	0.05*
Ethnicity (African, Coloured, White)	11 /1 /1	10 / 1/ 2	0.38	0.82
Medication (Mood[c] / ADHD)	2/1	0 / 0	6.19	0.01*
School (Primary / Secondary)	3/10	4 / 9	0.195	0.658

Note: [a] Female and Male categories for sex. [b] Age categories were based on WHO age range suggestions for children and adolescents. [c] Participants were receiving either Risperidol or Citalopram at low dosages. * $p < 0.05$

8.3.2 **Behavioural Outcomes Post Brain Training**

In the first research question, the study investigated whether the experimental group would indicate improved behavioural outcomes post-brain training.

Behavioral Data

Baseline comparisons between intervention and control group

At baseline, despite randomization to groups, the experimental group obtained a significantly higher score on the Geometric Puzzles (t = 2.52; $p = 0.001$; $d = 0.9$), indicating greater ability with visuospatial perception and mental rotation relative to the control group. There were no other significant differences ($p > 0.05$) between the groups on any of the baseline assessments, indicating equivalence (Table 8.2).

Table 8.2. Neuropsychological Performance Means and standard deviation in the Experimental and Control groups at Baseline

	Baseline						
	Experimental (n=13)			Control (n=13)			
	M	SD	Range	M	SD	Range	*Statistics, p*
NEPSY-II							
Auditory Attention	6.0	4.1	2-11	5.3	3.9	2-11	0.76
Response Set	5.3	3.2	3-13	6.3	2.8	3-11	0.36
Inhibition Naming	7.0	3.0	1-13	8.3	5.1	1-19	1
Inhibition	6.3	3.6	1-13	6.3	3.5	1-14	0.95
Inhibition Switching	6.1	4.1	1-12	5.7	3.0	1-10	0.78
Inhibition Errors	1.5	1.3	1-6	1.0	0.0	1-1	0.33
Comprehension of Instructions	3.0	2.6	1-9	2.6	2.2	1-7	0.61
Speeded Naming	7.3	2.9	3-12	7.8	3.8	1-13	0.73
Memory for Faces	9.5	3.1	2-13	7.4	3.2	3-14	0.10
Memory for Faces Delayed	6.4	3.1	2-13	5.8	2.7	1-9	0.60
Word List Interference	3.3	3.4	1-12	2.2	2.2	1-8	0.12
Word List Interference Recall	5.0	3.9	1-12	2.9	3.1	1-12	
Design Copy Global	1	0.0	1-1	1	0.0	1-1	1
Geometric Puzzles	7.1	3.0	2-11	4.31	2.7	1-9	0.01**[d]
BRIEF							
BRI [a]	19.0	5.5	4-27	23.3	7.9	11-38	0.39
MI [b]	26.0	6.1	12-35	28.3	7.5	24-50	0.65
GEC [c]	45.3	11.3	16-62	51.7	13.6	36-88	0.39

Note: [a] Behavioural Regulation Index, [b] Metacognition Index, [c] Global Executive Composite, [d] Denotes non-normally distributed scales. ** p < 0.01.

Testing the effect of the intervention: Differences between experimental and control groups at post-test

Differences in pre- and post-brain training scores are indicated in Table 8.3. For the NEPSY-II, the only significant difference in favour of the experimental group was the Inhibition (INI) task (difference = 1.5; 95% CI (5.69, 6.81); $F(1, 22) = 7.45$; $p = 0.012$, $d = 0.253$. The control group showed significantly greater scores on the Response Set on post-assessment (difference = 2.48; 95% CI (7.02, 9.17); $F(1, 21) = 5.61$; $p = 0.027$, $d = 0.21$), compared to the treatment group. Although the treatment group obtained greater mean scores on several NEPSY-II subtests post-training, these were not statistically significant. For the BRIEF functional scales, the treatment group showed significantly elevated scores in the BRI ([difference = 7.41; 95% CI (15.5, 19.1); $F(1, 23) = 15.71$; $p = 0.001$, $d = 0.4$]), and MI (difference = 8.59; 95% CI (20.18, 25.81); $F(1, 23) = 9.64$; $p = 0.05$, $d = 0.29$), compared to the control group.

Table 8.3. Mean and standard deviation for Treatment and Control group at pre and post assessment

	Treatment Group						Control Group					
	Pre-Assessment			Post Assessment			Pre-Assessment			Post Assessment		
	M	SD	Range	M	SD	Range	M	SD	Range	M	SD	Range
NEPSY-II												
Auditory Attention	6.0	4.1	2-11	7.3	3.4	2-11	5.3	3.9	2-11	6.8	3.6	2-11
Response Set	5.3	3.2	3-13	6.5	3.7	3-13	6.3	2.8	3-11	9.7	2.7	3-13
Inhibition Naming	7.0	3.0	1-13	5.8	1.9	1-8	8.3	5.1	1-19	6.1	0.7	5-7
Inhibition	6.3	3.6	1-13	7.0	1.5	3-9	6.3	3.5	1-14	5.5	1.6	3-9
Inhibition Switching	6.1	4.1	1-12	3.9	2.5	1-9	5.7	3.0	1-10	2.8	1.4	1-5
Inhibition Errors	1.5	1.3	1-6	2.4	1.8	1-7	1.0	0.0	1-1	2.9	1.4	1-5
Comprehension of Instruction	3.0	2.6	1-9	2.1	2.1	1-7	2.6	2.2	1-7	1.7	2.0	1-8
Speeded Naming	7.3	2.9	3-12	7.2	2.1	4-11	7.8	3.8	1-13	7.3	2.3	3-11
Memory for Faces	9.5	3.1	2-13	10.3	2.3	6-13	7.4	3.2	3-14	9.5	1.6	8-12
Memory for Faces Delayed	6.4	3.1	2-13	9.2	1.5	8-12	5.8	2.7	1-9	7.9	2.4	5-11
Word List Interference	3.3	3.4	1-12	5.2	3.6	1-12	2.2	2.2	1-8	3.6	1.9	2-8
Word List Interference Recall	5.0	3.9	1-12	8.7	4.1	1-15	2.9	3.1	1-12	6.3	2.9	1-13
Design Copy Global	1	0.0	1-1	1	0.0	1-1	1	0.0	1-1	1	0.0	1-1
Geometric Puzzles	7.1	3.0	2-11	11.7	2.4	7-15	4.31	2.7	1-9	8.6	3.7	1-13
BRIEF												
BRI	19.0	5.5	4-27	20.7	3.9	12-26	23.3	7.9	11-38	14.0	5.1	10-29
MI	26.0	6.1	12-35	26.9	7.8	15-41	28.3	7.5	24-50	19.1	6.4	13-35
GEC	45.3	11.3	16-62	48.4	10.4	32-66	51.7	13.6	36-88	33.1	11.1	24-64

Note: NEPSY-II: Neuropsychological Assessment - Second Edition, BRIEF: Behavioral Rating of Executive Functions. BRI: Behavioral Regulating Index, MI: Metacognition Index, GEC: Global Executive Composite.

8.3.3 **Functional Connectivity Post-Brain Training**

In the second research question, the study investigated whether the treatment group would indicate greater functional connectivity in either hemisphere (right or left) due to brain training. Figures 8.1 and 8.2 indicates average seed correlation differences *within* the Treatment group, and Control group, respectively, pre-and post-training.

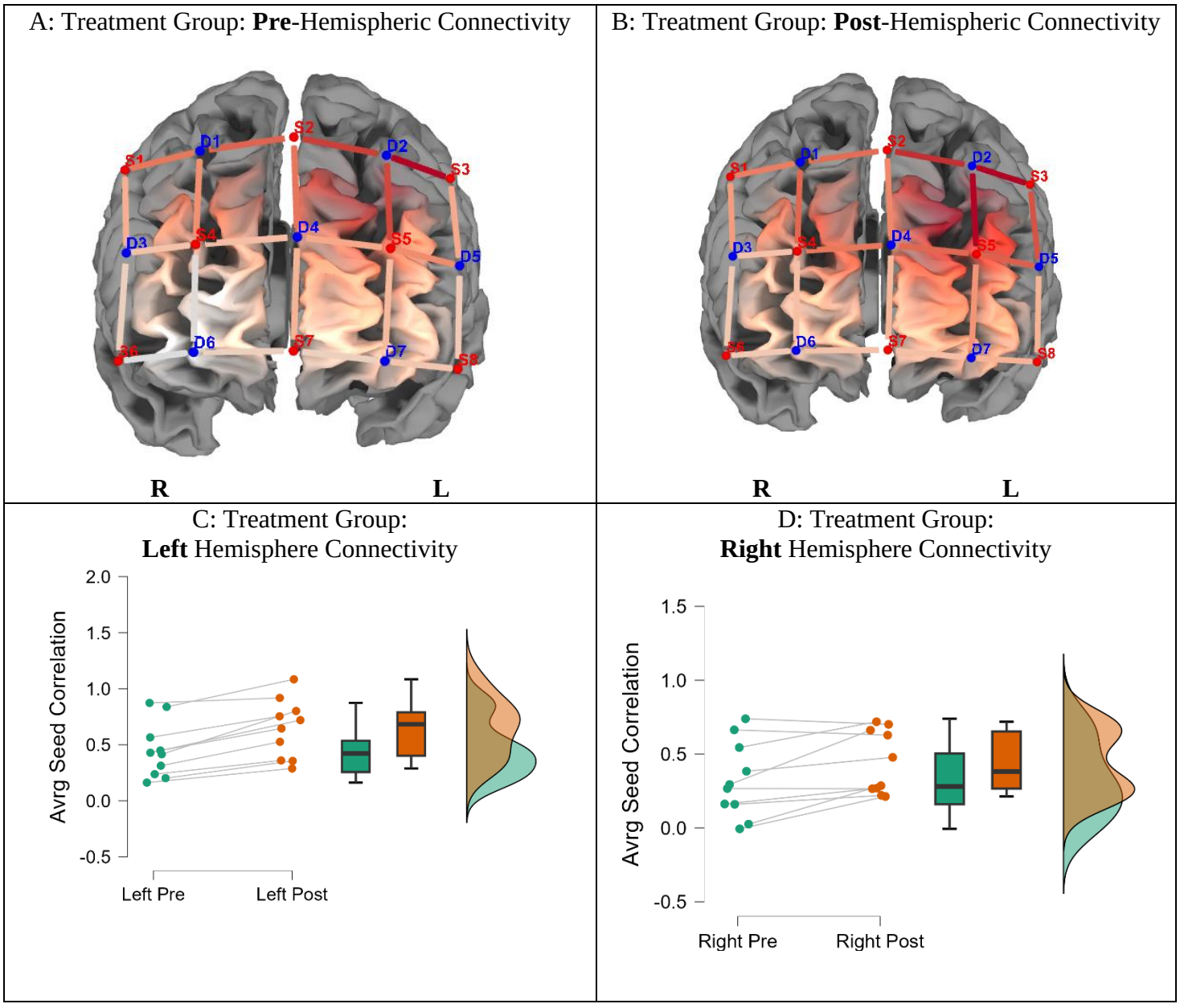


Figure 8.1. Functional Connectivity Across the Hemispheres for the Treatment Group: Seed correlations pre (A) and post the intervention (B) for the Treatment Group BY seed (S3-D2). Average differences for the left and right hemispheres, pre and post-training for the Treatment group, are indicated in captions C & D.

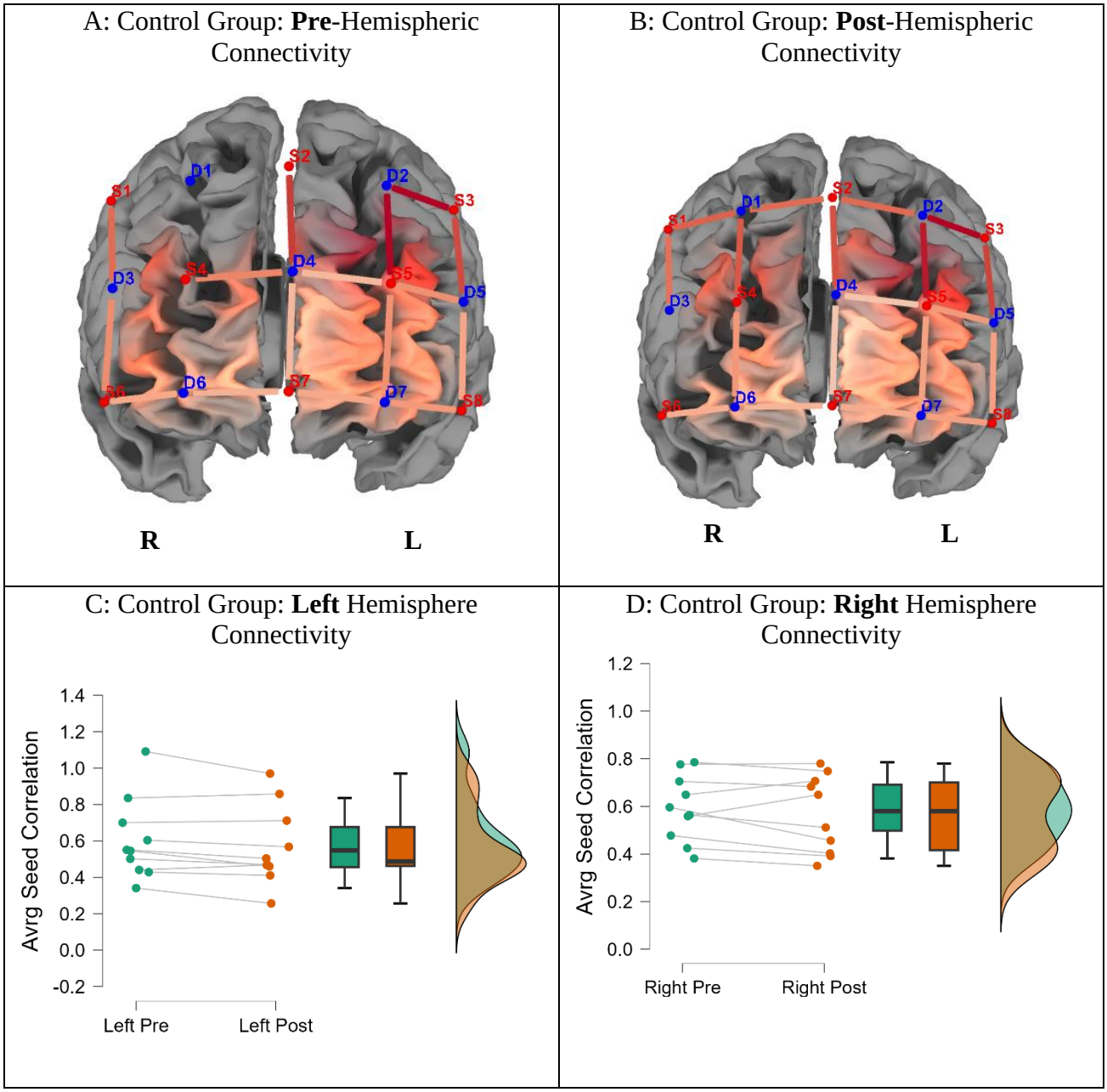


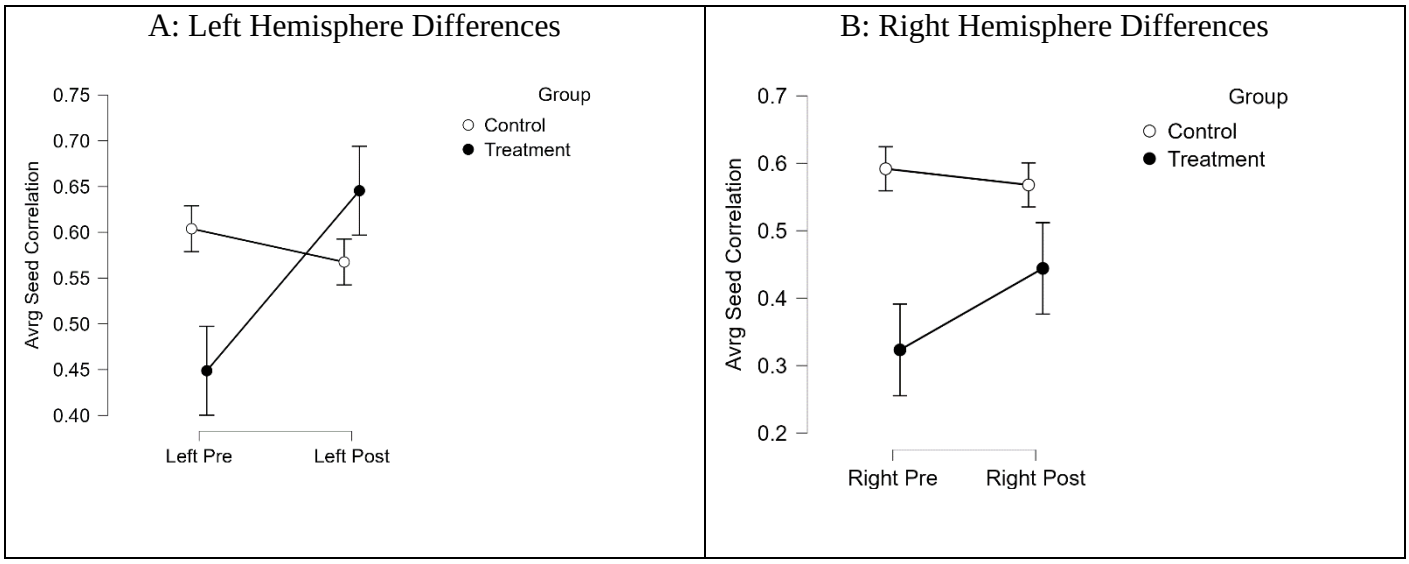
Figure 8.2. Functional Connectivity Across the Hemispheres, for the Control Group: Seed correlations pre (A) and post the intervention (B) for the Control Group BY seed (S3-D2). Average differences for the left and right hemispheres, pre and post-training for the Control group, are indicated in captions C & D.

Hemispheric Activation

Average seed-correlation differences between groups by hemispheres were executed by controlling for pretest scores using Analysis of Covariance (ANCOVAs). The treatment group showed significantly greater connectivity in the left hemisphere (difference = 0.1; 95%, CI

(0.57, 0.64); $F(1, 17) = 37.98$; $p = 0.0001$, $d = 0.7$), compared to the control group, post brain training. There were no significant differences between groups on right hemisphere connectivity. Table 8.4 summarizes group differences by hemisphere, emphasizing greater FC in the left hemisphere of participants in the treatment group, post-brain training ($M = 0.64$; $SD = 0.26$) compared to baseline ($M = 0.44$; $SD = 0.24$).

Table 8.4. Between Subject Differences in Hemisphere Activation



Note: **A**. The Treatment group indicated a significant increase in functional connectivity in left hemisphere activation, pre-and post-training. **B**. The treatment group showed increased functional connectivity in the right hemisphere, with a slight decrease in right hemisphere activation in the control group.

8.3.4 **Selection of Voxels for Rehabilitation Protocol**

In the final research question, the study investigated which voxels would 'survive' increased seed correlation thresholding (0.2, 0.4, 0.6, 0.8) post-training (within the experimental group). This data was used to estimate which voxel would indicate the largest correlation with the seed, thus providing a reasonable 'marker' for cognitive rehabilitation protocols. Figure 8.3 indicates correlation matrices, pre- and post-training, by group. Results showed that increased thresholding (at 0.8) led to the survival of two channels (S2-D2 & S3-D5), inclusive of voxels

in the left dorsolateral prefrontal cortex (x = -9; y = 41; z = 50) and those in the pars triangularis Broca's Area (x = -46; y = 39; z = 26) (Table 8.5) (Figure 8.4).

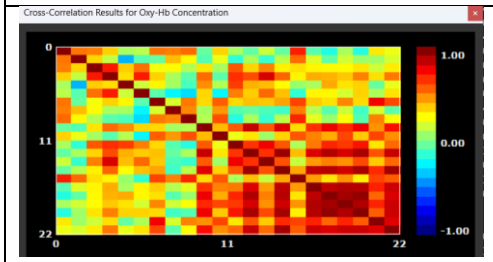
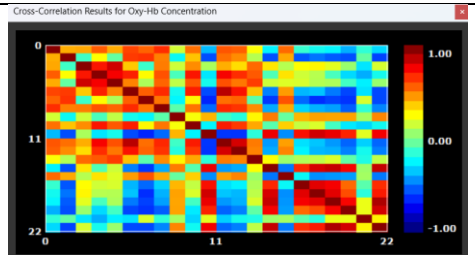
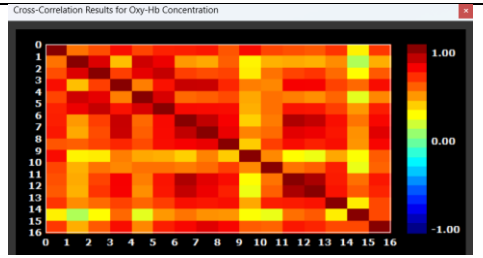
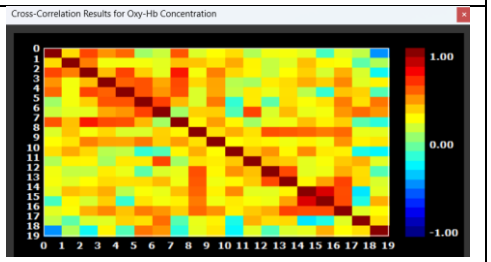
Treatment Group		Control Group	
Pre	**Post**	**Pre**	**Post**
			

Figure 8.3. Correlation Matrices Pre and Post Intervention: Correlation matrices for seed-based correlation connectivity in the HIV Treatment and Control Group, pre and post-training. The intensity maps indicate the highest FC as denoted in red blocks (strong correlation). Lower or weaker connectivity is denoted in yellow/blue boxes. The treatment group showed increased connectivity post the intervention in left activation. There was a slight decrease in connectivity in the control group at post-measures.

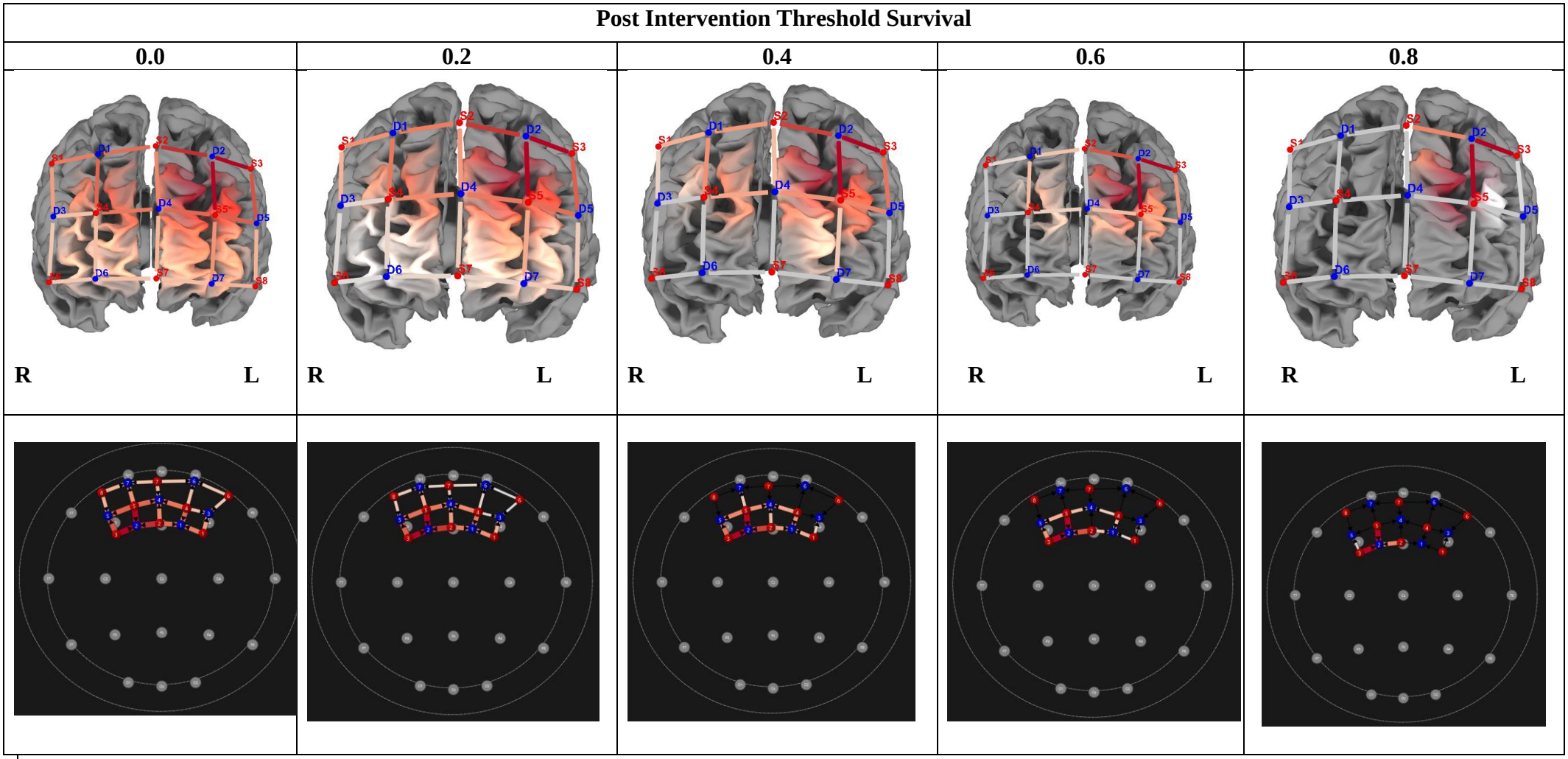


Figure 8.4. Threshold Survival: Experimental Group Post Intervention Averaging: Comparison of different threshold levels~~,~~ indicating surviving cortical regions~~,~~ post-intervention (Experimental Group). Heatmaps were calculated using seed-based correlation. The 2D maps below indicate the surviving thresholds. Warmer colours in the 3D maps indicate greater seed-based function connectivity (Seed = S3-D2).

Table 8.5. Cortical Regions Surviving 80% Thresholding

Channel	Optode name	MNI Position			BA	Anatomical Region
		x	***y***	***z***		
CH 4	S2 – D2	-9	41	50	9	Left dorsolateral prefrontal cortex
					8	Left includes frontal eye fields
CH 7	S3 - D5	-46	39	26	45	Left pars triangularis Broca's Area
					46	Left dorsolateral prefrontal cortex

8.4 Discussion

HIV crosses the BBB, leading to disturbed neuronal transmission, which is associated with decreased cognitive functions collectively referred to as HAND (Alford & Vera, 2018). Given the persistence of HAND in the era of cARTs, the study explored the extent to which neuroplasticity, in the component of attention training, may lead to improved functional connectivity (FC) and behavioural outcomes, as determined by near and far cognitive transfer gains. To determine neural mechanisms that underlie improved FC, the study employed seed-based correlational functional connectivity, with the left dorsolateral prefrontal cortex as the study primary seed. Analyses revealed nuanced findings related to functional connectivity and behavioural findings sequent attention training.

Contrary to previous studies, indicating near and far transfer cognitive gains, sequent cognitive training in adolescent neuroHIV (e.g., Boivin et al., 2019; Fraser & Cockcroft, 2020), the study found that attention training resulted in minimal behavioural gains. Primarily, findings indicated that the sole cognitive domain indicating significant changes in the treatment group after the intervention was the Inhibition subtest ($p = 0.012$, $d = 0.253$). This task assesses the ability to inhibit automatic responses in favour of novel responses. Notably, although the experimental group showed greater improvements (based on mean scaled scores) on multiple near (Auditory Attention, Inhibition Switching) and far (Memory and Learning, Visuospatial) cognitive measures post-intervention, these did not reach statistical significance. Similarly, there were no near or far transfer effects on parent-rated functional scales on the BRIEF.

Unexpectedly, the control group indicated improved performance on the Response Set (p = 0.027, d = 0.21) compared to the treatment group. Plausible explanations may exist for the above findings.

Firstly, the elongated nature of the intervention (12 weeks, 30 sessions) and the timing of the intervention exercises might have resulted in both intervention fatigue and diminished adherence to the intervention. Typically, as detailed in Zondo (2023), neuroHIV cognitive rehabilitation protocols have an intervention duration of 10 sessions or less (e.g., Boivin et al., 2010; Cody et al., 2020; Ownby & Acevedo, 2016; Pope et al., 2018; Vance et al., 2012), with a few studies involving interventions greater than 30 sessions (e.g., Fraser & Cockcroft, 2020; Livelli et al., 2015). Regarding the length of the intervention, the study chose to implement a more extended intervention period, compared to studies with shorter intervention durations (< 10), expecting more near-to-far transfer gains - this was not the case. There is reason to believe that the prolonged length of the intervention might have resulted in diminished enthusiasm for the intervention and fatigue (Bikic et al., 2018a), influencing post-assessment performance. Related to fatigue, the literature shows that individuals with chronic conditions, such as HIV, may be easily prone to greater fatigue after completing activities that require greater cognitive effort, such as those tasks involved in the intervention (Loades & Kagee, 2019; Ter Haar et al., 2021).

Similarly, the intervention protocol was implemented after school hours (3 pm - 5 pm) and occasionally over weekends; it is thus plausible that the timing of the intervention might have affected study adherence, as participants could not always make the intervention due to fatigue and lack of motivation. As such, although the intervention was customized for each participant, the nonlinear progress from one stage of the intervention to the next might have affected post-assessment scores. In line with the above, it is important to note that the control group performed better on the Response Set subtest compared to the treatment group.

This finding may be explained by natural cognitive maturation independent of intervention. As highlighted by Casey et al. (2018) and supported by Bangirana et al. (2006), since participants in our study were predominantly adolescents attending primary or secondary schooling, education might naturally foster improved cognitive flexibility coupled by intensive brain reorganization experienced during adolescence. Irrespective of our behavioural findings, other studies (e.g., Bikic et al., 2018a) have reported a lack of near and far transfer gains amongst experimental samples and greater cognitive gains amongst controls (Dovis et al., 2015) compared to the treatment group.

Notwithstanding behavioural findings, which showed limited between-group differences on neuropsychological measures post-intervention, the study revealed significant group differences between the groups on average seed correlation FC measures, specifically, greater left hemisphere connectivity in the experimental group at post-intervention. Although hemispheric a/symmetry has not been fully characterized in neuroHIV (Chang & Shukla, 2018), there is evidence of compromised white matter integrity, particularly in right hemisphere structures, implicated in visuospatial processing in children and adults infected with HIV (Hoare et al., 2011). Severe selective cortical thinning has also been observed in the left hemisphere (frontal eye field and perisylvian language areas) in neuroHIV (Thompson et al. 2005), with a comprehensive meta-analysis (Plessis et al., 2014), indicating a proclivity for neuroHIV to compromise the left inferior frontal gyrus, and subsequent function, when compared to controls. To this extent, significant group differences (HIV+ vs HIV-) in left hemispheres cortical thinning (left inferior frontal, LDFPF, left inferior parietal) have been the primary explicator for observed differences in selective attention and inhibition outcomes, as measured by the Flanker Interference Task (Lew et al., 2018).

Collectively, cortical thinning in the left frontal gyrus has been associated with symptoms associated with HAND (Plessis et al., 2014). Significantly, current study findings

indicate greater FC post-intervention within the treatment group, which may suggest possible compensatory processes in neuroHIV due to the intervention, in the left hemisphere. At a clinical level, these findings are similar to fMRI studies suggesting a lateralized pattern of functional connectivity, in which the left hemisphere has greater inter-hemispheric connectivity in clinical populations such as schizophrenia and autism (Ribolsi et al., 2014; Sha et al., 2021).

Lastly, the study investigated the effect of threshold survival (r = 0.2, 0.4, 0.6, 0.8) on seed correlation FC within the treatment group at post-intervention. Increased thresholding (r = 0.8) led to the survival of two channels within the L-DLPFC and frontal eye field (BA 9: x = - 46, y = 39. z = 20; BA 46: x = - 9, y = 4, z = 50). These findings are significant as they suggest that the L-DLPFC could be a potential marker for brain plasticity in adolescent neuroHIV. To this end, due to its modularity (efficiency) in processing multiple, distinct cognitive properties, including attention, memory, language, and learning (Jajcay et al., 2022), the left hemisphere is largely implicated in neuronal plasticity (Jajcay et al., 2022). By implication, although inconclusive, threshold survival outcomes may suggest that the LDLPFC may be a primary neural substrate for future brain plasticity protocols, especially given the heterogeneous nature of adolescent neuroHIV (Connor & Zeffiro, 2018).

Significantly, threshold survival findings may suggest that the CEN in concert with other functional networks, such as the LDLPFC and the default mode network (DMN), are relevant for cognition and play a critical role in neuroHIV and brain plasticity. In their study, Jia et al. (2023) found that working memory training increased function connectivity and normalization of the ventral default mode network (DMN) in adult HIV. The authors explain that DMN ‘normalization’, to that observed in HIV-negative controls, indicates the value of brain training to reverse compromised cognitive decline in adult neuroHIV.

The cojoined interpretation of the current study findings, and those by Jia et al. (2023), may confirm the dual connection between the CEN and the DMN (Rosenberg et al., 2016). To date, research indicates that the CEN and the DMN complement each other in the manner that the CEN is responsible for 'top-down attention processing', which is a task-orientated cognitive process required in maintaining task vigilance, whilst the DMN contributes to 'bottom-up processing', required when the mind is at rest (Clark & Noudoost, 2014). Study findings taken together with Jia et al. (2023) provide early considerations that cortical training may enhance the association between the CEN and the DMN. However, the role of the DMN and CEN in the context of HIV cognitive rehabilitation is still in its early stage.

Summarily, study findings suggest that improvements in brain training were primarily noted at the neuronal level, and these improvements did not explicitly transfer to behavioural outcomes following brain training. As previously pointed out in a comprehensive systematic review investigating neuronal changes following working memory training (Brooks et al., 2020), cortical changes often precede observable cognitive gains with cognitive gains, usually observed at later stages in brain training protocols.

8.4.1 **Limitations and Future Directions**

While the current article contributes to the investigation of adolescent neuroHIV, specifically neuroplasticity, and its effects on relevant cortical neural networks, there are limitations warranting discussion. Due to the high attrition rate experienced, the study had a relatively small sample size, consequently affecting the statistical power to extrapolate study findings reliably. Moreover, as observed in topographical brain maps (r-maps), the high scalp coupling indexes (SCI = 0.75) employed in the study (pre and post-fNIRS assessment) necessitated the removal of neuroimaging data from a few subjects (n = 3) affecting the final sample size for data analysis. It is recommended that future studies employ a larger sample size to cater for

attrition rates and employ a lower SCI index when conducting fNIRS research with participants of colour, as pigmentation may affect fNIRS pre-processing measures (Kwasa et al., 2022b).

In addition to sample size improvements, study design improvements are suggested. It is recommended that future neuroHIV studies, specifically with adolescent populations, employ an *active control group* instead of treatment as usual controls (Simons et al., 2016a). In terms of rehabilitation research, active controls have been noted to ascertain better the active ingredient in brain training protocols than passive controls. Lastly, the fNIRS protocol covered a limited region of interest (Table 1) to investigate seed-based connectivity and neuroplasticity. It is recommended that future studies cover regions, including the CEN and DMN, to investigate FC and neuroHIV brain training comprehensively.

Finally, there is a lack of consensus regarding optimal thresholds for investigating functional connectivity and survival analysis (Garrison et al., 2015). The study employed survival analysis based on an increment of $r = 0.2$. Although fiducial for the study, it is recommended that future studies employ automated thresholding methods for fNIRS-FC, as employed by Chan et al. (2020). Automated thresholding would bolster functional connectivity, such as assortativity measures. Functional connectivity assotativity would thus better estimate and quantify the tendency of different nodes within a network, and thus evaluate the tendency of nodes to connect to other nodes with a similar (positive assotativity) or a dissimilar connection (negative assotativity).

8.5 Conclusion

The study applied seed-based connectivity to rsfNIRS data to assess functional connectivity in brain training in adolescent neuroHIV. Findings indicated that attention training was associated with limited behavioural changes post-rehabilitation but improved functional connectivity in the left hemisphere for participants receiving attention training. Significantly, thresholding

indicated that LDLPFC may be a possible marker for brain training in the context of adolescent neuroHIV. Study findings hold promise for upscaling evidence-based brain training protocols to remediate maladaptive cognitive outcomes sequent neuroHIV.

8.6 Acknowledgements

The author would like to thank the directors of the children's shelter and the children's guardians for admitting their child/ward to the study. The author would further like to extend his gratitude to the 'elderly children' at the shelter who assisted in accompanying research participants to the research site and enabling rapport with the participants during the execution of the study. The author extends his gratitude to the Centre for African Studies (CAS) at Harvard University for hosting him during his fellowship at the university. The author also thanks Professors Aline Ferreira-Correira and Kate Cockcroft for their comments on the article draft.

8.7 Conflict of Interest

There are no conflicts of interest to declare.

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CHAPTER 9
Discussion and Conclusion

9.1 Introduction

This chapter assesses the primary findings detailed in Chapters Five to Eight. It examines the importance of the findings and their implications for understanding neuroHIV and its impact on cerebral function in adolescent HIV. The chapter concludes by exploring limitations associated with the study whilst proposing directions for future research.

9.1.1 Aim of the Study

HIV has a long-lasting impact on numerous people globally, especially at behavioural and cognitive levels. As it progresses after breaching the blood-brain barrier, HIV results in persistent systemic neuroinflammation within the cortex, resulting in neuronal dysregulation. This subsequently disrupts neurotransmitter systems, leading to aberrant neurotransmitter circuitry, and is believed to cause diminished cognitive proficiency in adult and paediatric samples (Cody & Vance, 2016; Ellero et al., 2017). Coupled with the above dysregulation, combination antiretroviral drugs (ARVs) do not reverse cognitive decline due to their neurotoxicity, which, in some instances, may exacerbate HIV-associated disorder (Ellero et al, 2017).

Notwithstanding HIV's dysregulation of cortical cytoarchitecture, the inherent malleability of the mammalian cortex opens a window for HIV cortical neuroplasticity, especially in young developing cortices (Boivin et al., 2010). Given the promise of cortical plasticity in mammalians, the present study (a) undertook a meta-analysis to synthesise the published evidence for the cognitive rehabilitation of attention in HIV+ paediatric and geriatric samples. The meta-analysis revealed that there is a shortage of research pairing behavioural and cognitive gains in HIV brain plasticity with objective markers, such as neuroimaging

measures to accompany HIV brain plasticity protocols. Given this absence, the study (b) investigated the efficacy of optical neuroimaging techniques, namely fNIRS, to explore hemodynamic responses associated with adolescent HIV brain training. Based on fNIRS efficacy, the study proceeded to examine whether (c) brain training in those with HIV, is associated with reduced hemodynamic responses when completing cognitive tasks, a possible indicator of neural efficiency, due to cortical neuroplasticity. Subsequently, the study investigated (d) whether brain plasticity enhances functional connectivity in the central executive network (CEN). Chapters Five to Eight discuss study findings in significant detail. The current Chapter seeks to integrate the study findings in line with the research objectives detailed in Chapter 1.

9.2 Main Findings

Findings derived using standardised mean differences (SMD) meta-analysis indicate that the cognitive remediation of attention in neuroHIV is associated with small but significant cognitive gains. Succinctly, converging evidence pertaining to HIV cognitive rehabilitation and neuroHIV seems to suggest the potential benefits of brain plasticity measures to reverse HAND, sequent neuroHIV. Most significantly, neuroimaging findings from the current study - based on fNIRS optical neuroimaging - suggest that, in adolescent neuroHIV, customised attention training is associated with reduced hemodynamic activation (i.e., reduced Blood Oxygen Level Dependency). To this effect, reduced hemodynamic activation in the DLPFC, at post-intervention, suggest the Central Executive Network (CEN) as a critical node and biomarker for HIV neuroplasticity in the context of HAND.

Significantly, key study findings indicated that attention-brain training was associated with minimal, if any, cognitive outcomes post-brain training. Concurrently, reduced hemodynamic activation, paired with increased (though minimal) cognitive gains on near

transfer measures (on the NEPSY-II and SCWT) suggest that, in adolescent neuroHIV, neuronal changes precede cognitive gains, sequent brain plasticity intervention (Brooks et al., 2020). Notably, the conjoined nature of decreased hemodynamic responses, paired with improved cognitive outcomes sequent intervention, may indicate improved neuronal efficiency sequent customised brain training.

Neural efficiency reflects the ability of the cerebral cortex to perform tasks more efficiently by using minimal brain energy metabolisms, such as glucose and adenosine triphosphate (ATP), to resolve cognitive tasks. The exact role of neural efficiency and neuronal resource expenditure in neuroHIV, HAND, ARVs, and brain plasticity is not yet fully understood. Nonetheless, findings from the current study, coupled with those from Jia et al. (2023), suggest that customised neuroHIV brain training, at least in attention and working memory, is associated with improved neural efficiency in relation to completing cognitive tasks at post-assessment. These associations may be related to improved cognitive outcomes in paediatric and geriatric neuroHIV. These findings, together with recent developments in ARV nanotechnology and individualised medicine, make it probable that customised brain plasticity measures may enhance neural efficiency and potentially improve cognitive resource allocation in neuroHIV and HAND.

Nonetheless, the neuroplasticity literature indicates that multiple indicators determine improved neural efficiency. For example, Sharp et al. (2018) suggest that neural efficiency may be significantly determined by physical activity, diet, and quality of education received. In the context of neuroHIV, findings from Boivin et al. (2016) suggest that among Ugandan children, key determinants such as parental care, home-schooling, and home coaching may predict improved cognitive outcomes when juxtaposed with customised brain training interventions. Although Bovin et al. (2016) did not measure neural efficiency in the objective sense of employing neuroimaging techniques, improved cognitive outcomes post-brain training, as

indicated by near and far transfer gains in executive function measures, may be indicative of neural efficiency in adolescent HIV.

Of parallel interest, not related to neuroHIV, decreased hemodynamic oxygenation in the DLPFC, coupled with increased performance on the Stroop Test, is evident in children living with autism following brain training (Kujach et al., 2018). This finding is important as it suggests that neuronal efficiency is particularly feasible in neural networks, such as the CEN, which play a significant role in processing top-down and bottom-up attention in other clinical states, independent of adolescent neuroHIV.

While the relationship between neuronal efficiency and HIV brain plasticity is not fully understood, findings from the current study shed light on the potential relationship between neural efficiency and cortical laterality. Functional connectivity findings, at post-intervention, particularly in the intervention group, seemed to indicate that the left DLPFC may be a reservoir for neural efficiency and a biomarker for cognitive rehabilitation in neuroHIV. Notwithstanding, the neuroscience literature does not purport that neural efficiency is lateralised but that it depends on multiple factors, including cortical maturation, genetics, and the environment (Anderson et al., 2011; Denes, 2015; Johnston, 2009). However, the nascent neuroHIV literature, particularly the brain plasticity literature, whether in the realm of HIV deep brain stimulation (DBS) or cortical plasticity, seems to highlight the role of the *left hemisphere* in HIV functional recovery (Jia et al., 2023; Ownby & Acevedo, 2016; Ownby & Kim, 2021). Although pubescent, the growing body of evidence indicates that multiple levels of evidence, including HIV plasma viral load, ARV neurotoxicity, and ARV commencement, may affect cortical plasticity, lateralization, and functional connectivity in neuroHIV.

9.3 Theoretical and Practical Contributions

The dissertation makes a substantial contribution to the fields of neurocognition, brain plasticity and neuroHIV. Most pertinent, the dissertation supports Green et al.'s (2019) model of HIV homeostatic synaptic scaling. Summarily, Green et al. (2019) purport that in neuroHIV, synaptic changes can either be aberrant or amenable to therapeutic interventions such as neuroprotective scaling. In this manner, neuroprotective scaling can include pharmacological or non-pharmacological therapies to preserve or upscale synaptic connectivity and improve cognitive function in neuroHIV. To this extent, neuroprotective factors (pharmaceutical and non-pharmaceutical) may reverse HIV-induced neuronal and synapse loss, preserving cortical integrity despite HIV's deleterious effect on the cortex (Jia et al., 2023). Within a neuronal and hemodynamic capacity, the study supports HIV homeostatic scaling, as findings suggest that brain plasticity results in neural efficiency as indicated by ΔHbO. To this end, reduced blood oxygen level dependency (BOLD) and increased functional connectivity post-intervention may be indicators of improved homeostatic synaptic scaling in neuroHIV, enhancing theoretical considerations that biochemical neuroprotective factors, may mediate cortical integrity, despite HIV neuroinvasion.

Secondly, the current study's findings, when taken together with objective measures of neuroHIV brain training using fMRI (i.e., Chang et al., 2013, 2017; Jia et al., 2023), emphasise the conjoined nature of the Central Executive Network (CEN) and Default Mode Network (DMN) in HIV neuro-restoration. Significantly, Jia et al. (2023) found that working memory training resulted in 'normalization' of the ventral default mode network (DMN), sequent to training. Findings from the thesis indicated that attention training was associated with reduced hemodynamic activation in the DLPFC (a key node CEN) when completing cognitive tasks post-training. Thus, converging evidence suggesting the 'normalization' of the DMN and reduced hemodynamic activation of the CEN may both point to the shared neural mechanism

of attention and working memory (Clark & Noudoost, 2014b; Logue & Gould, 2014; Panichello & Buschman, 2021), particularly the antiparallel nature of the CEN and DMN to regulate attention and working memory.

Thirdly, notwithstanding plausible network connectivity parallels proposed above, it is prerogative to emphasise the importance of the dorsolateral prefrontal cortex (left) as a possible biomarker for neuroHIV brain plasticity protocols. Seed-based scaffolding (Chapter 8) indicated that the L-DPFC survived thresholding at the highest possible scaffold (r = 0.8) concerning the primary seed. When taken together with other findings, this suggests the role of the DLPFC as a biomarker for mindfulness meditation training (Bauer et al., 2020), psychotherapy rehabilitation (Rosenbaum et al., 2018), and enhanced processing speed in healthy subjects (Curtin et al., 2019). Consequently, it is plausible to suggest that future neuroHIV brain training protocols (computerised or non-computerised) should focus on activities that activate the DLPFC, particularly the L-DPFC, to maximise neural efficiency and cortical connectivity.

Lastly, besides the proposed theoretical contributions, the practical contribution of this study is at a social justice level. To date, South Africa still experiences inequality in mental health services. The study bridges the gap between Psychology and its practical relevance to disadvantaged communities by extending cognitive rehabilitation protocols to children and adolescents in township and rural areas. When paired with everyday cognitive enhancing techniques such as schooling and exercise, HIV brain plasticity could be an essential conduit to meeting the mental health needs of children, such as those living with HIV, most in need of mental health services.

9.4 Limitations of Research Study

The limitations of each study are described in detail within the chapters (i.e., Chapters Four to Eight). Notwithstanding this, pertinent limitations are briefly mentioned below. Due to the nature of the study, namely that it was a multi-site, longitudinal study spanning two years (i.e., recruitment, pre-assessment, brain training, post-assessment) and conducted with a vulnerable population (i.e., children and adolescents living with HIV), high attrition rates were experienced. In addition, attrition also occurred due to fatigue and increased disease burden, leading to participants allocating more time to their medical regimen than the research objectives. In addition to the above, participants with multiple comorbid presentations (i.e., HIV and ADHD, HIV and psychomotor deficits) preferred to attend other care regimens and often dropped out of the study intervention. As such, the study's primary limitation is the small sample size (N=42), which was further reduced to 26 participants at the final stage. These limitations in sample size resulted in diminished statistical power, which limited data extrapolation.

In addition to diminished statistical power, pertinent limitations include implementing neuroimaging studies in the study's context. For example, irregular electricity and Wi-Fi supply (necessary to enable LSL code) affected data acquisition and led to the subsequent deletion of participant data. Although suggestions are provided below on overcoming Wi-Fi limitations, the loss of neuroimaging data resulted in reduced statistical power in the General Linear Model (GLM) analysis executed in the published articles. Further to the above, a significant limitation briefly alluded to in the published articles, worthy of further emphasis, is the absence of participant follow-up six months after the attention intervention. There is a significant emphasis within the rehabilitation literature for intervention studies to investigate the long-term effect of the *active ingredient* by conducting follow-up analysis post-intervention at one-month and six-month intervals (Simons et al., 2016). It is argued that this longitudinal analysis enables the

accurate investigation of the lasting effect of the intervention. Due to financial and time restraints, follow-up of the participants in the current study at six months was not feasible, presenting a significant limitation of the study.

9.5 Recommendations for Future Research

Each of the published chapters, as well as those under review, concluded with recommendations for future research. The section below briefly expands on suggestions not covered therein. These primarily center on (a) methodological, (b) fNIRS protocols, and (c) brain training considerations.

*1. **Methodological***

a. In addition to employing *both* active and passive control groups *within* the same study to investigate the effect of the active ingredient, it is recommended that neuroHIV rehabilitation studies publish preregistration trials *before* the execution of the rehabilitation protocols. This undertaking would enable design feedback, replicability, and robust suggestions on statistical methods to be employed in the primary study (Simons et al., 2016). An example of a preregistration trial platform is Protocols.io (https://www.protocols.io/; RRID:SCR_010490).

b. Linked to statistical analysis, many intervention studies, including the current one, adopt a null-hypothesis significance testing (NHST) approach to conclude the effect of the active ingredient on cognition (e.g., attention remediation) (Simons et al., 2016). It is recommended that future neuroHIV rehabilitation studies incorporate Bayesian statistical approaches instead of NHST approaches. The advantage of Bayesian analysis, especially in brain training research, is that it helps elucidate the benefits of the *active ingredient* (on the dependent variable) *relative* to the control group (either active or passive), relative to multiple confounding factors (i.e., length of rehabilitation, personality, group vs individual rehabilitation). In addition to the above, the Bayesian approach, by focusing on the relative

nature of the active ingredient, would thus emphasize the *size* and the *effect* of the brain training relative to the absence of any effect being detected (i.e., no training). The latter analysis, thus, increases the statistical power of the analysis by not relying on NHST (Baniqued et al., 2015; Melby-Lervåg, et al., 2016). An example of software that can easily implement Bayesian analysis is JASP, (https://jasp-stats.org/; RRID:SCR_015823), which provides both Bayesian and NHST for each statistical analysis and is open source.

c. There is considerable debate within the rehabilitation literature around implementing single or double-blinding protocols (Boot et al., 2013; Simons et al., 2016). For example, although 'double blinding'[32] is the golden standard in intervention research and reduces expectations and beliefs about the active ingredient, this method, as illustrated in the current study, is difficult to implement due to resource constraints. It is recommended that researchers employ research assistants who are *aware* of group allocation and the active ingredient to follow up on research participants easily and limit study attrition (Simons et al., 2016).

d. The literature cites the lack of investigation of 'soft variables' in cognitive intervention studies, such as personality, motivation, expectations, and resilience and how these influence / hinder 'near/far transfer' gains (Simons et al. 2016). It proposed that future research incorporate personality and resilience scales such as the Five Factor Model of Personality (Briggs & Cheeks, 1986) and the Resilience Scale for Children (Cajada et al., 2023), respectively, and employ these measures in a larger mixed models' analysis.

*2. **fNIRS Protocols***

a. Optical imaging techniques in the form of fNIRS are still relatively new in Sub-Saharan Africa contexts. Previous chapters highlight suggestions around hair and probe placement,

[32] 'Double blinding' or masking, refers to withholding of information to both research assistants, and research participants regarding groups assignment (e.g., experimental, active control, or passive control group) and treatment allocation (Schulz and Grimes 2002).

inter-subject variability at an individual and group level, the correct placement of probes (sources and detectors), and the correct establishment of fiducial points. In addition to the above, it is recommended that to ensure consistent Wi-Fi and electricity supply during data collection, researchers make up Wi-Fi Backup Routers, in addition to power banks, to power the fNIRS devices in cases of electricity supply disruption.

b. Participants in our study expressed a fear of wearing the fNIRS cap. It is suggested that future protocols explain to participants, in simple pictorial depictions, the logic and use of fNIRS, with a clear explanation of the role of optical imaging (light) in experimentation. This extra step would curtail experimental fear and aid learning and interest in the research.

3. ***Brain Training Protocols***

a. Although some researchers state no convincing evidence for brain training protocols (e.g., Melby-Lervag et al., 2016), other researchers provide evidence for the efficacy of such protocols (e.g., Olfers & Band, 2018; Au et al., 2016). Findings from the current study, as evidenced by meta-analytic and neuroimaging findings, seem to support the latter evidence. Notwithstanding, specific recommendations are suggested for brain interventions focused on adolescent neuroHIV samples. To this end, neuroHIV leads to deleterious effects on multiple cognitive constructs, namely, attention, working memory, processing speed and cognitive control (Moran et al., 2019; Vance et al., 2016). Current interventions within the reviewed literature appear to target *all* cognitive constructs, with no clear theoretical framework underpinning the multifaced computerised interventions (Moran et al., 2019; Wexler et al., 2021; Wang et al., 2017).

Thus, it is suggested that to develop evidence-based neuroHIV interventions, future studies should choose computerised protocols that target a specific cognitive construct (e.g., attention) and link this intervention to specific cortical networks known to be affected in

neuroHIV. Once the above is established, *downstream* (top-down) or *upstream* (bottom-up) cognitive interpretations of brain function sequent neuroHIV can be hypothesised and linked to the role of the intervention at a cortical level. It is suggested that focusing the intervention on a singular construct can help establish probable links between neuroHIV, cognition, and theoretical models underpinning cognition. Moreover, by focusing on the remediation of a single cognitive construct (i.e., attention), the use of validated computerised cognitive training software, such as ACTIVATE^{TM}, researchers can better investigate, how these software, (as opposed to those marketed online), can better maintain sustained participant engagement, and thus promote gradual cognitive improvement, thus providing an improved sense of the titration features, of concentrating on a single cognitive domain for cognitive rehabilitation, thus linking titration, to neuronal changes linked due to the intervention.

b. Although Chapter 4 made a case for Single Case Experimental Design (SCED) with short-duration interventions (15 – 20 minutes per session), it is recommended that baseline cognitive scores should be used to ascertain which participants may best benefit from neuroHIV interventions. Due to the heterogenic cognitive symptomatic profile of neuroHIV (Reger et al., 2005), not all participants are expected to benefit equally from the intervention. Moreover, it is recommended that once participants most in need of the intervention are identified, intervention protocols should best be tailored to meet their cognitive profile.

9.6 Conclusion

This study was undertaken following a ‘call to action’ for evidence-based experimental studies to investigate the role of neuroplasticity in the face of HAND (Weber et al., 2013), particularly with evidence further suggesting that ARVs may not reverse but worsen HAND (Gonzalez et al., 2020; Yuan & Kaul, 2019). Given pharmaceutical limitations linked to ARVs, the study sought to investigate the efficacy of non-pharmaceutical interventions, primarily computerised attention training, to reverse HAND. This training was corroborated by neuroimaging and

behavioural data. Findings indicated that, while attention training is feasible in adolescent neuroHIV, its effect, at least amongst adolescent populations, occurs primarily at a hemodynamic and neuronal basis (Brooks et al., 2020). Findings further indicated limited near and far transfer of cognitive gains following attention training. Interestingly, although minimal, attention training was associated with increased neural efficiency when completing incongruent tasks, but not congruent tasks, at post-intervention. These findings and conclusions indicating that attention training is associated with increased brain connectivity, particularly in the left dorsolateral prefrontal cortex, open a vista for the DLPFC to be a target and biomarker for adolescent HIV, neuroplasticity.

9.7 References

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APPENDICES

APPENDIX A

Information Letter to Director Requesting Gatekeeper Access to Shelter

Psychology
School of Human & Community Development
University of the Witwatersrand
Private Bag 3, Wits, 2050
Tel: 011 717 4503
Fax: 011 717 4559

Study Title: Neurocognitive Rehabilitation for a paediatric HIV/AIDS population: The case of Sustained Attention

Dear Director,

I am a PhD Psychology student and a member of the University of Witwatersrand's Neuroscience Research Laboratory (https://www.witsneurl.com/). For my research, I am interested in investigating cognitive difficulties that result from the Human Immunodeficiency Virus (HIV). Recent research indicates that despite advances in the management of HIV infection through the use of antiretroviral drugs (ARTs), children living with HIV continue to experience what is referred to as: HIV-Associated Neurocognitive Decline (HAND). This cognitive decline is thought to result from HIV entering the brain, and affecting brain functions, that lead to children experiencing difficulty paying attention, and creating long-term memories. For my research, I am interested in investigating brain plasticity and how brain training exercises can help reverse some of the decline experienced by children living with HIV.

Who can participate?

I am looking to recruit children at your shelter, between the ages of 7 and 16 years of age, living with HIV. In addition to your consideration, children will be asked to provide assent to

participate in the study and will be informed that they are free to withdraw from the study at any point, without being penalised in any way.

What will happen during the study?

For the study, children will complete a few tasks. Firstly, children will be requested to complete cognitive tasks that aim to assess attention skills. The cognitive tasks will be based on two instruments called the NEPSY, and the Conner's Continuous Performance Test (CPT). Children will complete these cognitive tasks, before and after the brain training exercises. The brain training exercises will be computerized and designed to specifically train attention skills. Each child who takes part in the study will be trained independently, by the researcher and his research assistant. Lastly, to investigate the benefits of the brain training exercises on children's attention skills, I will assess children's brain activity using a safe, non-invasive instrument called, functional near-infrared spectrometry (fNIRS). fNIRS is a neuroimaging technique that indicates hemodynamic (blood) responses due to brain activity. The data from fNIRS is obtained by using light sources and detectors that are placed on the children's scalp. The light sources and detectors indicate how much oxygenated blood haemoglobin is absorbed in the brain during a cognitive task. The more light is absorbed, the more active the brain region of interest. This procedure of brain analysis is commonly used in research with children living in Africa (e.g., Grazioli et al, 2019).

Duration of the Study and Role of Children:

All children will be assessed at the beginning of the study, immediately following the brain training exercises, and 6 months after completing the brain training exercises. All in all, the study will last for a duration of about 9 months. The brain training exercises will be completed at least three times per week, for about 30 minutes per session. Each child will receive 32 brain

training sessions, over a 3 month period using a training program known as the Computerised Progressive Attentional Training program (CPAT) (Shalev et al., 2007).

What will happen to the findings from the study?

All findings from the study will be kept confidential. If any data from the study is published, all identifying information such as the children's identity or the organisation's identity will be kept private. Moreover, all results emanating from the study will be shared with you as soon as they are available.

Who has approved this study?

This study has received ethical approval from the University of the Witwatersrand's Human Research Ethics (Medical) Committee.

Measures to Contain the Spread of COVID-19

Every effort will be made to prevent the spread of the COVID-19 virus including taking of participants' temperatures during the study, enforcing social distancing greater than 1.5 meters; enforcing a COVID-19 self-screen questionnaire every day during the study, disinfecting participants at regular intervals, as well as regularly disinfecting all equipment including, computers, pens, and pencils used during the research study. All researcher assistants entering the care shelter will be tested for COVID-19. The complete health and safety protocols that will be applied at the research site, will be reviewed by the Health and Safety Officer at Wits University.

Who is responsible for this study?

Please contact Mr Sizwe Zondo (S.Zondo@ru.ac.za / 046 603 8503), or the researcher supervisors of the study, Dr Aline Ferreira-Correia (Aline.FerreiraCorreia@wits.ac.za) or

Professor Kate Cockcroft (Kate.cockcroft@wits.ac.za), if you require further information about this study, or feedback on the progress of this research.

Contact Details of the HREC Administrator and Chair

Please contact Professor Clement Penny (Clement.Penny@wits.ac.za / 011 7172301), if there are any formal complaints or reservations about the ethical conduct of this research, stating the nature of your query. The Committee secretarial can also be contacted telephonically: 011 7172700/1234, or on email addresses: Zanele.Ndlovu@wits.ac.za and Rhulani/Mukansi@wits.ac.za. Any issues will be treated in confidence and investigated fully, and you will be informed of the outcome.

Should the above be to your satisfaction, and you provide consent for me to conduct research at your shelter, may you kindly append your signature to the below designation.

……..

Signature: Director

APPENDIX B

Participant Information Sheet and Informed Consent from Guardians and Parents

Psychology
School of Human & Community Development
University of the Witwatersrand
Private Bag 3, Wits, 2050
Tel: 011 717 4503
Fax: 011 717 4559

Study Title: Neurocognitive Rehabilitation for a paediatric HIV/AIDS population: The case of Sustained Attention

Dear Parent,

I am a Ph.D. student at the University of Witwatersrand, based in the Department of Psychology. For my Ph.D. research, I am investigating the effects of the Human Immunodeficiency Virus (HIV) on children's thinking abilities. I am particularly interested in exploring how a key component of our thinking, called 'sustained attention,' is affected in children living with HIV. Moreover, I am interested in investigating whether specific brain exercises can help improve children's attention skills. To achieve my research goals, I intend to recruit participants aged between the ages of 7 and 16 years of age to take part in the research study. With the help of the Director at (name of children's home) and with your consent, I kindly request the participation of your child in my research. The details of the study and other key consideration are detailed below.

Details of the Study

All protocol related to the study will be completed at the children's home where your child resides. The study will comprise of four parts.

Part 1 of the study will include: (1) you reading through this information sheet and completing a questionnaire. Once Part 1 is complete, we will proceed to Part 2.

Part 2 of the study will involve (1) me explaining the study to your child (15-20 minutes); and (2) your child reading and completing an informed assent form. Once your child has provided informed assent, they will complete a series of assessments spread over two days. Day One of the assessment will involve your child: (1) completing a series of pencil and paper tasks to assess attention. Day Two will include your child: (1) completing a computer-based tasks assessing attention skills. This session will involve her/him wearing a safe cap called a 'functional near-infrared spectrometry' (fNIRS) cap whilst completing the computer task. This cap measures your child's brain activity while completing the computer tasks. The two sessions above, will be done over two separate days, and will take approximately 40-60 mins to complete. Once part 2 of the study is complete, we will proceed to Part 3.

Part 3 of the study will involve your child completing a few computer-based sessions, that train cognitive skills. These brain training exercises will be completed at least three times per week, for about 30 minutes per session. In total, your child will receive approximately 32 brain exercise sessions, over a 3-month period. All brain training exercise will be completed after school and will not affect your child's schooling schedule. Once we complete the brain training sessions, your child will complete a few psychological assessments.

Lastly, Part 4 of the study will occur 6 months after Part 3 is complete. Here, your child will complete similar assessment to those completed in Part 2, of Day 1 and Day 2.

COVID-19 health and safety protocols in the children's shelter

Research indicates that a pathogen known as severe acute respiratory syndrome (SARS) causes Coronavirus 19 (COVID-19). Since the virus has a respiratory origin, it also has a respiratory portal of exit through respiratory droplets. These respiratory droplets can spread in close contact situations. To reduce the possible spread of COVID-19 during the study, a formal risk assessment and a written risk mitigation plan will be followed. The following health and

safety protocols will be included, and will be reviewed by the Health and Safety Officer at Wits University:

Health safety screening of participants and researchers before the study:

1) The COVID-19 self-screening questionnaire must be completed in hard copy before entering the study room location at the children's home (Appendix: P). If your child answers 'yes' to any of the questions, they will not be able to partake in the research study.

2) Upon arrival at the research room, your child's temperature will be taken, and the thermometer will be disinfected after each use. If your child's temperature is 37.4°C or higher, they will not be allowed to enter the study venue on the day of the study.

3) Before entering the research room, your child will be required to disinfect their hands with the sanitizer provided.

Health and safety protocol during the study:

1) A daily register will be kept with all names, and the date/time of all persons entering the research room at the shelter. This protocol is required for contact tracing, if necessary.

2) The register will be separate from the data collected and will be destroyed after the data collection is complete.

Precaution measures during the study:

1) Cloth or surgical facemasks will be properly fitted and worn all the time. Extra surgical masks will be made available to the children's home in the duration of the research.

2) Social distancing (> 1.5m) will be always maintained at the research site.

3) The number of participants in the research room will be restricted to only one participant at a time.

4) The children's home cleaning service will be requested to clean the research room and dispose of waste daily.

5) A4 size zip-lock plastic bags will be used to store informed consent/assent documents, completed paper questionnaires, and other documentation that need paper and pen application.

6) Bags with ties will be used dispose of any waste materials including used masks, and gloves.

7) The research venue will be well ventilated, and the windows and door will be opened after every testing session with participants.

8) Alcohol based hand-sanitizes will be regularly used to ensure that all contact equipment/devices and common-touch surfaces used in this study are properly sanitized.

9) There will be 45-minute intervals between participants to clean and disinfect all equipment, devices and surfaces used during the study.

10) Notices will be placed outside the research venue advising participants about COVID-19 regulations, and precautionary measures that can be taken, to prevent COVID-19. These posters have been downloaded from National Institute for Communicable Diseases (see https://www.nicd.ac.za/diseases-a-z-index/covid-19/covid-19-communication-resources/posters/).

Risks

There are no known harmful risks associated with the fNIRS cap. The fNIRS cap records brain activity whilst participants complete cognitive tasks. The cap records brain activity by analysing blood concentrations in response to a particular cognitive task. The fNIRS cap is safe to use and to wear. To prevent discomfort, we will ensure that the cap your child wears will fit his/her scalp and will be the correct size for him/her. The cap will be regularly disinfected during the study.

The COVID-19 virus continues to be a challenge in our country. We will take protective measure, to stop the possible spread of the virus, such as (a) ensuring the wearing of masks and

maintaining social distance during the research. If any of the researchers reports signs of COVID, after interacting with your child, we will contact you directly to inform you. Please also contact me immediately if your child experiences any sign and symptoms of the virus during the study, or after completing the research study.

Benefits

There are no direct benefits for participants in this study; however, the information that we gain from the study will greatly contribute to our understanding of brain exercise training for children living with HIV.

Confidentiality and Anonymity

All the information collected during the study will be kept confidential (private). Anonymity (name and other identifying information) and confidentiality is a high priority for us, and this will be always secured. All information collected from your child will be secured, and password-protected by the researchers. We will also never reveal your child's personal name but will instead use a number identifying system to distinguish them from other participants in the study.

Withdrawal from this Study

Your child is free to withdraw from the study at any time, and this decision will not be held against them.

Research Outputs

Findings from this study will be published and made available to the academic community through journal and conference publications. The director of the children's home where your child reside may request a copy of the research findings, but this will not affect your child as all data will be anonymous.

Contact Details of the Principal Investigator

Please contact Mr Sizwe Zondo (S.Zondo@ru.ac.za / 046 603 8503), or the researcher supervisors of the study, Dr Aline Ferreira-Correia (Aline.FerreiraCorreia@wits.ac.za) or Professor Kate Cockcroft (Kate.cockcroft@wits.ac.za), if you require further information about this study, or feedback on the progress of this research.

Contact Details of the HREC Administrator and Chair

Please contact Professor Clement Penny (Clement.Penny@wits.ac.za / 011 7172301), if there are any formal complaints or reservations about the ethical conduct of this research, stating the nature of your query. The Committee secretarial can also be contacted telephonically: 011 7172700/1234, or on email addresses: Zanele.Ndlovu@wits.ac.za and Rhulani/Mukansi@wits.ac.za. Any issues will be treated in confidence and investigated fully, and you will be informed of the outcome.

Thank you for taking the time to read this information sheet. If you are satisfied with the information provided, and consent in your child participating in the study, please sign the consent form below. In providing consent, you and your child will be contributing to our knowledge of understanding brain plasticity and HIV infections in our country.

Yours sincerely,

Mr Sizwe Zondo (S.Zondo@ru.ac.za),

Name of Parent/Guardian: _____

Place: _____
Date: _____
Signature: _____

Witnessed by:

Name of Witness: _____
Place: _____

Date: _____
Signature: _____

Date: 30/07/2021

APPENDIX C
PARTICIPANT ASSENT SHEET FOR MINORS

Psychology
School of Human & Community Development
University of the Witwatersrand
Private Bag 3, Wits, 2050
Tel: 011 717 4503
Fax: 011 717 4559

Study Title: Cognitive Rehabilitation for a paediatric HIV/AIDS population: The case of Sustained Attention

Dear Participant,

Why am I here?

My name is Sizwe Zondo and I am a student at Wits University, and I am conducting a study to understand how you mind works, and if brain exercise training can help to improve how you pay attention to things. I would like to invite you to join my study. This Participation Information Sheet for Minors explains the details of this study.

Details of Study

If you join the study, you will be asked to complete some tasks. These tasks include: (1) completing some pen and paper exercises; and (2) doing some thinking exercises on a computer. When you do the thinking exercises, you will wear something that looks like a cap around your head. The cap is very comfortable to wear, and it will not hurt you. We use the cap to see how you think as you complete the computer exercises. Below, you can see how the cap will be fitted on your head as you complete the computer exercises. Lastly, (3) during the study, I will ask to see you often to train you on improving your performance on the computer exercises.





How long will the study be?

We will do the computer training exercises at the care shelter where you reside. We will do the brain training exercises, at least three times per week, for 3 months. If you get tired during the brain training exercises, we will proceed by taking regular breaks. I will then ask to see you again 6 months after completing the brain training exercises.

Do my parents know about this?

This study's information has been given to your parents(s) or guardian, and s/he has agreed that you participate in the study. Although they agree for me to participate in the study, the decision to be involved is also mine.

What are the Risks of the study?

There are no known harmful risks associated with the fNIRS cap. The fNIRS cap records brain activity as you complete cognitive tasks. The cap records brain activity by analysing how much blood flows in your brain during the computer exercises that you will be doing. All in all, the fNIRS cap is safe to use and to wear. To prevent minimal discomfort, we will ensure that the cap you wear will fit your scalp and be in the correct size for you.

The COVID-19 virus continues to be a challenge in our country. The virus is spread when we cough and touch surfaces that may be infected with the virus. We will take protective measures to stop the possible spread of the virus, such as (a) ensuring the wearing of masks,

(b) and maintaining social distance during the research. Several health and safety measures will be put into place to prevent the spread of the virus during the study. These measures will be reviewed by the Health and Safety Officer at Wits University. If any of the researchers report signs of COVID, after interacting with you, we will contact you directly to inform you. Please also contact me immediately if you experience any sign of the virus after completing the research study.

What are the benefits of the study?

As a participant in this study, there may be no direct benefit for you; however, the information that we gather from the study will contribute to our understanding of the value of brain training exercise in children.

What about confidentiality and anonymity?

All the information collected during the study will be kept confidential (private). Anonymity (your name and other identifying information) and confidentiality are a high priority for us, and this will be always secured. All information collected during the study will be secured, and password-protected by the researchers. We will also never use your personal name but will instead use a number identifying system to distinguish you from other participants in the study.

What about withdrawal from this study?

You are free to withdraw from the study at any time, and this decision will not be held against you. Please discuss your decision with your parent and the researcher. No one will be angry if you decide to stop the research study.

What else should I know about the study: Research Outputs

Findings from this study will be published and made available to the academic community through journal and conference publications. The director of the children's home where you

reside may request a copy of the research findings, but this will not affect you as all data will be anonymous.

What if I have questions?

For questions about the study, please contact me, Mr. Sizwe Zondo at 046 603 8503), or the researcher supervisors of the study, Dr. Aline Ferreira-Correia (Aline.FerreiraCorreia@wits.ac.za) or Professor Kate Cockcroft (Kate.cockcroft@wits.ac.za). If you have concerns about your rights as a participant, you can contact the Chair of the Human Research Ethics Committee, Professor Clement Penny (Clement.Penny@wits.ac.za / 011 7172301). The Committee secretarial can also be contacted telephonically: 011 7172700/1234, or on email addresses: Zanele.Ndlovu@wits.ac.za and Rhulani/Mukansi@wits.ac.za. Any issues will be treated in confidence and investigated fully, and you will be informed of the outcome.

AGREEMENT TO BE IN THE RESEARCH STUDY

Your signature below means you have read the above information about the research study and that you have had a chance to ask questions to help you understand what you will do during the study. Your signature also means you can agree to withdraw from the study at any point should you want to.

Name of Participant: _____
Date _____
Place _____
Signature _____

Name of Parent or Guardian _____
Date _____
Place _____
Signature _____
Witnessed by

Name of Witness _____

Date _____
Place _____
Signature _____

Date: 30/07/2021

APPENDIX D

Demographic Questionnaire

Psychology
School of Human & Community Development
University of the Witwatersrand
Private Bag 3, Wits, 2050
Tel: 011 717 4503
Fax: 011 717 4559

Your name:	Date:
Child's Name:	School:
Age of Child:	Date of Birth
Name of Shelter	

1. Child's Sex: (circle one):	Male	Female	
2. Child's Grade:			
3. Home language: (circle one):	isiZulu	isiXhosa	Other
4. Handedness (circle one):	Left	Right	Ambidextrous
5. Who is the primary caregiver of the child?			
6. What is your relationship to the child? (circle one):	Mother	Father	Guardian

7. Has your child been diagnosed with HIV? (circle one):	Yes	No
8. Is your child on ARVs?	Yes	No
9. Does your child take part in regular activities such as reading and math? If yes, please specify as well as describe the regularity of these activities?		
10. How would you describe your child's personality?		

11. Does your child have a history of any of the following?

(a) **Neurological disorder**: Has your child been diagnosed with any diseases of the brain, spine, or nerves?

Yes ☐ No ☐

If Yes, please specify_____

(b) **Traumatic brain injury**: Has your child ever suffered a major blow to the head that left them unconscious for more than 30minutes?

Yes ☐ No ☐

If Yes, please specify_____

(c) **Psychiatric disorders**: Has your child shown any pattern of behavior that seemed abnormal/atypical which led to seeking help at a mental hospital?

Yes ☐ No ☐

If Yes, please specify_____

(d) **History of pre-natal or birth complications**: Were there any complications during pregnancy (did the pregnancy take the normal 9months) or complicated delivery (e.g., was the child pulled out using forceps)?

Yes ☐ No ☐

If Yes, please specify_____

(e) **History of learning disability or special education**: Has your child ever had any difficulty with learning concepts, to a point where s/he ended up needing special classes?

Yes ☐ No ☐

If Yes, please specify_____

(f) **Two or more repeated grades**: Has your child ever had to repeat any grades at school?

Yes ☐ No ☐

If Yes, please specify_____

(g) **The use of psychotropic medication:** Has your child ever taken medication that changes their mood or behavior?

Yes ☐ No ☐

If Yes, please specify_____

APPENDIX E

UNIVERSITY OF THE WITWATERSRAND ETHICAL CLEARANCE

UNIVERSITY OF THE WITWATERSRAND, JOHANNESBURG

R14/49 Mr Sizwe Zondo

HUMAN RESEARCH ETHICS COMMITTEE (MEDICAL)

CLEARANCE CERTIFICATE NO. M211073

NAME: (Principal Investigator)	Mr Sizwe Zondo
DEPARTMENT:	School of Human and Community Development: Psychology Nkosi's Haven in Johannesburg The Home of Joy in Grahamstown / Makhanda
PROJECT TITLE:	Cognitive Rehabilitation for a paediatric HIV/AIDS population: The case of Sustained Attention
DATE CONSIDERED:	29/10/2021
DECISION:	Approved unconditionally
CONDITIONS:	
SUPERVISOR:	Prof K. Cockcroft and Dr A. Ferreira-Correia
APPROVED BY:	Dr CB Penny, Chairperson, HREC (Medical)
DATE OF APPROVAL:	09/12/2021

This clearance certificate is valid for 5 years from date of approval. Extension may be applied for.

DECLARATION OF INVESTIGATORS

To be completed in duplicate and **ONE COPY** returned to the Research Office Secretary on the Third Floor, Faculty of Health Sciences, Phillip Tobias Building, 29 Princess of Wales Terrace, Parktown, 2193, University of the Witwatersrand. I/we fully understand the conditions under which I am/we are authorized to carry out the above-mentioned research and I/we undertake to ensure compliance with these conditions.Should any departure be contemplated, from the research protocol as approved, I/we undertake to resubmit the application to the Committee. **I agree to submit a yearly progress report.** The date for annual re-certification will be one year after the date of convened meeting where the study was initially reviewed. In this case, the study was initially reviewed in **October** and will therefore be due in the month of **October** each year. Unreported changes to the application may invalidate the clearance given by the HREC (Medical).

Principal Investigator Signature — Date: 09/25/21

PLEASE QUOTE THE PROTOCOL NUMBER IN ALL ENQUIRIES

APPENDIX F

SAMPLE OF STROOP COLOUR WORD TEST (SCWT)

Control	Congruent	Incongruent
Dog	Red	red
Chair	yellow	yellow
Window	green	green
Boat	blue	blue
Fence	red	red
Bottle	blue	blue
Cup	yellow	yellow
Book	green	green
Table	blue	blue
Tissue	red	red
Desk	blue	blue
Computer	yellow	yellow
School	green	green
Library	blue	blue
Donkey	red	red
Dog	blue	blue
Taxi	yellow	yellow
Car	green	green
Mall	blue	blue
Drink	red	red
School	blue	blue
Water	yellow	yellow
President	green	green
Boy	blue	blue