PREPARING FOR USE OF A COMPUTERIZED BATTERY TO IDENTIFY NEUROCOGNITIVE IMPAIRMENTS AMONG CHILDREN AND ADOLESCENTS AFFECTED BY THE HUMAN IMMUNODEFICIENCY VIRUS IN BOTSWANA

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ABSTRACT

PREPARING FOR USE OF A COMPUTERIZED BATTERY TO IDENTIFY NEUROCOGNITIVE IMPAIRMENTS AMONG CHILDREN AND ADOLESCENTS AFFECTED BY THE HUMAN IMMUNODEFICIENCY VIRUS IN BOTSWANA

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The human immunodeficiency virus (HIV) infection and *in utero* exposure increase the risk of neurocognitive impairment among pediatric populations. In Sub-Saharan Africa, HIV is prevalent, but standardized cognitive screening does not exist. To facilitate access to neurocognitive screening in this setting, the Penn Computerized Neurocognitive Battery (PennCNB) was culturally adapted and translated for use in Botswana. The PennCNB streamlines the evaluation of neurocognitive functioning by measuring performance accuracy and response speed on major cognitive domains, which offers many advantages for implementation in resource-limited settings (e.g., automated scoring and data interpretation). This body of research prepares for the utilization of the tool in Botswana by examining measures of validity and engaging in pre-implementation inquiry to help address the substantial research-to-practice gap. HIV-affected children and adolescents (HIV-infected and HIV-exposed-uninfected) age 7-17 years were enrolled from a pediatric HIV clinic in Gaborone, Botswana for these studies. Participants completed the PennCNB assessment. Confirmatory and exploratory factor analyses demonstrated strong discriminant and convergent validity of the battery, thus supporting the design of the adapted PennCNB measuring four neurocognitive domains: executive functioning, episodic memory, complex cognition, and sensorimotor/processing speed. When

evaluating the classification accuracy of the battery against the best, most feasible local data (e.g., clinical interview, pencil-and-paper psychological assessments, and school reports), the tool exhibited acceptable criterion validity. The children and adolescents rated the PennCNB as highly acceptable, which is promising for the success of implementation. To further understand factors likely to impact the successful integration of the tool into clinical settings, semi-structured interviews were completed with key stakeholders (e.g., mental health clinicians, non-mental health clinicians, and leadership) in the public medical sector. Results underscored the need for cognitive screening, revealed anticipated barriers and facilitators to using the PennCNB, and suggested implementation strategies. Overall, this research provided valuable insight into the psychometric properties of the adapted PennCNB and input to inform specific implementation strategies for Botswana. Future implementation of the tool will facilitate early detection of neurocognitive deficits, which is critical for supporting the functional and educational attainment of HIV-affected children and adolescents in this high-need and other resource-limited settings in the region.

TABLE OF CONTENTS

LIST OF TABLES

LIST OF ILLUSTRATIONS

CHAPTER 1. INTRODUCTION

Background Information

The human immunodeficiency virus (HIV) contributes to substantial morbidity and mortality among children and adolescents in Sub-Saharan Africa. In Botswana, the country with the third highest prevalence of HIV (Central Intelligence Agency, 2019), approximately 12,000 children age 0-14 years are living with HIV (HIV+) (World Health Organization, 2017). Further, *in utero* HIV exposures occur in roughly a quarter of all births (Slogrove et al., 2020). Together, HIV+ and HIV-exposed, uninfected (HEU) are referred to as "HIV affected." As a result of the availability of free antiretroviral therapy (ART) for Batswana (citizens of Botswana), many HIV+ individuals have survived to live relatively healthy lives (Farahani et al., 2014; World Health Organization, 2017). However, HIV-affected children and adolescents continue to experience increased risk of neurocognitive deficits, specifically in the domains of attention, episodic memory, executive functioning, information processing speed, and psychomotor functioning (Le Doare et al., 2012; Ruel et al., 2012; Smith et al., 2012; Walker et al., 2013). Due to limitations on functional and educational attainment, early detection of neurocognitive deficits among HIV-affected children is critical. However, validated neurocognitive assessment does not exist in this setting.

Ntemoga Study

To address the scarcity of neurocognitive screening, a team of investigators at the University of Pennsylvania and the Botswana-Baylor Children's Clinical Centre of Excellence (CoE) developed the Ntemoga study to validate the Penn Computerized Neurocognitive Battery (PennCNB) for use in Botswana (Scott et al., 2020). A multifaceted Setswana (local African Bantu language) word commonly translated as

"cognition", the name "Ntemoga" was chosen by a local stakeholder group to encompass the central importance of a person's cognitive functioning to their identify (example quotes presented at the start of each chapter of this dissertation).

Composed of "neurobehavioral probes" (Gur et al., 1992) validated by functional neuroimaging, the PennCNB measures performance accuracy and response speed on major cognitive domains (Gur et al., 2010; Moore et al., 2015). The neurobehavioral probes include variations of neuropsychological tests commonly administered on paper (e.g., Trailmaking) and tests that can be performed more precisely via a computer (e.g., finger tapping). The version of the battery developed for Botswana includes modules selected *a priori* based on 1) neurocognitive domains commonly affected by HIV infection and *in utero* HIV or ART exposure (Cohen et al., 2015; Phillips et al., 2016; Ruel et al., 2012), 2) demonstrated sensitivity to mild impairment, 3) suitability for resource-limited settings, 4) suitability for large-scale administration, and 5) suitability for translation and adaptation across cultures. The PennCNB used in this study consists of 13 tests measuring executive functioning, episodic memory, complex cognition, and sensorimotor/processing speed (Scott et al., 2020).

Cultural adaptation and translation of the PennCNB involved a rigorous process of translation and back-translation (Guillemin et al., 1993; van Widenfelt et al., 2005), local stakeholder input (e.g., representatives from Ministry of Health and Wellness, Ministry of Education, teachers, physicians, mental health clinicians, and young adults) on linguistic and cultural components, and pilot testing among a cohort of children and adolescents in Botswana. The final version of the battery is available in locally appropriate English and Setswana.

The PennCNB has the potential to streamline assessment of neurocognitive functioning. Although administered via a computer, the PennCNB does not require internet access. The assessment takes approximately one to one and a half hours to complete, which substantially reduces the amount of time required to facilitate psychological assessment in this setting. Thus, the PennCNB offers many advantages for resource-limited settings, such as increased standardization and reliability, automated scoring and data generation, and ease of administration.

Problem Statement

Due to the adaptation and translation of the PennCNB, there is a need to formally evaluate of the psychometric properties of the battery to determine its validity for use in the target population. Further, a substantial knowledge-to-practice gap exists in clinical medicine and public health, where the process of facilitating evidence into practice lags by an average of 17 years. Thus, to effectively facilitate the implementation of PennCNB-based neurocognitive screening in Botswana, an understanding of the context in which the PennCNB may be implemented is also needed.

Research Purpose

This body of work prepares for the utilization of the PennCNB in Botswana by examining measures of validity and engaging in pre-implementation inquiry. Specifically, this research aims:

1. To assess the structural validity of the PennCNB adapted for use in Botswana among HIV-affected children and adolescents (Chapter 2)
2. To evaluate the predictive validity of the adapted PennCNB among HIV+ children and adolescents in Botswana utilizing the best, most feasible data

available and expert consensus to constitute a "gold standard" evaluation (Chapter 3)

3. To assess the acceptability of the adapted PennCNB among HIV-affected children and adolescents and to understand factors associated with perceptions of the acceptability of the battery (Chapter 4)
4. To elicit key stakeholders' (mental health clinicians, non-mental health clinicians, and clinical leadership) perspectives to identify factors likely to be related to successful future implementation of the PennCNB into clinical settings in Botswana (Chapter 5)

Chapter 2 (convergent and discriminant validity) and Chapter 3 (criterion validity) will contribute to the validation of the adapted PennCNB, while Chapter 4 and Chapter 5 will inform the development of specific implementation strategies to maximize the likelihood of successful integration of the PennCNB into clinical settings in Botswana. Together, this research will help advance the agenda from the cultural adaptation of the PennCNB to the provision of accessible screening for neurocognitive impairments in a high-need setting.

CHAPTER 2. STRUCTURAL VALIDITY OF A COMPUTERIZED BATTERY FOR YOUTH AFFECTED BY HUMAN IMMUNODEFICIENCY VIRUS IN BOTSWANA

"Acknowledge that I matter"

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Abstract

Children born to mothers infected with the human immunodeficiency virus (HIV) during pregnancy experience increased risk of neurocognitive impairment. In Botswana, HIV infection is common among youth, but standardized cognitive screening is limited. The Penn Computerized Neurocognitive Battery (PennCNB), a tool that streamlines evaluation of neurocognitive functioning, was culturally adapted for use among youth in this high-burden, low-resource setting. The current study examined the structural validity of the culturally adapted PennCNB. A cohort of 7-17 year old children living with HIV (HIV+) and HIV-exposed-uninfected (HEU) children were enrolled from the Botswana-Baylor Children's Clinical Centre of Excellence in Gaborone, Botswana. Confirmatory and exploratory factor analyses were performed on speed, accuracy, and efficiency measures for 13 PennCNB tests. Fit of the confirmatory factor analysis was acceptable, which supports the design of the battery measuring four neurocognitive domains: executive functioning, episodic memory, complex cognition, and sensorimotor/processing speed. However, the model revealed high inter-factor correlation. Exploratory factor analysis suggested that tests assessing executive functioning and sensorimotor/processing speed clustered together rather than forming differentiable factors. Overall, this research provides valuable insight into the structural validity of a neurocognitive battery adapted for use in a non-Western setting, suggesting that the PennCNB could serve as a useful tool for the assessment of neurocognitive function in Botswana and, potentially, other resource-limited settings.

Introduction

The human immunodeficiency virus (HIV) contributes to substantial morbidity among children in Sub-Saharan Africa. In Botswana, approximately 12,000 children age 0-14 years are living with HIV (HIV+) (World Health Organization, 2017). Children affected by HIV, both HIV+ and HIV-exposed-uninfected (HEU) (i.e., perinatally exposed *in utero* by HIV+ mothers), demonstrate greater neurocognitive deficits than their HIV unexposed peers (Le Doare et al., 2012; Sherr et al., 2014; Smith et al., 2012; Walker et al., 2013). Neurocognitive deficits in children living with HIV exist in the domains of attention, episodic memory, executive functioning, information processing speed, and psychomotor functioning (Ruel et al., 2012; Smith et al., 2012). Notably, while HIV is *far* more prevalent among children and adolescents in Botswana than among children in most economically-matched (i.e., upper middle income) nations, comprehensive HIV-related neurocognitive assessment is essentially unavailable in Botswana (Mbakile-Mahlanza et al., 2015).

To address the gap in access to neurocognitive screening, the Penn Computerized Neurocognitive Battery (PennCNB), a tool that streamlines the evaluation of neurocognitive performance (Gur et al., 2010; Moore et al., 2015), was culturally adapted and translated through an iterative process of translation, back-translation, and discussions of cultural differences with assistance from a key stakeholder group (see Scott et al., 2020). Composed of "neurobehavioral probes" (Gur et al., 1992) validated by functional neuroimaging, the battery adapted for Botswana yields performance values for modules measuring four neurocognitive domains (Moore et al., 2015; Scott et al., 2020). Variations of the tests included in the PennCNB have been used extensively to identify

neurocognitive deficits among pediatric populations (Gur et al., 2012; Hartung et al., 2016; Moore et al., 2015; Swagerman et al., 2016). The battery has been culturally adapted and translated into multiple languages (Izgi et al., 2021; Service et al., 2020), including Xhosa (a Bantu African language) (Campbell et al., 2017; Scott et al., in press). Moreover, the battery has been administered to samples of children and adults living with HIV (Scott et al., 2018).

The use of a computerized battery such as the PennCNB presents several advantages over paper-and-pencil measures for clinical and research applications across countries and cultures, including ease of administration, increased standardization and reliability, and automated scoring and data generation. However, a computerized battery adapted for use in a non-Western setting may not reveal the same structure as that in the original setting due to differences in factors such as language, level of computer familiarity, and culture. Previous research has evaluated the psychometric properties of the core pediatric version of the PennCNB (comprising 14 tests) among a community sample age 8-21 years in the United States (Moore et al., 2015), but formal validation of the adapted instrument has not been conducted in Botswana or in an HIV+ sample. Therefore, this study aimed to assess the structural validity of the PennCNB adapted for use in Botswana.

Methods

A detailed protocol (open access) was previously described (Scott et al., 2020). All procedures were approved by the Institutional Review Boards at the University of Pennsylvania, the Health Research and Development Committee within the Ministry of

Health and Wellness of Botswana, and the Botswana-Baylor Children's Clinical Centre of Excellence.

Participants

Youth age 7-17 years were recruited from the Botswana-Baylor Children's Clinical Centre of Excellence (CoE), a clinic specializing in the care and treatment of HIV+ and HEU children in Gaborone, Botswana. School-aged children were specified because some of the PennCNB subtests are not suitable for younger children. In Botswana, primary and secondary school levels begin with Standard 1 (equivalent to first grade in the United States) and conclude with Form 5 (equivalent to 12th grade) (Statistics Botswana, 2019). This study's sampling strategy ensured the inclusion of HIV+ and HEU individuals. HIV+ participants were randomly selected from eligible CoE patients, while HEU participants were purposively sampled from the families of patients enrolled for HIV care at the CoE (i.e., caregivers were asked whether they had additional children who were HIV negative). HIV positive status was confirmed with the patients' medical records, and HEU status was self-reported by the caregivers (i.e., reports mother was living with HIV during pregnancy but the child has a documented negative HIV test result). Eligible participants were proficient in English or Setswana and did not have severe physical impairments or developmental delays that would prohibit completion of the PennCNB assessments. Fifteen patients in the randomly-selected HIV+ cohort were excluded due to age (turned 18 at time of recruitment), severe mental retardation, lack of parent to provide consent, deafness, blindness, or transferring care outside of the clinic. Informed consent and assent were completed prior to data collection. Demographic data and health information were reported by participants' caregivers. All participants were

compensated for participating in the study based on recommendations from the local IRB (40 pula, about equal to $4 USD).

Computerized Neurocognitive Battery Administration

The Botswana PennCNB adapted for use in this study includes modules from pediatric and adult batteries validated among the original cohorts in Philadelphia (Appendix Figure 2.1). The core pediatric version of the PennCNB comprises 14 tests that measure five neurobehavioral domains (executive control, episodic memory, complex cognition, social cognition, and sensorimotor speed) (Gur et al., 2012; Moore et al., 2015). For this study, 13 tests were selected to measure neurocognitive domains commonly affected by HIV infection and *in utero* HIV or antiretroviral therapy exposure (Cohen et al., 2015; Phillips et al., 2016; Ruel et al., 2012), as well as those expected to be relatively unaffected by HIV (Table 2.1). Tests included in the core pediatric 14-test battery that measure social cognition (i.e., emotion identification and age differentiation) were excluded due to limited evidence of impairment in HIV+ or HEU individuals. A Go/No-Go task (Moore et al., 2017), Trailmaking Tests (Parts A and B), and a Digit Symbol Substitution Test (Bachman et al., 2010) were added from additional versions of the PennCNB used in both adult and school-aged populations to enhance assessment of executive function and processing speed. Additional considerations for selection of the modules in the Botswana PennCNB included suitability for large-scale administration, suitability for resource-limited settings, suitability for translation and adaption across cultures, and sensitivity to individual differences and mild impairments (Scott et al., 2020). The PennCNB tests in the adapted battery were ultimately grouped into four neurocognitive domains (executive functioning, episodic memory, complex cognition,

and sensorimotor/processing speed) based on a combination of neurobehavioral theory and knowledge of previous factor structures (Moore et al., 2017; Moore et al., 2019; Moore et al., 2015; Gur et al., 2021). The battery underwent a rigorous cultural and language adaptation process informed by WHO guidelines that involved iterations of back-translating, piloting of tests and items, discussions about challenging concepts, and further modifications to select the most linguistically and conceptually appropriate Setswana (an African Bantu language) terminology as well as locally appropriate English terminology (Guillemin et al., 1993; van Widenfelt et al., 2005). The Setswana PennCNB and Botswana-English PennCNB contain the same content. Prior to finalization, the batteries were piloted among a sample of 10 patients living with HIV enrolled at the CoE (Scott et al., 2020). Previous literature described each of the tests in detail (Gur et al., 2012; Gur et al., 2010; Scott et al., 2020), and the following briefly summarizes each test by cognitive domain.

Tests measuring executive functioning included the Fractal N-Back Test (FNB), Penn Continuous Performance Test (PCPT), Penn Go/No-Go (GNG), and Penn Trailmaking Test Part B (TMTB). In the FNB test, participants are presented with a series of fractal images at 1 Hz, and they respond either to a pre-specified target fractal (0-back condition), whenever a fractal repeats the preceding fractal (1-back condition), and whenever the fractal is the same as the fractal presented 2 images before (2-back condition). In the PCPT, participants must press the space bar when a 7-segments display on the screen forms a number (first half of the test) or a letter (second half of the test) and not press for non-numbers or non-letters, respectively. In the GNG, participants must press the spacebar of the computer when the letter “x” appears in the upper half of the

screen only, with y's and lower-half x's serving as distractors. TMTB requires participants to connect dots on the screen in alternating numerical and alphabetical order (i.e., 1, A, 2, B, 3, C).

Tests measuring episodic memory included the Penn Face Memory Test (FMEM) and Visual Object Learning Test (VOLT). FMEM presents a series of twenty faces and requires participants to select these previously presented faces from a mixed set of images containing new, distractor faces. Similarly, VOLT presents a series of three-dimensional Euclidean shapes, and participants must determine from a mixed series whether the shape appeared previously. The recall trial for the Digit Symbol Substitution Test (DSSTr), which tests which symbols were paired with numbers, was also included as an assessment of incidental memory.

Tests measuring complex cognition included the Penn Conditional Exclusion Test (PCET), Penn Line Orientation Test (PLOT), and Penn Matrix Reasoning Test (PMAT). In the PCET, participants must determine which of four shapes does not belong in the group. Rules for exclusion change three times throughout the test following 10 consecutively correct responses, unbeknownst to the participant. In the PLOT, two line segments appear on the screen, and participants must rotate one of the segments until the two lines become parallel. The PMAT utilizes Raven's progressive matrix reasoning principles (Bilker et al., 2012) by presenting a series of geometric shapes and requiring participants to select the shape that completes the pattern.

Finally, tests measuring sensorimotor/processing speed included the Finger Tapping Test (CTAP), Digit Symbol Substitution Test (DSST), Motor Praxis Test (MPT), and Penn Trailmaking Test Part A (TMTA). For the CTAP, participants must

press the spacebar of the computer with the index finger (first the dominant hand and then the non-dominant hand, alternating for 5 trials) as quickly as possible in a predetermined amount of time (10 seconds). For the DSST, nine symbol-digit pairs serve as a reference set, and participants must indicate whether target digit-symbol pairs presented on the screen match the reference. In the MPT, the participant must use the computer mouse to click on a green square that appears and then disappears in different places on the screen. TMTA is similar to TMTB, but participants must connect the dots in sequential order without alternating between numbers and letters (i.e., 1, 2, 3).

The PennCNB was administered on a laptop by trained research staff to all participants in a quiet, private space in the CoE. Standard operating procedures for administration were followed, which comprised reading the PennCNB instructions aloud to each participant and providing practice PennCNB modules before the actual assessment began to ensure task comprehension. The tests were administered in a fixed order. Participants were presented with the option to complete the Setswana version of the PennCNB or the Botswana-adapted English version of the battery. Administrators documented their impressions of any situations that may have impacted validity of a test session (e.g., interruptions or difficulties manipulating the computer mouse).

Statistical Analysis

Analyses were performed on raw data for each test within each domain of the PennCNB, which included accuracy (correct or incorrect) and speed (mean response time) values for each test. Efficiency scores were calculated as the standardized sum of the z-standardized accuracy and speed (Response Time multiplied by -1 so that higher is faster) scores (Moore et al., 2015). Speed scores were included as an efficiency measure

for four modules because they only yielded speed values (CTAP and MPT) or had too few levels of data to justifiably be treated as continuous (TMTA and TMTB). Tests flagged as invalid (e.g., if there was a technical problem with the computer hardware during administration) were coded as missing, and missing data were imputed from a random forest model.

A common approach to factor analysis involves first running exploratory analysis (EFA) in one part of the sample (e.g., 50%) and then using that configuration (which variables load on which factors) to specify a confirmatory analysis (CFA) in the other part of the sample. However, this sequence was suboptimal for this analysis because 1) the sample size was not large enough, even for split-half cross-validation, and 2) a theory-based configuration to test already existed. Thus, first, CFA was conducted on the efficiency scores to evaluate the previously hypothesized factor structure of the PennCNB tests in the HIV+ and HEU cohort. The confirmatory factor analysis (Brown, 2014) was theory-based and had already received empirical support (Moore et al., 2017; Moore et al., 2015; Service et al., 2020). It posited four factors (the neurobehavioral domains of executive functioning, episodic memory, complex cognition, and sensorimotor/processing speed) inherent in the design of the PennCNB and supported by the analyses performed in the first structural validation of the PennCNB in the normative population (Moore et al., 2015). Thus, the analyses aimed to confirm the *a priori* domains of cognitive performance, again obviating the need for starting with exploratory factor analyses to determine which tests load on which factors. Loadings for the latent factors were standardized to have a mean of 0 and a variance of 1. Second, upon completion of the CFA, EFAs (Williams et al., 2010) were conducted on the speed, accuracy, and

efficiency measures to examine inconsistencies between EFA and CFA results. The EFAs allowed for further examination of the underlying factor structure of the PennCNB in this population (Moore et al., 2015). For example, if a test "cross-loads" on multiple factors beyond the one to which it theoretically belongs, then the EFAs will reveal that trend. Note that testing structural validity by way of factor analysis, whether EFA or CFA, is a method of testing both convergent validity (scores correlate relatively strongly with theoretically-similar constructs) and discriminant validity (scores correlate relatively weakly with theoretically-dissimilar constructs) simultaneously. This is because either poor convergent validity *or* poor discriminant validity will result in poor fit of the factor models by causing model misspecifications (tests loading outside their own constructs and/or failing to load within their own). Standard cut-off values (e.g., CFI > 0.95, SRMR < 0.08, and RMSEA < 0.06 indicating acceptable fit) were used to determine the fit of the models (Hu & Bentler, 1999). Default oblique rotation ("oblimin") was performed.

Multiple sensitivity analyses were performed, such as a comparison of the factor structure and fit of the models including three and five factors in exploratory analyses and retaining invalid test values rejected by auto-validation. In addition, the CFA and EFA models were to examine for fit among subsets of the cohort: youngest age strata of children aged 7 and 8 years due to potential influence of lack of comprehension on test performance (N = 165), HEUs to assess generalizability of the HIV-affected cohort (N = 173), participants who completed the English version of the PennCNB to examine factor differences by battery language (N = 189), and both HEUs or participants who completed the English version of the PennCNB (N = 157). Results had negligible impacts on

findings and are thus not presented. All analyses and plots were completed in R (v3.3.3; R Core Team, 2017).

Results

Participant Characteristics

A sample of 209 participants were enrolled (Table 2.2). Most of the participants (N = 173) were HIV+ with a mean age of 11.54 years (SD = 3.08). Sex distribution was approximately equal, and all participants identified as Black African. Four participants had not completed any formal education. Most of the participants (N = 189) completed the Setswana version of the PennCNB rather than the Botswana-adapted English version of the battery.

Confirmatory Factor Analysis

Figure 2.1 displays the standardized results of the CFA on the PennCNB efficiency scores for the four-factor model pre-specified according to neurocognitive theory. All factor loadings were in the strong range (i.e., greater than 0.6). The model also revealed high inter-factor correlations, as all factor pairs were correlated at a value greater than 0.791 (complex cognition/episodic memory: 0.889; complex cognition/executive functioning: 0.846; complex cognition/sensorimotor speed: 0.791; episodic memory/executive functioning: 0.867; episodic memory/sensorimotor speed: 0.895; executive functioning/sensorimotor speed: 0.952. The model yielded acceptable fit, with a comparative fit index (CFI) of 0.965, root mean-square error of approximation (RMSEA) of 0.066, and standardized root mean-square residual (SRMR) of 0.035 (Table 3). The sensitivity analyses that examined the fit of the models within subgroups of the sample all demonstrated strong fit (Appendix Table 2.1).

Exploratory Factor Analysis

Based on subjective evaluation of the scree plot (Figure 2.2; Appendix Figure 2.2), one factor (unidimensional model) might be sufficient to explain covariances among PennCNB efficiency scores. Table 2.3 presents the measures of fit for models with one, two, three, four, and five factor solutions. Using CFI as an indicator, the two-factor (0.96), three-factor (0.96), four-factor (0.97), and five-factor (0.97) models had acceptable fit. When evaluating the RMSEA, the one-factor (0.088) and two-factor (0.070) solutions had moderate fit, while solutions with three (0.044), four (0.032), and five (0.000) factors yielded acceptable fit. The model with the lowest Bayesian Information Criterion (BIC) included two factors (BIC = −211).

Table 2.4 presents the four-factor solution and inter-factor correlations. The PennCNB subtests loaded as follows: Factor 1 (CPT, GNG, CTAP speed, MPT speed, FNB), Factor 2 (PCET, PMAT, PLOT), Factor 3 (TMTA speed, DSST, TMTB speed, DSSTr), and Factor 4 (VOLT, FMEM). The tests with the strongest loadings for Factors 1 through 4 were CPT (0.88), PCET (0.82), TMTA speed (0.94), and VOLT (0.45), respectively. Factors 1 and 3 had the highest inter-factor correlation (0.74). When relating the individual factor scores with age of the participants, age was statistically-significantly associated with scores for each of the four factors and in the expected direction (in this age group, older = higher scores; results not presented).

Discussion

The PennCNB has the potential to streamline neurocognitive assessment among HIV-affected children and adolescents in Botswana by providing an alternative to the limited and burdensome traditional, paper-based cognitive testing methods. To ensure the

structural validity of the modified battery, this study aimed to assess the factor structures of speed, accuracy, and efficiency scores for the 13 PennCNB tests. The results provide valuable insight into the interpretation of the PennCNB data. Moreover, they suggest that a computerized neurocognitive battery adapted for use with children and adolescents in a non-Western setting with limited computer familiarity has a similar factor structure to that seen in Western settings (i.e., originally validated PennCNB in Philadelphia). Further, this is the first effort to systematically evaluate the factor structure of the PennCNB among a population of individuals affected by HIV.

The good fit of the models suggests that this adapted version of the PennCNB is a structurally valid tool for use in this setting, and the approach to design based on theory and previous evidence is partially supported. The fit of the CFA models in the sensitivity analyses further support the hypothesized structure. The PennCNB tests included in the prior validation do not overlap exactly with the tests composing the Botswana battery, but the loadings were consistent for the common tests. Factor 1 (CPT and FNB), Factor 2 (PCET, PLOT, and PMAT), and Factor 4 (FMEM and VOLT) appear to measure executive functioning, complex cognition, and episodic memory, respectively. However, when examining the additional tests added to the battery, according to the EFA, the factors do not separate into discrete cognitive domains. GNG, CTAP speed, and MPT speed loaded onto Factor 1, while TMTA speed, DSST, and TMTB speed loaded onto Factor 3. Thus, the tests measuring executive functioning and sensorimotor speed group together in Factor 1. Factor 3 appears to simply measure speed. Previous research shows a lack of differentiation in pediatric samples between processing speed and executive functioning (Mungas et al., 2013), though few studies have examined measures of

sensorimotor speed in factor analyses of youth samples. When evaluating the sensitivity analyses, the EFAs become unstable at the small sample sizes, thus supporting the approach of utilizing the full sample including HIV+ and HEU participants who completed either the Setswana or Botswana-English version of the PennCNB.

The high correlations among all factors have both psychometric and theoretical implications. From a psychometric perspective, the high correlation indicates that a great deal of the covariance among the factors can be explained by a single "g" factor, potentially indicating sizeable, nonspecific influences on cognitive function. From a practical measurement perspective that values parsimony, a single factor (unidimensional model) may be optimal. From this perspective, any attempt to parse the factors further would generate scores that are so collinear that interpretation of their effects in analyses would be difficult. However, prior studies in children between 8 and 15 years old show similarly high inter-factor correlations using the NIH Toolbox, especially when compared to an adult sample (Mungas et al., 2013). From a theoretical perspective, there is good reason to expect the tests to cluster according to localization of brain function (Genderson et al., 2007; Gur et al., 1992; Roalf et al., 2014;). Moreover, there is evidence that these tests align well with theoretical neurobehavioral domains (Moore et al., 2015). In addition, neurocognitive deficits secondary to neurological disease or injury often affect specific brain functions, which may be obscured if one examines level of performance in only a single factor. For example, verbal fluency and verbal comprehension are highly correlated, but measuring both constructs is needed to differentiate expressive from receptive aphasia.

This research had potential limitations. First, all participants were enrolled from the CoE in the capital city of Gaborone, which may limit the generalizability of the findings. However, the pathophysiology linking HIV and neurocognitive impairments should not differ based on geographical location. Second, certain tests from potentially relevant domains (e.g., verbal memory) were not included due to difficulties with cultural and language adaptations. Third, although there was sufficient statistical power to perform the factor analyses, the sample size limited the ability to perform cross-validation and resulted in unstable EFAs upon excluding subsets of the sample. Due to the lack of available cognitive assessments in Botswana and other resource-limited settings, rapidly disseminating information about the structural validity of the PennCNB is crucial to supporting the cognitive function of children affected by HIV. Fourth, even though the content of the Setswana and English versions of the Botswana PennCNB are the same, there may be subtle differences in test instructions that add variance to performance. Therefore, results of the Botswana-English version of the PennCNB should be interpreted with caution.

Future research will further evaluate the psychometric properties and utility of the PennCNB adapted for use in Botswana. Forthcoming analyses will assess the reliability (e.g., measures of internal consistency and test-retest) and criterion validity of the battery, including its relationship with academic and affective-behavioral problems, as judged by clinicians blind to the PennCNB results. In addition, future research will also assess the association of performance on this battery with age, sex, and HIV and HEU status to provide further information about its validity and potential utility within this setting. Implementation science research evaluating the acceptability of the tool among youth, as

well as eliciting medical and educational stakeholder perspectives, will inform the development of implementation strategies specific for this setting.

Conclusion

This research offers important insights into the psychometric properties of the PennCNB that was adapted for assessment of youth affected by HIV in Botswana. The structural validity of the battery, as evaluated through factor analyses, is strong, which demonstrates that the tool measures the intended neurocognitive domains. Consistent with prior studies in children, executive functioning and sensorimotor/processing speed were less differentiated in this pediatric sample than typically seen in adult samples. Initial results suggest that the adapted PennCNB could serve as a useful tool for the assessment of neurocognitive functioning in Botswana and, potentially, other resource-limited settings.

Table 2.1. Penn Computerized Neurocognitive Battery Tests Administered

Cognitive Domain	Test
Executive Functioning	Fractal N-Back Test (FNB)
	Penn Continuous Performance Test (PCPT)
	Penn Go/No-Go (GNG)
	Penn Trailmaking Test, Part B (TMTB)
Episodic Memory	Digit Symbol Substitution Test, recall (DSSTr)
	Penn Face Memory Test (FMEM)
	Visual Object Learning Test (VOLT)
Complex Cognition	Penn Conditional Exclusion Test (PCET)
	Penn Line Orientation Test (PLOT)
	Penn Matrix Reasoning Test (PMAT)
Sensorimotor/Processing Speed	Finger Tapping Test (CTAP)
	Digit Symbol Substitution Test (DSST)
	Motor Praxis Test (MPT)
	Penn Trailmaking Test, Part A (TMTA)

Table 2.2. Participant Characteristics

	N (%)
Total	209
Mean age (years)	11.54
7	16 (7.66)
8	28 (13.40)
9	18 (8.61)
10	31 (14.83)
11	20 (9.57)
12	20 (9.57)
13	13 (6.22)
14	19 (9.09)
15	15 (7.18)
16	9 (4.31)
17	20 (9.57)
HIV Status	
HIV+	173 (82.78)
HEU	36 (17.22)
Sex	
Female	107 (51.20)
Male	102 (48.80)
Education	
None	4 (1.91)
Standard 1	19 (9.09)
Standard 2	26 (12.44)
Standard 3	29 (13.88)
Standard 4	18 (8.61)
Standard 5	25 (11.96)
Standard 6	19 (9.09)
Standard 7	21 (10.05)
Form 1	15 (7.18)
Form 2	16 (7.66)
Form 3	13 (6.22)
Form 4	3 (1.44)
Form 5	1 (0.48)
College or Technical School	0
Some University	0

Table 2.3. Fit Indices from Confirmatory and Exploratory Factor Analyses on PennCNB Efficiency, Speed, and Accuracy Scores

			Fit Indices			
Analysis	**Measure**	**Factors**	**CFI**	**RMSEA**	**SRMR**	**BIC**
CFA	Efficiency	4	0.965	0.066	0.035	6647
EFA	Efficiency	1	0.95	0.088	0.050	-208
EFA	Efficiency	2	0.96	0.070	0.033	-211
EFA	Efficiency	3	0.96	0.044	0.024	-204
EFA	Efficiency	4	0.97	0.032	0.019	-169
EFA	Efficiency	5	0.97	0.000	0.013	-135
EFA	Speed	1	0.85	0.113	0.077	-128
EFA	Speed	2	0.88	0.066	0.049	-219
EFA	Speed	3	0.91	0.045	0.030	-204
EFA	Speed	4	0.92	0.038	0.024	-165
EFA	Speed	5	0.93	0.036	0.019	-126
EFA	Accuracy	1	0.77	0.055	0.055	-286
EFA	Accuracy	2	0.80	0.048	0.044	-247
EFA	Accuracy	3	0.83	0.039	0.035	-209
EFA	Accuracy	4	0.84	0.028	0.030	-171
EFA	Accuracy	5	0.85	0.018	0.024	-132

CFA = confirmatory factor analysis; EFA = exploratory factor analysis; CFI = comparative fit index; RMSEA = root mean-square error of approximation; SRMR = standardized root-mean square residual; BIC = Bayesian Information Criterion.

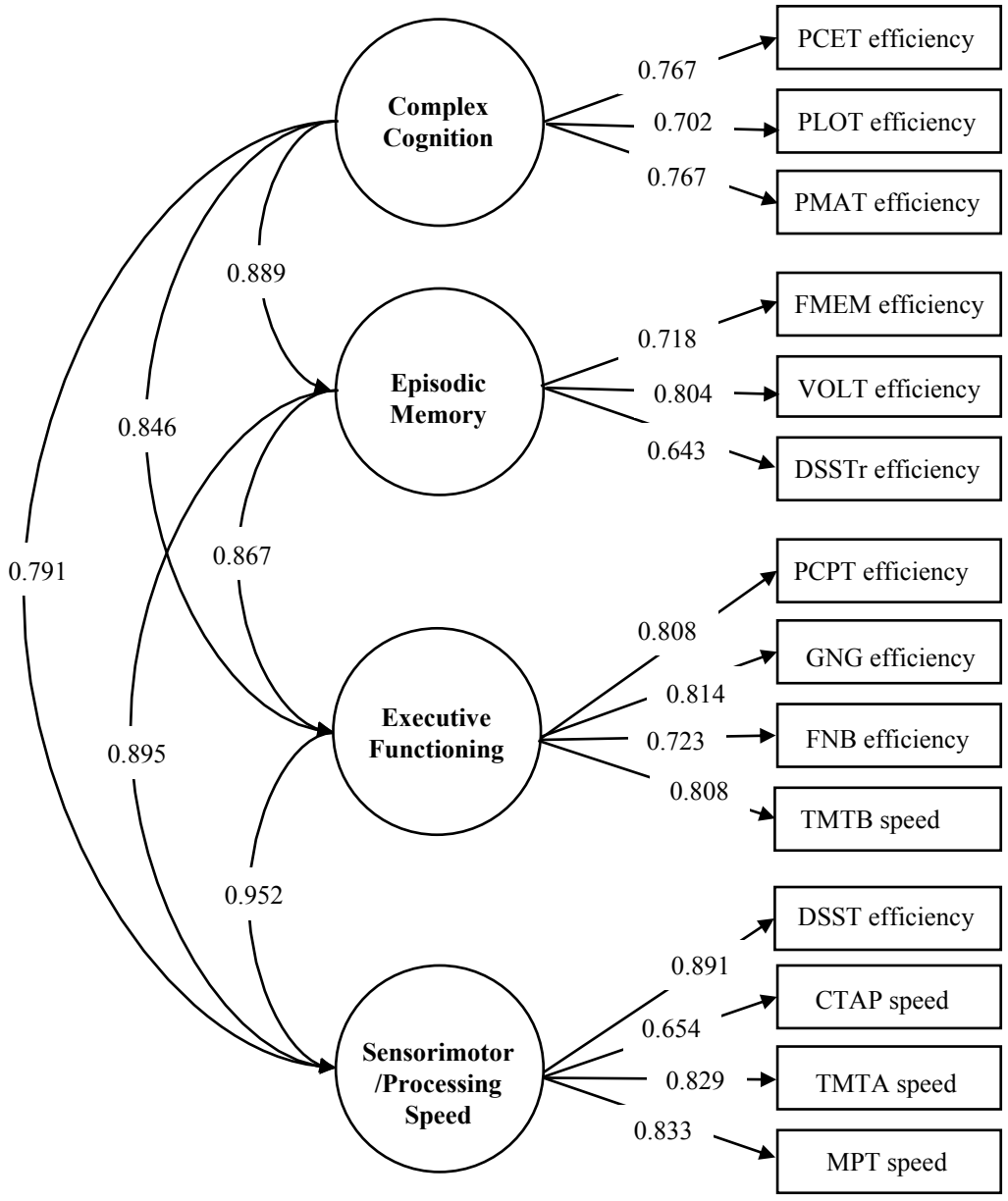
Table 2.4. Factor Loadings from Exploratory Factor Analysis on PennCNB Efficiency Scores

	Factor			
Module	**F1**	**F2**	**F3**	**F4**
CPT efficiency	**0.88**	0.00	-0.03	0.02
GNG efficiency	**0.74**	0.10	0.00	0.06
CTAP speed	**0.59**	-0.14	0.25	-0.01
MPT speed	**0.36**	0.28	0.36	-0.10
FNB efficiency	**0.36**	0.14	0.21	0.16
PCET efficiency	-0.03	**0.82**	0.00	0.01
PMAT efficiency	0.03	**0.67**	0.02	0.13
PLOT efficiency	0.29	**0.45**	-0.07	0.09
TMTA speed	0.00	-0.02	**0.94**	0.03
DSST efficiency	0.20	0.17	**0.51**	0.18
TMTB speed	0.25	0.37	**0.40**	-0.17
DSSTr efficiency	-0.05	0.19	**0.36**	0.32
VOLT efficiency	0.23	0.17	0.16	**0.45**
FMEM efficiency	0.25	0.22	0.11	**0.30**

Factor Correlations

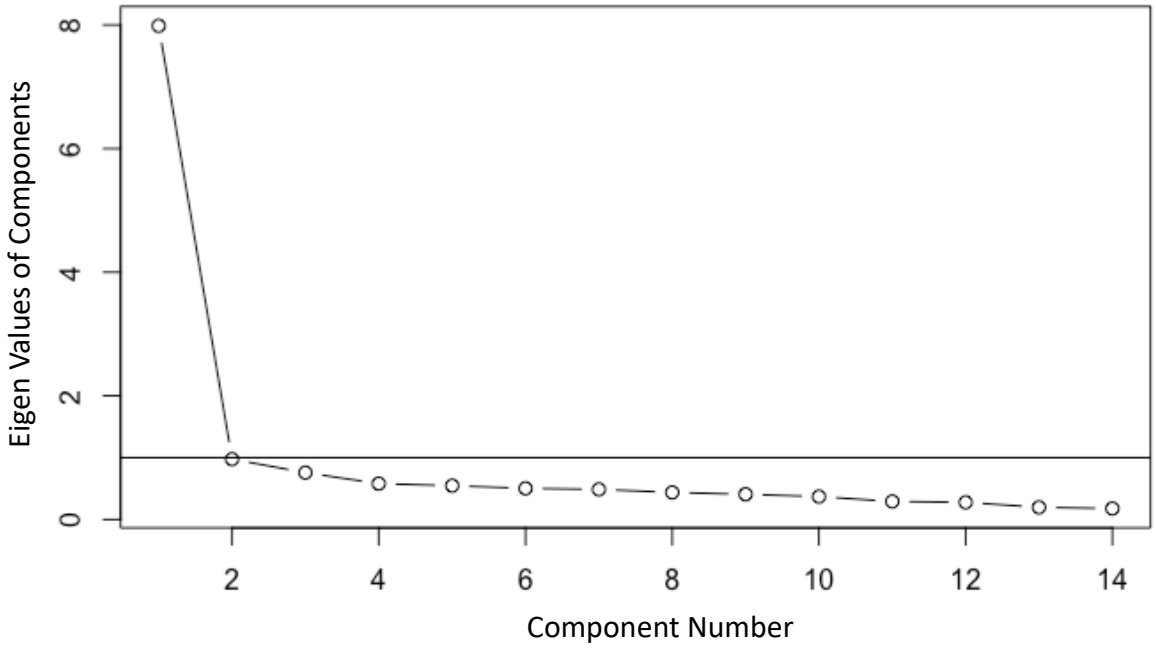
	F1	**F2**	**F3**	**F4**
F1	-	0.70	0.74	0.38
F2	0.70	-	0.58	0.51
F3	0.74	0.58	-	0.37
F4	0.38	0.51	0.37	-

Figure 2.1. Confirmatory Factor Analysis on PennCNB Efficiency Scores



Loadings and inter-factor correlations are standardized.

Figure 2.2. Scree Plot on PennCNB Efficiency Scores



CHAPTER 3. PREDICTIVE VALIDITY OF A COMPUTERIZED BATTERY FOR IDENTIFYING NEUROCOGNITIVE IMPAIRMENTS AMONG CHILDREN LIVING WITH HIV IN BOTSWANA

“Understand me”

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Abstract

Children living with HIV (HIV+) experience increased risk of neurocognitive deficits, but standardized cognitive testing is limited in low-resource, high-prevalence settings. The Penn Computerized Neurocognitive Battery (PennCNB) was adapted for use in Botswana. This study evaluated the criterion validity of a locally adapted version of the PennCNB among a cohort of HIV+ individuals aged 10-17 years in Botswana. Participants completed the PennCNB and a comprehensive professional consensus assessment consisting of pencil-and-paper psychological assessments, clinical interview, and review of academic performance. Seventy-two participants were classified as cases (i.e., with cognitive impairment; N = 48) or controls (i.e., without cognitive impairment; N = 24). Sensitivity, specificity, positive predictive value, negative predictive value, and the area under receiver operating characteristic curves were calculated. Discrimination was acceptable, and prediction improved as the threshold for PennCNB impairment was less conservative. This research contributes to the validation of the PennCNB for use among children affected by HIV in Botswana.

Introduction

The human immunodeficiency virus (HIV) is a leading cause of morbidity among children in Sub-Saharan Africa (UNAIDS, 2020). In Botswana, approximately 10,000-15,000 individuals age 0-14 years are living with HIV (HIV+) (World Health Organization, 2017). Due to the availability of free antiretroviral therapy (ART) in Botswana, many children who were perinatally infected with HIV have survived to live relatively healthy lives (Farahani et al., 2014). However, children living with HIV experience increased risk of neurocognitive deficits, specifically in the domains of attention, episodic memory, executive functioning, information processing speed, and psychomotor functioning (Le Doare K, 2012; Phillips et al., 2016; Ruel et al., 2012; Smith et al., 2012). These deficits are multifactorial. It has been hypothesized that some of the increased risk of impairment is due to *in utero* toxicities (Wedderburn et al., 2019), such as HIV replication in specific brain cells, ART toxicity, and opportunistic infections, resulting in direct damage to the central nervous system (Blokhuis et al., 2016; Churchill & Nath, 2013; Crowell et al., 2014). Early life nutritional and social deprivation, late access to treatment, and greater HIV disease severity can exacerbate the deficits (Behen, et al., 2008; Le Doare et al., 2012). Studies show that initiation of ART in HIV+ children can cease progression of neurocognitive dysfunction, but ART cannot reverse dysfunction (Lazarus et al., 2015; Linn et al., 2015). Thus, to support the functional and educational attainment of HIV+ children and adolescents, early detection and treatment of neurocognitive impairments is critical.

Due to the lack of comprehensive neurocognitive assessments in Botswana, the Penn Computerized Neurocognitive Battery (PennCNB) was culturally and linguistically

adapted for use in this setting (Scott et al., 2020). Composed of "neurobehavioral probes" (Gur et al., 1992) validated by functional neuroimaging (Roalf et al., 2014), the PennCNB measures performance accuracy and response speed for major neurocognitive domains (Gur et al., 2010; Moore et al., 2015). The neurobehavioral probes include adaptations of common "pencil and paper" tests traditionally administered by neuropsychologists (e.g., Trailmaking tests), as well as tests that can be performed more precisely via computer (e.g., finger tapping). Importantly, the PennCNB has the potential to streamline neurocognitive assessment, which presents many advantages for implementation (especially in resource-limited settings), such as increased standardization and reliability, ease of administration, and automated scoring and database generation. The version of the PennCNB adapted for use in Botswana includes 13 tests selected *a priori* based on the cognitive domains commonly impaired among children with HIV infection and *in utero* HIV or antiretroviral therapy exposure (Cohen et al., 2015; Phillips et al., 2016; Ruel et al., 2012; Scott et al., 2020). Through a rigorous cultural and language adaptation process informed by WHO guidelines, the battery was translated into Setswana (local language) and locally appropriate English (Guillemin et al., 1993; Scott et al., 2020; van Widenfelt et al., 2005). Variations of the tests composing the adapted PennCNB have been used extensively to identify neurocognitive deficits among pediatric populations (Gur et al., 2012; Hartung et al., 2016; Moore et al., 2015; Swagerman et al., 2016).

Previous research examined the structural validity of the adapted PennCNB among a cohort of HIV+ and HIV-exposed-uninfected (HEU) children in Botswana (Van Pelt et al., revise and resubmit), providing evidence of the convergent and discriminant

validity of the tool. However, establishing the validity of the battery on the population-level differs from demonstrating the extent to which the PennCNB correctly classifies neurocognitive deficits on an individual level. Thus, understanding the extent to which the adapted PennCNB accurately identifies children with clinically significant neurocognitive impairment and children without clinically significant impairment is a critical next step in the validation of the tool.

Assessing the criterion validity (e.g., agreement with a gold standard assessment) provides an estimate of a battery's ability to predict outcomes, and these outcomes (criteria) are often established measures that have well-described theoretical links to the trait measured by the scores under scrutiny. However, in Botswana and similar resource-limited settings, a rigorous gold standard for cognitive screening is not available. Therefore, this research aimed to evaluate the predictive validity of the adapted PennCNB in Botswana utilizing the best, most feasible data available and expert consensus to constitute a "gold standard" evaluation.

Methods

This sub-study evaluating criterion validity is part of a larger research project that is described in detail elsewhere (Scott et al., 2020). All procedures were approved by the Institutional Review Boards at the Health Research and Development Committee within the Ministry of Health and Wellness of Botswana, the Botswana-Baylor Children's Clinical Centre of Excellence (CoE), and the University of Pennsylvania.

Participants

HIV+ children aged 10-17 years enrolled for care at the CoE, a facility providing pediatric HIV care and treatment in Gaborone, Botswana, were recruited for

participation. Patients eligible for inclusion were proficient in English or Setswana, did not have severe physical impairments or profound developmental delays that would prohibit completion of the PennCNB assessment, and did not receive medications to treat cognitive or attention problems (e.g., attention-deficit/hyperactivity disorder (ADHD)). The majority of participants for this sub-study were randomly selected from the larger study cohort. To ensure inclusion of enough participants with neurocognitive impairment, the randomly selected participants were supplemented by purposively recruiting patients enrolled for care at the CoE who were previously identified as having cognitive impairment by the clinic psychologist. "Cases" were defined as individuals with clinically significant neurocognitive impairment that impacted their functional behavior, and "controls" were defined as children without clinically significant neurocognitive impairment. A detailed description of the methodology used to classify each participant is given in the next section. Informed consent and assent were obtained prior to data collection, and demographic data and health information were reported by participants' caregivers.

Professional Consensus Classification

Due to the limited validated cognitive assessments in Botswana available to serve as a gold standard test, the team completed a multi-step, team-based approach to systematically evaluate the neurocognitive function of each possible participant. First, a local, experienced clinical psychologist completed a comprehensive assessment that included a local standard-of-care cognitive assessment and added supplementary interview components. The local assessment consisted of the following: 1) the Montreal Cognitive Assessment (MoCA) (Nasreddine et al., 2005), a 30-question cognitive

screener that assesses cognitive ability in eight domains (orientation, short-term memory, executive function, language abilities, abstraction, attention, animal naming, and clock-drawing test); 2) the Draw-a-Person Test (Naglieri, 1988), an assessment that measures cognitive maturity and mental age; 3) an intake interview that elicited information about the child's current school performance, educational and developmental history, mental health, possible diagnosis of dyslexia, history of school performance for other siblings, and caregiver perceptions of intelligence and comprehension; and 4) a review of school records and history of academic performance. The MoCA is not typically administered to young children, but the local psychologist uses this assessment in practice because it is culturally acceptable and effective as a screening tool for cognitive impairments. Suggested adjustments to the cut-off score for determining impairment in younger and less-educated populations were applied to the MoCA scores (Nasreddine et al., 2005). In Botswana, primary school starts with Standard 1 (equivalent to 1st grade in the United States) and ends with Form 5 (equivalent to 12th grade) (Statistics Botswana, 2019). Upon review of the data, the clinical psychologist preliminarily classified each potential participant as a case or control and determined impairment in three cognitive domains (executive functioning, episodic memory, and sensorimotor function). Prior to inclusion in the final cohort, the preliminary classifications and corresponding data were discussed by a group of four clinicians with local and international expertise in neuropsychology, psychology, pediatrics, and HIV to ensure consistency of assessments and determine assignment of case/control status and impairment in each of the subdomains. The team was blinded to PennCNB performance when classifying participants. To be considered a "case", a participant needed to demonstrate evidence of abnormalities on the clinical

psychologist's assessments and some functionally limiting impairment at school and/or home. When the group lacked consensus (i.e., the group could not confidently classify a patient according to the data), individuals were considered "unclassifiable" and excluded from the final cohort (N = 27). For example, children who performed averagely in school but had impairments on the assessments for the professional consensus classification were not utilized as controls, because controls were meant to represent typically developing children. Likewise, children with average scores on the formal assessments (e.g., MoCA) who were failing at school were considered "unclassifiable". Thus, classification was conservative with identifying cases/controls, so the final cohort represents "extremes" of impairment/no impairment.

PennCNB Administration

Table 3.1 lists the 13 tests composing the PennCNB adapted for use in Botswana and the cognitive domains measured by each module. The tests were previously described in detail (Gur et al., 2012; Gur et al., 2010; Scott et al., 2020). Briefly, the battery measured executive functioning (Fractal N-Back Test, Penn Continuous Performance Test, Penn Go/No-Go, and Penn Trailmaking Test Part B), episodic memory (Penn Face Memory Test, Visual Object Learning Test, and Digit Symbol Substitution Test recall), complex cognition (Penn Conditional Exclusion Test, Penn Line Orientation Test, and Penn Matrix Reasoning Test), and sensorimotor/processing speed (Finger Tapping Test, Digit Symbol Substitution Test, Motor Praxis Test, and Penn Trailmaking Test Part A).

The PennCNB was administered on a laptop by a trained member of the research team in a private space in the CoE. Individuals facilitating the PennCNB assessments

were blinded to the participants' status as cases or controls. Standard operating procedures for administration were followed, which included reading the PennCNB instructions aloud to each participant and providing practice PennCNB modules to ensure task comprehension before beginning the actual assessment. Participants had the option to complete the Setswana version of the PennCNB or the Botswana-adapted English version of the battery. The tests were administered in a fixed order.

Statistical Analysis

Determination of PennCNB Classification

The PennCNB yields accuracy (total or percent correct) and speed (mean response time) values for each test. Neurocognitive efficiency scores were calculated as the average of the z-standardized accuracy and speed (Response Time multiplied by -1 so that higher is faster) scores (Moore et al., 2015). To determine impairment/no impairment from the PennCNB data, composite scores were calculated from the efficiency data, which were then age-adjusted and z-standardized. Composite scores were used because generating composite scores will be more feasible for the implementation of the PennCNB in resource-limited settings compared to more sophisticated psychometric approaches such as calculating and interpreting factor scores. As mentioned above, the participants recruited for this study were a subset of a larger cohort of HIV+ and HIV-exposed-uninfected (HEU) children (N = 306) at the CoE who had completed the PennCNB assessment (Scott et al., 2020). To create z-standardized scores, PennCNB scores for the classified cases and controls were compared to the distribution of scores from this larger sample of 306 children. For the primary analysis, individuals with composite scores -1.5 SD from the global mean or -2 SD from the mean on any of the

specific domains (executive functioning, episodic memory, or sensorimotor speed) were considered overall PennCNB-impaired; all other participants were considered overall PennCNB-unimpaired. To classify impairment in the specific cognitive domains, participants with scores -1.5 SD from the mean were considered impaired in the respective domain. To account for the potential enrichment of cognitive deficits in the sample due to the inclusion of only HIV+ and HEU participants, sensitivity analyses that evaluated different thresholds for determining impairment (-1.5 SD, -1.0 SD, -0.5 SD, and 0 SD) were performed.

Classification Accuracy

To examine the predictive validity of the PennCNB, PennCNB efficiency scores were used to "predict" the professional consensus classifications. The primary analysis assessed overall impairment by evaluating the PennCNB's ability to distinguish between children with clinically significant impairment and children without clinically significant impairment (i.e., agreement between case/control classifications). A secondary analysis explored the PennCNB's agreement with the gold standard within specific domains of neurocognitive impairment (executive functioning, episodic memory, and sensorimotor function). PennCNB tests measuring complex cognition were included in the calculation of overall impairment, but this domain was excluded in the secondary analysis due to an inability to confidently classify impairment in complex cognition in the professional consensus assessment. Domains considered unclassifiable according to the professional consensus assessment for an individual child were considered missing for the secondary analyses. Sensitivity (i.e., true positive rate), specificity (i.e., true negative rate), positive predictive value (PPV; proportion of positive calls that are correct), negative predictive

value (NPV; proportion of negative calls that are correct), and the area under receiver operating characteristic curves (AUC) were calculated to assess the ability of the PennCNB to identify cases and controls (Ghanem et al., 2009; Kumar & Indrayan, 2011; Zou et al., 2007). The utility of the classification was determined based on standard values, where 1 indicated perfect prediction (AUC of 0.5 = no discrimination, AUC of 0.7-0.8 = acceptable discrimination) (Hosmer & Lemeshow, 2000). Cross-validation procedures were unnecessary because the classification rules (prediction model) were determined *a priori* (i.e., there was no prediction model to build). All analyses and plots were completed in R (v3.3.3; R Core Team, 2017) and Stata Statistical Software (15.1; College Station, 2017).

Results

Participant Characteristics

Seventy-two participants (48 cases and 24 controls) were enrolled (Table 3.2). The mean age of cases (13.69 years) and controls (13.33 years) was approximately equal. All individuals identified as Black African. Overall, sex distribution was approximately equal. Cases included more males (58.33%), and controls included more females (62.50%). Most participants (N = 65 (90.28%)) completed the Setswana version of the PennCNB rather than the English version of the tool (cases: 100% Setswana; controls: 71% Setswana).

Prevalence of Neurocognitive Impairment among Participants

Table 3.3 displays the number of participants classified as having neurocognitive impairment overall and within the specific neurocognitive domains for each of the classification approaches. Based on the professional consensus procedures, 48

participants were considered cases overall, with 31 demonstrating deficits in executive functioning (13 unclassifiable), 40 in episodic memory (6 unclassifiable), and 3 in sensorimotor speed (17 unclassifiable). When applying the -1.5 SD cut-off to the PennCNB scores, results yielded 13 overall PennCNB-impaired and 59 overall PennCNB-unimpaired. As expected, the number of participants determined to have impairment overall increased as the cut-off became less conservative: -1.0 SD (23 PennCNB-impaired, 49 PennCNB-unimpaired), -0.5 SD (30 PennCNB-impaired, 42 PennCNB-unimpaired), and 0 SD (41 PennCNB-impaired, 31 PennCNB-unimpaired). When examining the specific neurocognitive domains, the PennCNB data did not capture all of the deficits in episodic memory as identified through the professional consensus approach (-1.5 SD: 7, -1.0 SD: 18, -0.5 SD: 31, 0 SD: 38), but the number of participants considered to have impairment in executive functioning (-1.5 SD: 11, -1.0 SD: 20, -0.5 SD: 27, 0 SD: 39) or sensorimotor speed (-1.5 SD: 7, -1.0 SD: 14, -0.5 SD: 23, 0 SD: 36) eventually surpassed the professional consensus counts.

Classification Accuracy of Overall Impairment

Table 3.4 presents the results for the diagnostic accuracy of the PennCNB across the range of cut-off points. The sensitivity increased as the cut-off for determining neurocognitive impairment approached the mean (-1.5 SD: 0.2292, -1.0 SD: 0.4375, -0.5 SD: 0.5833, 0 SD: 0.7292), while the specificity remained constant at 0.9167 until examining the 0 SD cut-off (0.7500). Overall, the probability of identifying impairment among participants with a neurocognitive deficit was high (positive predictive value > 0.846 for all thresholds). Based on the 0.70 threshold, overall predictive utility of the

battery became acceptable at the -0.5 SD (AUC = 0.7500) and 0 SD cut-off points (AUC = 0.7396) (Figure 3.1).

Classification Accuracy of Specific Neurocognitive Domains

The accuracy of the classifications varied across the specific neurocognitive domains (Table 3.4). Overall, the specificity was high for each of the domains. The positive predictive value for sensorimotor speed was poor (PPV < 0.200 for all thresholds). Similar to the primary analysis, the models demonstrated acceptable discrimination at the -0.5 SD and 0 SD cut-offs for executive functioning and sensorimotor speed, but the prediction for episodic memory was borderline unacceptable (AUC = 0.6904) at the least conservative threshold.

Discussion

Children and adolescents living with HIV experience increased risk of neurocognitive deficits, but standardized neurocognitive screening is not available in low-resource, high-prevalence settings in Sub-Saharan Africa. This study aimed to assess the criterion validity and predictive/classification utility of the PennCNB adapted for use in Botswana against a professional consensus classification consisting of a multi-step, team-based approach utilizing the best available local psychological assessment tools. Results provided insight into the criterion validity of the adapted tool, as well as the range of classification accuracy/utility that can be expected from the tool at various classification cut-offs.

Overall, the adapted PennCNB demonstrated acceptable discrimination, indicating that the battery accurately identified impairment and had reasonable agreement with locally available best practices at the individual child level. These findings provide

evidence of criterion validity while encouraging additional inquiry. Using norms generated from this HIV+ and HEU cohort, results suggested that -0.5 SD may be an optimal cut-off for interpretation of the PennCNB data. However, since norms for some subtests could be skewed in this cohort, future work will establish norms in HIV-unexposed and uninfected (HUU) children in Botswana to assess differences in classification accuracy. Moreover, normative values established in HUU children will assist with more generalized application of the PennCNB in clinical practice. Sensitivity analyses were performed to assess different cut-offs and account for this potentially enriched sample. When evaluating cut-offs, there are tradeoffs between the sensitivity and specificity of the tool. Determination of the optimal point should aim to maximize both sensitivity and specificity, but decisions need to consider the potential negative outcomes of false positives (e.g., misidentifying children as having neurocognitive deficits, which can result in stigma) and false negatives (e.g., missing children in need of cognitive support).

The low sensitivity and poor prediction at more conservative cut-offs was a statistical byproduct of having a sample highly enriched for cognitive impairment, such that no conservative cut-off could work given the number of positive cases. The low sensitivity may also be attributable to unmeasured factors that impact children's cognitive function. For example, the Botswana-adapted versions of the PennCNB did not include specific linguistic assessments due to the relatively difficulty of creating comparable linguistic assessments across languages and cultures. The linguistic assessments on the MoCA are limited, and the professional consensus classification did not attempt to

diagnose specific language impairments. Nevertheless, linguistic deficits can impact performance both on the PennCNB and at school.

Notably, findings suggested low positive predictive values for sensorimotor speed. Sensitivity and specificity reflect characteristics of the test, but the prevalence of an outcome influences the positive predictive value and negative predictive value (Parikh, Mathai, Parikh, Chandra Sekhar, & Thomas, 2008). This study was powered to provide a probability of 80% of detecting a difference in the AUC of two ROC curves at a critical value of 0.70 using a one-sided test of significance with a p-value equal to 0.05. Although statistically sufficient, this yielded a relatively small sample size that limits precision of the estimates. Three participants were classified as having a sensorimotor deficit according to the professional consensus classifications (17 unclassifiable in this domain). In a sample with a greater prevalence of sensorimotor impairment (i.e., population sample of HIV-affected youth), it is possible that the predictive values will improve.

Since a gold standard for neurocognitive evaluation does not exist in this setting, the approach to determining the professional consensus classifications may have resulted in some misclassification of case/control status. Further, the potential for misclassification may have increased for the specific cognitive domains of impairment in the secondary analyses due to the slight differences in domains between the PennCNB and MoCA, as well as the MoCA's limited assessment of specific domains of cognitive functioning, potentially resulting in lower sensitivity within specific domains. Standardized assessments included all elements of evaluations currently completed by the local psychologist supplemented by qualitative assessments, and expert clinicians helped

to monitor fidelity and consistency of the assessments. Nonetheless, the professional consensus assessments were not as rigorous as validated gold standard tools.

Demonstrating acceptable criterion validity of the PennCNB has practical implications for implementation. Since administration of the PennCNB can be performed by individuals with limited training, showing that the battery has acceptable agreement with classification established by a professional evaluator for individual children suggests that the PennCNB may be reasonably relied on to identify children who would benefit from additional support. Although the PennCNB provides advantages such as ease of administration and automated scoring, implementation of the PennCNB in clinical settings in Botswana will require additional efforts, such as training in administration of the tool, establishment of data interpretation guidelines, and possibly inclusion of additional evaluations to examine literacy and linguistic cognitive deficits.

Conclusions

Findings indicated that the PennCNB adapted for use in Botswana demonstrated acceptable criterion validity, suggesting that the battery could be a valuable tool for identifying neurocognitive impairments among children and adolescents in this, and other, resource-limited settings with a scarcity of specialized psychologists. Future research should refine the determination of cut-off points to provide adequate interpretation of the scores in practice. The successful implementation of the PennCNB may facilitate early detection of neurocognitive deficits, which is critical for supporting the functional and educational attainment of youth living with HIV in resource-limited settings such as Botswana.

Table 3.1. Penn Computerized Neurocognitive Battery Tests Administered

Cognitive Domain	Test	Description
Executive Functioning	Fractal N-Back Test (FNB)	Presents series of fractal images at 1 Hz and requires response either to pre-specified target fractal (0-back), whenever fractal repeats preceding fractal (1-back), or whenever fractal is same as fractal presented 2 images before (2-back).
	Penn Continuous Performance Test (PCPT)	Press space bar when a 7-segment display forms a number (1st half of test) or a letter (2nd half of test) and not press for non-numbers or non-letters.
	Penn Go/No-Go (GNG)	Press space bar when letter "x" appears in upper half of screen with y's and lower-half x's as distractors.
	Penn Trailmaking Test, Part B (TMTB)	Connect dots on screen in alternating numerical and alphabetical order.
Episodic Memory	Digit Symbol Substitution Test, recall (DSSTr)	Recall portion of DSST testing which symbols were paired with which numbers.
	Penn Face Memory Test (FMEM)	Presents series of 20 faces and requires selection of previously-presented faces from mixed set of images containing distractors.
	Visual Object Learning Test (VOLT)	Presents series of 3D Euclidean shapes to determine, from mixed targets and distractors, whether shape appeared previously.
Complex Cognition	Penn Conditional Exclusion Test (PCET)	Determine which of 4 shapes does not belong in group.
	Penn Line Orientation Test (PLOT)	2 line segments appear on screen and require rotation of 1 segment until lines become parallel.
	Penn Matrix Reasoning Test (PMAT)	Presents series of geometric shapes and requires selection of shape that completes a pattern.
Sensorimotor/Processing Speed	Finger Tapping Test (CTAP)	Press space bar with index finger as quickly as possible for 10

	seconds for 5 trials with alternating hands.
Digit Symbol Substitution Test (DSST)	9 symbol-digit pairs serve as a reference set and require indication whether digit-symbol pairs presented match reference.
Motor Praxis Test (MPT)	Use computer mouse to click on a green square that appears and disappears in different places on the screen and gets increasingly small.
Penn Trailmaking Test, Part A (TMTA)	Connect dots in sequential order.

Table 3.2. Participant Characteristics

	Total N (%)	**Cases N (%)**	**Controls N (%)**
Total	72	48	24
Mean age (years)	13.57	13.69	13.33
Sex			
Female	35 (48.61)	20 (41.67)	15 (62.50)
Male	37 (51.39)	28 (58.33)	9 (37.50)
Education			
None	2 (9.72)	2 (4.17)	0
Standard 1	0	0	0
Standard 2	0	0	0
Standard 3	6 (8.33)	6 (12.50)	0
Standard 4	8 (11.11)	5 (10.42)	3 (12.50)
Standard 5	15 (20.83)	8 (16.67)	7 (29.17)
Standard 6	7 (9.72)	4 (8.33)	3 (12.50)
Standard 7	9 (12.50)	5 (10.42)	4 (16.67)
Form 1	7 (9.72)	5 (10.42)	2 (8.33)
Form 2	7 (9.72)	7 (14.58)	0
Form 3	9 (12.50)	5 (10.42)	4 (16.67)
Form 4	2 (2.78)	1 (2.08)	1 (4.17)
Form 5	0	0	0

Table 3.3. Frequency of Participants with Neurocognitive Impairment by Domain and Classification Approach

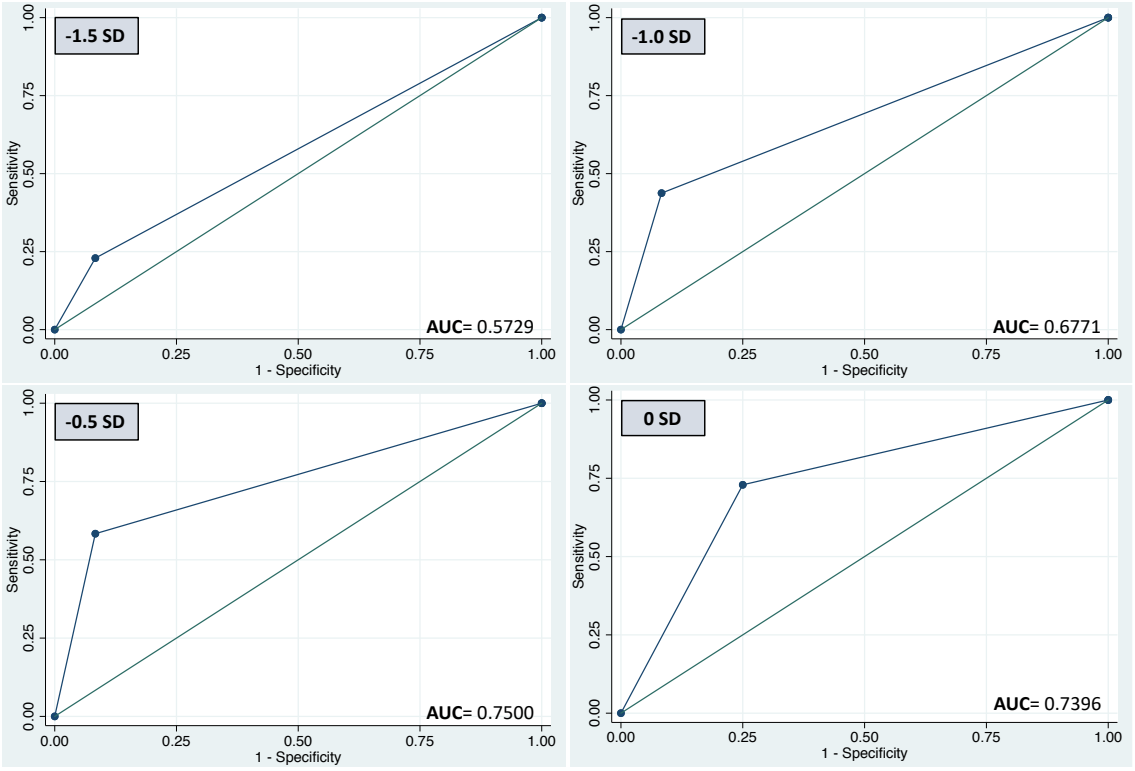
		Cognitive Domain		
Classification Approach	Overall	Executive Functioning	Episodic Memory	Sensorimotor/Processing Speed
Gold Standard*	48	31	40	3
-1.5 SD	13	11	7	7
-1.0 SD	23	20	18	14
-0.5 SD	30	27	31	23
0 SD	41	39	38	36

*Some participants were considered unclassifiable in the specific neurocognitive domains

Table 3.4. Descriptive Classification Accuracy

	Sensitivity (%)	Specificity (%)	PPV (%)	NPV (%)	AUC
-1.5 SD					
Overall impairment	22.92	91.67	84.6	54.6	0.5729
Executive functioning	29.03	96.43	90.0	55.1	0.6273
Episodic memory	15.00	96.15	85.7	42.4	0.5558
Sensorimotor/processing speed	33.33	92.31	20.0	96.0	0.6282
-1.0 SD					
Overall impairment	43.75	91.67	91.3	44.9	0.6771
Executive functioning	41.94	89.29	81.3	58.1	0.6561
Episodic memory	37.50	88.46	83.3	47.9	0.6298
Sensorimotor/processing speed	33.33	82.69	10.0	95.6	0.5801
-0.5 SD					
Overall impairment	58.33	91.67	93.3	52.4	0.7500
Executive functioning	58.06	85.71	81.8	64.9	0.7189
Episodic memory	57.50	84.62	85.2	56.4	0.7106
Sensorimotor/processing speed	66.67	78.85	15.4	97.6	0.7276
0 SD					
Overall impairment	72.92	75.00	85.4	58.1	0.7396
Executive functioning	77.42	71.43	75.0	74.1	0.7442
Episodic memory	65.00	73.08	78.8	57.6	0.6904
Sensorimotor/processing speed	100.00	59.62	12.5	100.0	0.7981

Figure 3.1. Comparison of Receiver Operating Characteristic Curves for Overall Impairment



CHAPTER 4. ACCEPTABILITY OF A COMPUTERIZED NEUROCOGNITIVE BATTERY TO IDENTIFY COGNITIVE IMPAIRMENTS AMONG CHILDREN AND ADOLESCENTS IN BOTSWANA

“Take me seriously”

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Abstract

Human immunodeficiency virus (HIV) infection and *in utero* exposure increase the risk of neurocognitive deficits, but comprehensive neurocognitive screening is unavailable in settings with high HIV prevalence (e.g., Sub-Saharan Africa). The Penn Computerized Neurocognitive Battery (PennCNB) was culturally adapted and translated for use among children and adolescents in Botswana. This study assessed perceptions of acceptability of the adapted PennCNB among a cohort of HIV+ and HIV-exposed-uninfected (HEU) young people (N = 155, aged 7-17 years) in Gaborone, Botswana. Immediately following completion of the PennCNB, participants completed a three-point Likert scale survey eliciting perspectives of acceptability of the overall PennCNB and the 13 individual modules and provided open-ended responses to elaborate upon acceptability ratings. Descriptive statistics were calculated, and predictors (age, sex, and PennCNB performance) of unacceptable response were evaluated using logistic regressions. A content analysis was completed on the open-ended responses. Participants reported high acceptability of the overall PennCNB (98%). With regard to individual modules, the Penn Trailmaking Test, Part A (measuring sensorimotor/processing speed) received the highest acceptability rating (82%), while the Penn Face Memory test (measuring episodic memory) was the least acceptable (40% unacceptable). Age and performance on the PennCNB were associated with an unacceptable response for Fractal N-Back (OR = 0.873 per year) and the Penn Line Orientation Test (OR = 0.620 per SD of performance), respectively. Themes about the content of the cognitive assessment (e.g., difficulty), features of the modules (e.g., aesthetics), and participant characteristics (e.g., self-efficacy) were articulated as reasons for reporting the PennCNB tests as acceptable or unacceptable. Overall, this

research offers promise for successful implementation of the PennCNB for use among pediatric populations in Botswana.

Introduction

The association between the human immunodeficiency virus (HIV) and pediatric neurocognitive impairment is well-documented. Children living with HIV (HIV+) and children exposed to HIV *in utero* but uninfected (HEU) exhibit greater neurocognitive deficits than their HIV-uninfected peers, specifically in the domains of attention, episodic memory, psychomotor functioning, and information processing speed (Le Doare et al., 2012; Ruel et al., 2012; Smith et al., 2012; Walker et al., 2013). Early detection of neurocognitive impairments facilitates educational and functional attainment of HIV+ and HEU children and adolescents. However, in many high HIV-prevalence settings such as Sub-Saharan Africa, comprehensive neurocognitive screening is currently unavailable due to a lack of validated instruments and limited mental health personnel (Mbakile-Mahlanza et al., 2015; Ponsford, 2017).

To address the scarcity of pediatric neurocognitive assessment in Botswana, the country with the third highest prevalence rate of HIV (Central Intelligence Agency, 2019), the Penn Computerized Neurocognitive Battery (PennCNB) was culturally adapted and translated for use in this setting (Scott et al., 2020). The PennCNB measures performance accuracy and response speed for major cognitive domains through "neurobehavorial probes" (Gur et al., 1992) validated by functional neuroimaging (Roalf, Ruparel, et al., 2014), thus streamlining the evaluation of neurocognitive functioning and providing advantages for implementation in resource-limited settings (e.g., ease of administration, automated scoring and data generation, and increased standardization and reliability) (Gur et al., 2010; Moore et al., 2015). Adaptation of the PennCNB for use in Botswana involved a multi-step, systematic process of translation and back-translation

(Guillemin et al., 1993; van Widenfelt et al., 2005) and local stakeholder input on cultural and linguistic components. For example, stakeholders provided feedback on the racial diversity of faces for the facial memory test, simplification of language, explanation of concepts such as "parallel lines" for which there is no defining term in Setswana (the local African Bantu language), and explanation of computer components such as "mouse." Pilot testing was conducted among a cohort of children and adolescents aged 7-17 years (N = 10) (Scott et al., 2020). The final version of the adapted battery is available in Setswana and locally appropriate English, both of which contain the same test content. The Setswana PennCNB and Botswana-English PennCNB consist of 13 modules measuring cognitive domains affected by HIV (executive functioning, episodic memory, complex cognition, and sensorimotor/processing speed) (Table 4.1; further described in detail) (Gur et al., 2012; Gur et al., 2010; Scott et al., 2020; Van Pelt et al., revise and resubmit). The adapted tool was validated among children and adolescents in Botswana (Van Pelt et al., under review; Van Pelt et al., revise and resubmit).

Due to the substantial lag in integrating evidence-based research into practice (Morris et al., 2011), it is critical to engage in pre-implementation inquiry to facilitate effective implementation and uptake. Acceptability (i.e., implementation stakeholders' perception that a service is "agreeable, palatable, or satisfactory") is a leading indicator of implementation success and a perceptual implementation outcome (Lyon & Bruns, 2019; Proctor et al., 2011). Tools that are perceived as unacceptable may prevent successful adoption, uptake, and sustainment. Thus, to prepare for the future implementation of the PennCNB in Botswana, this study aimed to 1) assess the acceptability of the adapted

PennCNB among a cohort of children and adolescents affected by HIV and 2) understand factors associated with perceptions of acceptability of the battery.

Methods

Participants

Children age 7-17 years (N = 155) were recruited from the Botswana-Baylor Children's Clinical Centre of Excellence (CoE), a clinic specializing in the care of approximately 2,000 children and adolescents affected by HIV in Gaborone, Botswana. As the main pediatric HIV referral center in the country, the CoE attracts both local patients in and around greater Gaborone as well as children and adolescents from distant district sites, where children may have poorer health and need of specialized treatment, prefer to receive care outside of community for confidentiality reasons, or desire to continue care despite moving out of the area. HIV+ participants were randomly selected from CoE patients in the target age group, and HEU participants were purposively sampled from the families of patients enrolled for care at the CoE (i.e., caregivers were asked whether they had additional children who were HIV negative). Participants were eligible if they 1) did not have severe developmental delays or physical impairments preventing completion of the PennCNB assessment and 2) were proficient in English or Setswana. Informed consent and assent were completed prior to data collection. Demographic and health-related data were reported by participants' caregivers. All procedures were approved by the Institutional Review Boards at the Health Research and Development Committee within the Ministry of Health and Wellness of Botswana, the University of Pennsylvania, and the Botswana-Baylor Children's Clinical Centre of Excellence.

Procedure

PennCNB Assessment

Participants completed the PennCNB assessment in the language of their choice (Setswana or Botswana-English). Trained research staff administered the assessment in a quiet, private space in the CoE. Standard operating procedures for administration were followed, which included reading the PennCNB instructions aloud in either Setswana or English, as appropriate, to each participant and providing practice PennCNB modules before the actual assessment began to ensure task comprehension. Task comprehension was evaluated through a combination of administrators' observation of patients' practice sessions and performance-based rules inherent in the design of the battery. The tests were administered in the same order for all participants: Motor Praxis Test, Penn Face Memory Test, Digit Symbol Substitution Test, Penn Continuous Performance Test, Penn Conditional Exclusion Test, Go No-Go, Visual Object Learning Test, Penn Trailmaking Part A, Penn Trailmaking Part B, Fractal N-Back Test, Penn Matrix Reasoning Test, Finger Tapping Test.

Acceptability Data Collection

Participants completed a brief oral questionnaire upon the conclusion of their PennCNB assessment. Existing measures of acceptability guided the development of the questionnaire, but the instrument was adapted for the target population. A five-point Likert scale was collapsed into a three-point Likert scale, as it was determined as most appropriate for the cultural context based on multiple conversations with Botswana-based stakeholders. In Setswana, there is no linguistic distinction between "very acceptable" and "acceptable," so multiple positive and negative response options are not meaningful.

Questionnaires were read aloud in the language preferred by the participant (Setswana or English) by a member of the research team independent from the individual who administered the PennCNB assessment. Specifically, participants were asked: "Did you like taking this test?" Responses were recorded as "liked" (i.e., acceptable), "neutral," or "disliked" (i.e., unacceptable). For each "acceptable" response, the research assistant asked the participants what they liked about taking the test. For each "unacceptable" response, the research assistant asked the participants what they did not like about taking the test. These open-ended responses were transcribed for qualitative analysis.

Since some participants may have a favorable opinion of the overall battery but not of specific tests, additional inquiry regarding each of the 13 PennCNB tests was completed. To assist with recall, a visual that contained an image of each of the PennCNB modules was presented to the participants during questioning (Appendix Figure 4.1). Participants were instructed to point to the tests that they liked taking and then to the tests that they did not like taking, and their responses were recorded accordingly. The tests that were neither "liked" nor "disliked" (i.e., the participant did not point to the test) were classified as "neutral." For each "acceptable" test, the research assistant asked the participants what they liked about taking the test. For each "unacceptable" test, the research assistant asked the participants what they did not like about taking the test. Open-ended responses were documented for qualitative analysis as explained above for the overall PennCNB.

Statistical Analysis

Descriptive statistics on acceptability ratings of the overall PennCNB and individual modules were calculated. Age, sex, and test-specific PennCNB performance

were evaluated as predictors of acceptability for each module. To determine PennCNB performance, efficiency scores were calculated as the standardized sum of the z-standardized accuracy (correct responses) and speed (mean response time) values; standardized response time was multiplied by -1 so that higher scores indicate faster performance (Moore et al., 2015). Acceptable and neutral response options on the questionnaire were grouped to create a dichotomous outcome variable (i.e., unacceptable vs. acceptable/neutral). Logistic regression models were run to test association between the predictor variables and an unacceptable outcome. All analyses were completed in R (v3.3.3; R Core Team, 2017) and Stata Statistical Software (15.1; College Station, 2017).

Qualitative Analysis

Open-ended responses stated in Setswana were translated into English by bilingual members of the research team. Responses were organized by PennCNB module and perceptions of acceptability (i.e., acceptable or unacceptable). All responses were uploaded into NVivo Qualitative Data Analysis Software (QSR International Pty Ltd. Version 12, 2018) for data management and analysis.

An inductive approach to analysis was conducted. A content analysis (Bengtsson, 2016; Hsieh & Shannon, 2005) on free-response text was performed to inform the development of a codebook (Saldana, 2009). Constructs were refined to condense similar concepts (e.g., easy and simple) (Graneheim & Lundman, 2004). An initial coding scheme was applied line-by-line to all data by two independent investigators (A.E.V.P. and C.V.A.). Disagreements were resolved through discussion with the research team, and a revised codebook consisting of 16 codes was applied (kappa = 0.82) (McHugh, 2012): aesthetics, computer familiarity, confusion, difficulty, duration of test, easy,

enjoyable, game-like, instructions (both clear and unclear), knowledge, pace, self-efficacy, stimulation (as well as lack of stimulation), and tired. Constructs were stratified by PennCNB module.

Results

Participant Characteristics

A total of 155 participants completed the acceptability questionnaire (Table 4.2). The majority of the participants were HIV+ (86%). Sex distribution was approximately equal, but age was slightly right-skewed (median age = 11 years). All participants identified as Black African (Batswana). Most participants (N = 140) completed the Setswana version of the battery rather than the Botswana-English version of the PennCNB. On average, participants took 75 minutes (range: 54-109 minutes) to complete the PennCNB assessment.

Acceptability ratings

Table 4.3 presents the distribution of acceptability responses for the overall PennCNB and the specific modules.

Overall, participants reported high acceptability for the PennCNB (98%). Tests measuring sensorimotor speed, executive functioning, and complex cognition were perceived to be the most acceptable. The modules with the highest ratings of acceptability were the Penn Trailmaking Test, Part A (82%), Penn Trailmaking Test, Part B (81%), and Motor Praxis Test (77%). In total, six tests (Finger Tapping; Fractal N-Back Test; Motor Praxis Test; Penn Continuous Performance Test; Penn Trailmaking Test, Part A; and Penn Trailmaking Test, Part B) had a greater proportion of participants selecting acceptable compared to neutral and unacceptable responses.

For five modules, neutral ratings were most common (Digit Symbol Substitution Test, Penn Conditional Exclusion Test, Penn Go/NoGo, Penn Matrix Reasoning Test, and Visual Object Learning Test). An equal number of participants rated the Penn Line Orientation Test as acceptable and neutral. Neutral-rated modules assessed episodic memory, complex cognition, and executive functioning.

The three participants who rated the overall PennCNB as unacceptable took the Setswana version of the tool (results not presented). The Penn Face Memory Test measuring episodic memory was the only module for which more participants found the test unacceptable (40%) compared to acceptable (31%) or neutral (29%).

Predictors of Acceptability

Table 4.4 shows the results of the logistic regression models for each of the PennCNB modules. Sex was not a statistically significant predictor of acceptability for any of the tests. Age was associated with an unacceptable response for Fractal N-Back (OR = 0.873, p-value = 0.049), where older children were more likely to endorse that the test was acceptable. In addition, performance on the PennCNB (i.e., efficiency score) was associated with an unacceptable response for the Penn Line Orientation Test (OR = 0.620, p-value = 0.044).

Participant Perspectives

Table 4.5 lists the frequency of codes for each of the PennCNB tests. Discussion surrounded the content of the cognitive assessment, features of the modules, and participant characteristics. For the overall PennCNB, the majority of participants described the battery as game-like (N = 72), followed by enjoyable (N = 36) and stimulating (N = 26). The three participants who found the overall PennCNB

unacceptable attributed their response to the difficulty of the modules and general confusion. For all of the specific modules, the ease of the test was the most commonly articulated reason for acceptable ratings, while most participants stated difficulty as the primary factor for not liking the specific tests.

Content of Cognitive Assessment

Overwhelmingly, participants described completing the PennCNB assessment as playing games, which were fun and enjoyable. The majority of respondents thought the PennCNB as a whole was easy to complete and gave favorable opinions of multiple tests. For individuals who found the PennCNB tests difficult, explanations of what made them difficult were limited. The large number of stimuli was mentioned as causing difficulty for Penn Face Memory. Many participants (N = 134) found the PennCNB modules positively stimulating, recognizing that tests required concentration and challenged their thinking. Conversely, some participants (N = 16) described a lack of stimulation due to being unchallenged or bored by the assessment.

Features of Modules

Some participants commented on the aesthetics of the modules (N = 52), such as the appearance of the faces in the Penn Face Memory test. Opinions on the faces varied with some respondents referring to them as beautiful or scary or expressing preference for children's faces over adult faces. Opinions on the instructions varied, as some respondents found them easy to follow (N = 28) while others were confused by them (N = 4). Notably, participants who proposed the duration of assessment as justification for their acceptability rating did not think the test took too long to complete. However,

individuals indicated that the stimuli moved too quickly in some of the tests (e.g., Penn Face Memory Test and Digit Symbol Substitution Test).

Participant Characteristics

Participants often attributed unacceptable perceptions to confusion during the assessments (N = 63), specifically the Penn Face Memory Test. For those who considered the battery acceptable, some highlighted the novelty of using a computer (N = 13) (e.g., first time using a computer or taught them how to use components of a computer such as the spacebar and mouse). A few participants appreciated the knowledge required to complete the tasks (N = 6) (e.g., "It was interesting as it needed the knowledge of angles" in reference to the Penn Line Orientation Test and "It was easy to play as it required the knowledge of numbers" in reference to Penn Trailmaking Test, Part A). Further, respondents described a sense of self-efficacy in their perceived ability to answer questions correctly (N = 45). However, some participants' inability to remember content contributed to their unacceptable opinions of some of the tests measuring episodic memory. Lastly, a couple of participants stated that they were tired by the end of the assessment and, therefore, did not like the Finger Tapping test, the penultimate module that requires repeated use of the index finger.

Discussion

The PennCNB was translated and validated for use among children and adolescents in Botswana, a resource-limited, high HIV-prevalence setting in Sub-Saharan Africa. This study elicited perceptions of acceptability of the adapted PennCNB among target users, making this the first effort to systematically evaluate the acceptability of a culturally adapted and translated version of the tool. Young people reported favorable

opinions of the battery and provided valuable insights to guide implementation of the PennCNB for use in clinical settings.

Overall, children and adolescents reported high acceptability of the PennCNB. With the exception of one test (Fractal N-Back), the lack of association between age and acceptability of the PennCNB is noteworthy because this study enrolled participants younger than previous research utilizing the battery. This positive reception supports the suitability of this valid (Van Pelt et al., under review; Van Pelt et al., revise and resubmit) tool for use in pediatric populations. Further, the high acceptability among young people, the target users of the tool, offers promise for successful implementation of the adapted PennCNB in Botswana and potential scaling up in other regions (Lyon & Bruns, 2019; Proctor et al., 2011).

Although participants found the overall PennCNB to be acceptable, results suggested the need for potential adaptations of some of the individual modules. Younger participants were more likely to rate Fractal N-Back as unacceptable due to difficulty and confusion. Providing additional practice time before administration and clarifying the test instructions may make this module more suitable for the pediatric population. In addition, the tests measuring episodic memory received lower ratings of acceptability. To address the concerns about the aesthetics, future work can explore systematic modifications to the faces in the Penn Face Memory test. The included faces were intended to be emotionally neutral, which may have contributed to perceptions of being “scary”. Computer-generated faces or younger faces may be more appropriate and increase acceptability (Cao et al., 2014). Finally, some participants reported being tired toward the end of the assessment suggests that a shorter yet valid battery may be preferable.

There are several limitations to this study. Social desirability bias may have occurred. Members of the research team who did not administer the PennCNB assessment completed the acceptability questionnaire with the participants to mitigate this potential limitation. Misclassification of the outcome may have resulted from orally collecting the data. Research assistants asked participants to confirm the accuracy of the classification to minimize this concern. Further, a three-point Likert scale was chosen rather than a common five-point scale to decrease the ambiguity between the two positive and two negative response options within the cultural context. This methodology was piloted, and misclassification did not occur. Finally, participants took over an hour to complete the PennCNB assessment. The acceptability questions were asked at the conclusion of the administration of the PennCNB, so participants may have experienced fatigue when responding to the questionnaire.

Overall, this research suggested that the adapted PennCNB is highly acceptable among children and adolescents in Botswana, which is promising for the successful implementation of the tool in the future. Adoption of the PennCNB has the potential to streamline neurocognitive assessment for this high-need pediatric population. The nature of the PennCNB allows for task-shifting to non-mental health clinicians, which may reduce the burden on local providers and increase access to screening for children and adolescents currently waiting years to see a provider. However, to optimize the battery to facilitate implementation for this setting and other resource-limited settings in the region, adaptations addressing the factors highlighted in this study should be considered.

Table 4.1. Penn Computerized Neurocognitive Battery Tests

Test	Description	Use in Pediatric Populations
	Executive Functioning	
Fractal N-Back Test (FNB)	Presents series of fractal images at 1 Hz and requires response either to pre-specified target fractal (0-back), whenever fractal repeats preceding fractal (1-back), or whenever fractal is same as fractal presented 2 images before (2-back).	(Satterthwaite et al., 2013; Sullivan et al., 2016)
Penn Continuous Performance Test (PCPT)	Press space bar when a 7-segment display forms a number (1st half of test) or a letter (2nd half of test) and not press for non-numbers or non-letters.	(Goldenberg et al., 2012; Gur et al., 2012; Hartung et al., 2016; Moore et al, 2015; Sullivan et al., 2016; Swagerman et al., 2016)
Penn Go/No-Go (GNG)	Press space bar when letter "x" appears in upper half of screen with y's and lower-half x's as distractors.	*(Bezdjian et al., 2009; Casey et al., 1997)
Penn Trailmaking Test, Part B (TMTB)	Connect dots on screen in alternating numerical and alphabetical order.	*(Lee et al., 2014; Reitan & Wolfson, 2004)
	Episodic Memory	
Digit Symbol Substitution Test, recall (DSSTr)	Recall portion of DSST testing which symbols were paired with which numbers.	
Penn Face Memory Test (FMEM)	Presents series of 20 faces and requires selection of previously presented faces from mixed set of images containing distractors.	(Goldenberg et al., 2012; Gur et al., 2012; Hartung et al., 2016; Moore et al., 2015; Sullivan et

		al., 2016; Swagerman et al., 2016)
Visual Object Learning Test (VOLT)	Presents series of 3D Euclidean shapes to determine, from mixed targets and distractors, whether shape appeared previously.	(Goldenberg et al., 2012; Gur et al., 2012; Mollon et al., 2016; Moore et al., 2015; Sullivan et al., 2016; Swagerman et al., 2016)
Complex Cognition		
Penn Conditional Exclusion Test (PCET)	Determine which of 4 shapes does not belong in group.	(Goldenberg et al., 2012; Gur et al., 2012; Hartung et al., 2016; Moore et al., 2015; Sullivan et al., 2016; Swagerman et al., 2016)
Penn Line Orientation Test (PLOT)	2 line segments appear on screen and require rotation of 1 segment until lines become parallel.	(Gur et al., 2012; Hartung et al., 2016; Moore et al., 2015; Swagerman et al., 2016)
Penn Matrix Reasoning Test (PMAT)	Presents series of geometric shapes and requires selection of the shape that completes a pattern.	(Gur et al., 2012; Hartung et al., 2016; Moore et al., 2015; Sullivan et al., 2016;

		Swagerman et al., 2016)
	Sensorimotor/Processing Speed	
Finger Tapping Test (CTAP)	Press space bar with index finger as quickly as possible for 10 seconds for 5 trials with alternating hands.	(Goldenberg et al., 2012; Gur et al., 2012; Swagerman et al., 2016)
Digit Symbol Substitution Test (DSST)	9 symbol-digit pairs serve as a reference set and require indication whether digit-symbol pairs presented match reference.	(Bearden et al., 2007; Mollon et al., 2016; Sullivan et al., 2016)
Motor Praxis Test (MPT)	Use computer mouse to click on a green square that appears and disappears in different places on the screen and gets increasingly small.	(Gur et al., 2012; Swagerman et al., 2016)
Penn Trailmaking Test, Part A (TMTA)	Connect dots in sequential order.	*(Lee et al., 2014)

*These tests have not been used directly within pediatric populations, but similar tasks have been used extensively among children and adolescents.

Table 4.2. Participant Characteristics

Variable	N (%)
Total	155
Median Age (IQR)	11 (9-13)
Sex	
Female	77 (49.68)
Male	78 (50.32)
Race/Ethnicity	
Black African (Batswana)	155 (100)
HIV Status	
HIV+	134 (86.45)
HEU	21 (13.55)
PennCNB Language Choice	
Setswana	140 (90.32)
English	15 (9.68)

Table 4.3. PennCNB Acceptability by Test

Test	Acceptable N (%)	Neutral N (%)	Unacceptable N (%)
Overall PennCNB	152 (98.06)	0	3 (1.94)
Executive Functioning			
Fractal N-Back Test	68 (43.87)	48 (30.97)	39 (25.16)
Penn Continuous Performance Test	66 (42.58)	57 (36.77)	32 (20.65)
Penn Go/NoGo	60 (38.71)	66 (42.58)	29 (18.71)
Penn Trailmaking Test, Part B	125 (80.65)	26 (16.77)	4 (2.58)
Episodic Memory			
Penn Face Memory Test	48 (30.97)	45 (29.03)	62 (40.00)
Visual Object Learning Test	61 (39.35)	73 (47.10)	21 (13.55)
Complex Cognition			
Penn Conditional Exclusion Test	52 (33.55)	66 (42.58)	37 (23.87)
Penn Line Orientation Test	67 (43.23)	67 (43.23)	21 (13.55)
Penn Matrix Reasoning Test	62 (40.00)	74 (47.74)	19 (12.26)
Sensorimotor/Processing Speed			
Finger Tapping Test	75 (48.39)	65 (41.94)	15 (9.68)
Digit Symbol Substitution Test	66 (42.58)	70 (45.16)	19 (12.26)
Motor Praxis Test	120 (77.42)	25 (16.13)	10 (6.45)
Penn Trailmaking Test, Part A	127 (81.94)	23 (14.84)	5 (3.23)

Table 4.4. Predictors of Acceptability by PennCNB Test

	unadjusted		adjusted	
	OR	**p-value**	**OR**	**p-value**
Fractal N-Back				
Age	0.873	**0.049**	0.875	0.053
Sex	0.697	0.332	0.710	0.365
PennCNB performance	0.965	0.848	0.957	0.811
Penn Continuous Performance Test				
Age	0.990	0.886	0.991	0.898
Sex	0.717	0.405	0.734	0.443
PennCNB performance	0.791	0.218	0.797	0.234
Penn Go/NoGo				
Age	0.887	0.116	0.882	0.104
Sex	1.51	0.323	1.561	0.292
PennCNB performance	1.101	0.648	1.093	0.657
Penn Trailmaking Test, Part B				
Age	1.027	0.879	1.024	0.894
Sex	3.04	0.340	2.725	0.396
PennCNB performance	0.587	0.149	0.584	0.182
Penn Face Memory Test				
Age	0.953	0.407	0.952	0.398
Sex	1.090	0.793	1.120	0.732
PennCNB performance	0.866	0.384	0.862	0.373
Visual Object Learning Test				
Age	0.941	0.467	0.938	0.450
Sex	1.374	0.503	1.398	0.481
PennCNB performance	0.957	0.851	0.957	0.848
Penn Conditional Exclusion Test				
Age	0.951	0.453	0.950	0.448
Sex	0.916	0.815	0.856	0.685
PennCNB performance	1.331	0.146	1.351	0.131
Penn Line Orientation Test				
Age	1.169	0.054	1.170	0.058
Sex	0.563	0.232	0.688	0.466
PennCNB performance	0.620	**0.044**	0.667	0.097
Penn Matrix Reasoning Test				
Age	0.997	0.973	1.000	0.996
Sex	0.686	0.446	0.663	0.410
PennCNB performance	1.238	0.412	1.259	0.381
Finger Tapping Test				
Age	0.872	0.184	0.874	0.198
Sex	1.543	0.433	1.482	0.485
PennCNB performance	0.674	0.112	0.693	0.143
Digit Symbol Substitution Test				

Age	0.881	0.168	0.885	0.182
Sex	0.534	0.215	0.546	0.235
PennCNB performance	0.996	0.986	0.988	0.959
DSSTr efficiency*	0.848	0.477	0.847	0.469
Motor Praxis Test				
Age	1.080	0.487	1.079	0.495
Sex	1.521	0.529	1.505	0.540
PennCNB performance	0.934	0.833	0.927	0.817
Penn Trailmaking Test, Part A				
Age	0.888	0.490	0.887	0.487
Sex	1.5	0.662	1.505	0.662
PennCNB performance	0.840	0.675	0.870	0.728

*Adjusted estimate is from model that includes DSSTr efficiency score instead of DSST efficiency score.

Table 4.5. Content Analysis of Participant Perspectives by PennCNB Test

Code	Test													
	Overall	FNB	PCPT	GNG	TMTB	FMEM	VOLT	PCET	PLOT	PMAT	CTAP	DSST	MPT	TMTA
						Acceptable (N)								
Aesthetics	2	7	1	2	2	4	3	4	2	5	1	3	3	1
Computer familiarity	9	0	0	1	0	0	0	0	0	0	1	0	2	0
Duration of test	0	0	0	1	0	0	1	1	0	0	0	0	0	0
Easy	24	30	34	29	90	16	26	23	44	37	42	34	74	98
Enjoyable	36	13	8	13	11	7	7	8	9	4	21	10	15	9
Game-like	72	3	1	1	3	0	1	1	1	1	1	2	7	4
Instructions	2	2	2	2	3	0	0	1	2	0	2	3	7	2
Knowledge	1	0	0	0	0	0	0	0	1	3	0	0	0	1
Other	1	0	0	0	2	0	0	0	0	2	0	0	2	0
No specific reason	7	5	10	6	11	5	8	6	3	3	3	7	9	9
Pace	0	0	3	1	0	0	0	0	0	0	0	0	1	0
Self-efficacy	2	4	0	1	1	12	11	1	1	4	0	6	2	0
Stimulation	26	11	10	10	8	6	8	10	8	8	7	8	6	8
						Unacceptable (N)								**0**
Aesthetics	0	3	1	0	0	6	1	0	1	0	0	0	0	1
Confusion	1	8	5	4	0	21	3	8	3	2	1	4	2	3
Difficulty	2	24	15	18	1	21	15	23	11	10	3	10	2	0
Duration of test	0	0	0	0	0	0	0	0	0	1	0	1	0	0
Instructions	0	0	1	0	0	0	0	1	1	0	0	0	1	0
Other	0	0	0	1	0	0	0	0	0	0	1	1	0	0
No specific reason	0	4	7	3	1	4	1	2	4	3	4	3	2	1

Pace	0	0	0	1	0	3	0	0	1	0	0	2	1	0
Self-efficacy	0	1	0	1	0	5	1	3	0	2	0	0	0	0
Stimulation	0	1	1	0	1	3	0	3	1	1	1	1	2	1
Tired	0	0	0	0	0	0	0	0	0	0	5	1	0	0

*Note that a single participant may have articulated multiple reasons for finding a test acceptable/unacceptable.

CHAPTER 5. MEDICAL STAKEHOLDER PERSPECTIVES ON IMPLEMENTING A COMPUTERIZED BATTERY TO IDENTIFY NEUROCOGNITIVE IMPAIRMENTS AMONG YOUTH IN BOTSWANA

"Acknowledge my presence"

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Abstract

HIV infection and *in utero* exposure, common in Sub-Saharan Africa, are associated with pediatric neurocognitive impairment. Cognitive screening can identify impairments, but it is rarely used in this setting. The Penn Computerized Neurocognitive Battery (PennCNB), an evidence-based cognitive screening tool, was adapted for use in Botswana. To facilitate future implementation, 20 semi-structured interviews were conducted to elicit key stakeholders' perspectives on factors likely to be related to successful uptake of the PennCNB in clinical settings. An integrated analytic approach combining constructs from the Consolidated Framework for Implementation Research and modified grounded theory was used. Results underscore the need for cognitive screening in Botswana and the acceptability of the PennCNB. Implementation barriers include limited time and resources, whereas facilitators include standard procedures for introducing new tools into medical settings and for training implementers. Recommended implementation strategies include integrating screening into the existing workflow, implementing the tool in the medical and educational sectors, and targeting selection of children for assessment. This research addresses the research-to-practice gap by engaging in pre-implementation inquiry and designing for implementation. Results will inform the development of strategies to maximize the likelihood of successful implementation of the PennCNB to identify neurocognitive impairment in children in this high-need setting.

Introduction

The human immunodeficiency virus (HIV) contributes to significant morbidity and mortality in Sub-Saharan Africa (UNAIDS, 2018). In Botswana, *in utero* HIV exposures occur in roughly a quarter of all births (Slogrove et al., 2020). Due to the availability of free antiretroviral therapy (ART) in Botswana, survival to secondary school ages and beyond has become the norm for children born with HIV in this setting (Farahani et al., 2014; World Health Organization, 2017), but survival is not without HIV-related sequelae. For example, both children living with HIV (HIV+) and HIV-exposed-uninfected (HEU) children demonstrate greater neurocognitive deficits than their HIV-uninfected peers (Le Doare et al., 2012; Ruel et al., 2012; Smith et al., 2012). To support the educational and functional attainment of HIV-affected children and adolescents, early detection of neurocognitive impairments is crucial. However, systematic cognitive screening does not exist in this setting. Current screening approaches are time-consuming and require several hours of a professional psychologist's time, including manual calculation of scores using pencil and paper tests.

To increase neurocognitive screening in Botswana, the Penn Computerized Neurocognitive Battery (PennCNB) was culturally-adapted, translated, and validated for use among youth (age 7-17 years) in Botswana (Scott et al., 2020; Van Pelt et al., revise and resubmit). Composed of "neurobehavioral probes" (Gur et al., 1992) validated by functional neuroimaging, the PennCNB streamlines neurocognitive assessment by evaluating performance accuracy and response speed on major cognitive domains (Gur et al., 2010; Moore et al., 2015). The Botswana version of the PennCNB includes specific modules that measure cognitive domains impacted by HIV. Due to the "game-like" tests,

researchers have successfully utilized the PennCNB in multiple pediatric populations (Hartung et al., 2016; Yi et al., 2016). Thus, the PennCNB is a relatively low-cost, publicly available tool for the screening of neurocognitive deficits among children and adolescents in Botswana. The next step in making the PennCNB widely available is to understand how best to integrate the tool into routine practice, taking into account the resource-limited nature of this setting (Yapa & Barnighausen, 2018).

To effectively facilitate the implementation of PennCNB-based screening, an understanding of the context in which the PennCNB may be implemented, the barriers and facilitators to its use, and suggested implementation strategies are needed. The Consolidated Framework for Implementation Research (CFIR) provides a framework for the systematic evaluation of factors that may influence implementation. The CFIR includes the following five domains: intervention characteristics (e.g., features of the PennCNB), outer setting (e.g., broader sociopolitical context), inner setting (e.g., clinic leadership structure and policies), characteristics of individuals (e.g., clinicians' beliefs about PennCNB), and implementation process (Damschroder et al., 2009; Keith et al., 2017). A recent review revealed that few studies have applied CFIR in the pre-implementation phase of research in low- and middle-income countries (LMICs) (i.e., preparation for implementation of a tool) (Means et al., 2020), thus representing a novel application that can offer a generalizable process to other tools to be implemented in medical settings in LMICs. This research aimed to elicit key stakeholders' perspectives to identify factors likely to be related to successful future implementation of the PennCNB into clinical settings in Botswana.

Methods

Participants

To diversify perspectives and ensure inclusion of key stakeholders, participants were initially recruited from two stakeholder groups: clinical implementers and clinical leadership. Implementers were defined as individuals involved in the direct care of patients (e.g., nurses), and leadership were defined as individuals involved in the decision-making for medical services (e.g., clinic director and policy makers). After conducting several interviews and reflecting upon preliminary themes, sampling in the clinical implementer group was enriched for perspectives from both mental health and non-mental health clinicians, thus resulting in three final stakeholder groups: mental health clinicians, non-mental health clinicians, and clinical leadership. Sampling focused on stakeholders in the public sector to increase the generalizability of the findings to other LMICs, for public medical centers have fewer resources and treat more patients from low-income communities compared to facilities in the private sector. Purposive sampling followed by snowball sampling began with three primary institutions: The Ministry of Health and Wellness (MoHW), the University of Botswana, and the Botswana-Baylor Children's Clinical Centre of Excellence. The MoHW leads funding and decision-making for all public medical services in the country. The University of Botswana houses the only medical school and public health training program in the country and guides the MoHW on introducing care innovations in government medical centers. The Botswana-Baylor Children's Clinical Centre of Excellence, a collaborative partnership between the Government of Botswana and the Baylor International Pediatric AIDS Initiative, specializes in the treatment and care of children living with HIV in and around Gaborone, Botswana. Since some participants described a history of both

leadership and clinical responsibilities, stakeholders were categorized based on their roles and responsibilities at the time of enrollment. For example, practicing clinicians who had previous leadership responsibilities were considered part of the clinical implementer group. Participants were recruited by email and phone. Written informed consent and demographic data were obtained from all participants. The intentions of the research team were shared during this process. All procedures were approved by the Institutional Review Board at the University of Pennsylvania and the Health Research and Development Committee within the MoHW of Botswana. No participants withdrew from the study.

Procedure

The CFIR guided the development of the semi-structured interview guide (Appendix Material 5.1). Example questions corresponding to the CFIR domains included the following: What features of the PennCNB may help with the successful implementation in your "setting"? (intervention characteristics); How commonly do you encounter children with neurocognitive impairments in your community? (outer setting); Who would be responsible for making the decision on whether or not to use the PennCNB in your "setting"? (inner setting); What staff characteristics (e.g., self-efficacy or beliefs about the CNB) may make the use of the PennCNB in your "setting" difficult? (characteristics of individuals); Who would administer the PennCNB to patients? (implementation process). All interview materials were piloted among a stakeholder group established for the cultural adaptation of the PennCNB in Botswana (Scott et al., 2020).

Prior to conducting the interviews, the interviewer facilitated an introduction to the PennCNB that included a detailed description of the tool accompanied by images of the 13 PennCNB modules and a demonstration of a test for individuals who needed additional explanation. Sufficient time was provided to allow participants to ask questions about the PennCNB before transitioning to the interview guide. All interviews were conducted in English by a doctoral candidate at the University of Pennsylvania (A.E.V.P.) trained in qualitative research and global health, and the majority of the discussions occurred in-person in a private space in the participant's workplace. Due to the coronavirus disease 2019 (COVID-19) pandemic, some interviews were conducted via video conference. The interviewer had no previous relationships with the participants. The interviewer completed a preliminary review of the emergent themes at the conclusion of each interview to assess thematic saturation for sufficient participant recruitment.

All interviews were audio-recorded and transcribed, and the transcripts were uploaded into NVivo Qualitative Data Analysis Software (QSR International Pty Ltd. Version 12, 2018) for data management and analysis. Transcripts were not provided to participants for review. One participant reviewed draft versions of this manuscript and provided feedback on the interpretation of findings. Field notes were stored in a secure folder. The Consolidated Criteria for Reporting Qualitative Research (COREQ) guided the reporting of this research (Tong et al., 2007).

Data Analysis

An integrated analysis combining deductive and inductive approaches was conducted (Bradley et al., 2007). Constructs from CFIR were identified *a priori,* and iterative coding to ascertain recurrent themes based on modified grounded theory was

performed to develop an initial codebook (Saldana, 2009). To further define strategies and aid in the development of future implementation, suggested implementation strategies were sub-coded using the Expert Recommendations for Implementing Change (ERIC) taxonomy (Powell et al., 2015; Waltz et al., 2015). The ERIC taxonomy consists of 73 discrete implementation strategies grouped into the following nine clusters: use evaluative and iterative strategies; provide interactive assistance; adapt and tailor to context; develop stakeholder interrelationships; train and educate stakeholders; support clinicians; engage consumers; utilize financial strategies; and change infrastructure. An initial coding scheme was applied to two transcripts by two independent coders (McHugh, 2012; Miles et al., 2014). Disagreements were resolved through discussion with the research team, and the final codebook was applied to all of the interview transcripts by one investigator. To increase the robustness of and assess the reliability of the coding scheme, double coding occurred on 25% of the transcripts (kappa = 0.86). All stakeholder groups were analyzed together.

Results

Participant Characteristics

Twenty individuals were interviewed (Table 5.1). Sex distribution was equal. Participants included both early-career and more established stakeholders (range of time in current job: 2-31 years; age range: 26-62 years). The majority of the participants were nurses (30%) or physicians (30%) by training. Based on roles and responsibilities at the time of the interview, the sample included nine non-mental health clinicians, seven mental health clinicians (e.g., psychologist), and four leaders (e.g., MoHW program

officer and center director). Most of the participants (65%) did not have prior exposure to the PennCNB. Interviews lasted, on average, 40 minutes (range: 20-69 minutes).

Themes by CFIR Domain

Table 5.2 presents the main themes organized by CFIR domain, and Table 5.3 highlights the barriers and facilitators to implementation irrespective of domain.

Outer Setting

Mental health and cognitive issues were described interchangeably by the majority of participants, perhaps due to a lack of a unifying definition of cognitive impairment in the local context. Opinions on healthcare workers' awareness of cognitive issues varied, but the majority of participants commented that community members do not understand the root cause of mental health and cognitive problems. Instead, underlying neurocognitive deficits are commonly attributed to behavioral issues (e.g., "playful" child), or children are labelled with terms describing poor intelligence (e.g., "dumb" or "stupid"), which often results in stigma and families' hesitancy to seek out support. Respondents described cognitive impairment as most commonly identified by poor school performance. There were variable responses related to awareness of the prevalence of neurocognitive impairment among children in the community. All interviewees noted that cognitive and mental health resources in Botswana are extremely scarce, especially the lack of available clinicians with the needed expertise. Existing methods for cognitive screening rely primarily on subjective evaluation (e.g., informal observation of behavior during collection of medical history or discussion with patients and caregivers) or academic performance. Children typically require a referral to receive a psychological assessment, but the limited capacity has resulted in long queues lasting

months to years to see a psychologist for cognitive and mental health evaluations. Thus, respondents expressed a strong need for the PennCNB.

Intervention Characteristics

The discussion of the characteristics of the PennCNB included opinions on the strengths and weaknesses of its delivery via computer. Generally, with regard to strengths, participants described the "game-like" tests as appealing to children and easy to use for all stakeholders, suggesting implementation feasibility. The automated scoring of the battery was described as an improvement over the manual calculation of scores necessary with current screening methods. Some participants suggested that the tool's validity made it more likely to be effective at identifying cognitive impairments compared to current methods. The lack of specialized mental health training required to administer the battery was also highlighted as a strength of the tool, especially given a lack of local psychologists. Although the majority of participants considered the computerized aspect as an asset, some respondents expressed concern about computer availability in specific settings and children's computer literacy. However, most participants perceived children's computer literacy and familiarity as high due to the integration of computers in schools and prevalent use of smartphones in the community. Some individuals acknowledged the practice PennCNB tests administered to ensure task comprehension before the actual assessment as a way to navigate potential limitations with low levels of computer familiarity among children. Finally, the length of the PennCNB (~1.5 hours to complete assessment) could present challenges due to time constraints.

Inner Setting

Participants stated that while the MoHW generally has the authority to approve integration of a new tool in the medical sector, implementation within specific institutions (e.g., CoE) also requires approval from the institutional director. Participants from the MoHW referenced specific committees responsible for approving a tool of this nature. Before beginning a new initiative, potential implementers typically attend training workshops that follow a train-the-trainer approach. There is a high degree of reliance on written guidelines, and standard procedures for incorporating new tools are expected. In some settings, necessary resources (e.g., quiet space for administration and technological support for PennCNB maintenance) may not exist. With regard to clinician access to computers, participants explained that multiple individuals may share a computer for various clinical and administrative tasks, thus limiting the availability of a computer for PennCNB assessment. Across all locations, respondents emphasized a shortage of staff of all specialties, limited mental health clinicians, and the higher ratio of nurses to physicians. In some settings, staff turnover is common, and district health management teams play an integral role in implementation.

Characteristics of Individuals

Overall, respondents expressed high acceptability of the tool, emphasizing that the PennCNB will help children and provide an important, necessary resource. Participants stressed the importance of clinician training on the administration of the tool to allow them to facilitate implementation. Despite recognizing the importance of the neurocognitive screening, participants anticipated that implementers have many other responsibilities and tasks which may make it difficult for them to add this responsibility to their workload. In addition, respondents described potential user barriers, for patients

who already have to wait a long time to see a provider may oppose waiting longer for an additional assessment. Thus, children and/or their caregivers may not find the duration of the PennCNB assessment acceptable, particularly if the time it takes for one child to complete the PennCNB results in longer waits for other children to see a provider.

Implementation Process

Stakeholders recommended various strategies for implementing the PennCNB in Botswana.

Setting and target participants. Participants proposed administering the tool in both the medical sector (e.g., clinics) and the educational sector (e.g., schools). To bridge the gap between the two settings, some individuals highlighted school health programs as a potential venue for implementation. The majority of respondents described targeted screening for children with the greatest need (e.g., as assessed through school performance, referrals, observation of patients during intake, or high-burden clinics), while some participants suggested universal screening of all children to avoid missing cognitive impairment.

Implementers. Stakeholders advised leveraging current roles by having clinicians who already interact directly with patients (e.g., nurses, psychologists, and healthcare auxiliary) administer the assessment; guidance and counselling teachers were recommended for the school setting. Respondents suggested that information technology personnel be responsible for maintenance of the battery, when available in a setting. To increase adherence, participants encouraged integrating the PennCNB assessment into existing guidelines (e.g., HIV treatment guidelines) or standard procedures. Further, some

respondents proposed designating a specific day for PennCNB assessments at implementing sites.

ERIC implementation strategies. Stakeholders recommended multiple implementation strategies that align with the Expert Recommendations for Implementing Change (ERIC) taxonomy (Table 5.4). Overall, participants stressed the importance of receiving buy-in from all stakeholders (e.g., healthcare workers, government, and parents). For leadership and clinicians, respondents encouraged communicating the value of the tool and emphasizing its role in helping children. For the community, participants recommended increasing awareness of neurocognitive impairment to encourage individuals to seek out support for cognitive issues. Before integrating the PennCNB into practice, stakeholders expressed the need for education on how to administer the tool and interpret the data, which could occur through the common train-the-trainer workshops. Some respondents recommended designating a computer for PennCNB administration at implementation sites. In addition, some participants recommended administering the assessments in a dedicated room.

Discussion

Countries in Sub-Saharan Africa experience high rates of HIV infection and *in utero* HIV exposure in pediatric populations but lack resources for screening of related neurocognitive sequelae. This study employed a novel application of the CFIR in the pre-implementation phase to elicit perspectives on factors likely to be related to the successful implementation of the PennCNB into community settings in Botswana. Stakeholders expressed a strong need for cognitive screening and high acceptability of the adapted PennCNB tool, suggesting the added value of the tool in this high-need

setting. Barriers and facilitators to implementation, such as limited time and resources and standard procedures for introducing new tools into medical settings, were highlighted. Respondents provided insightful input for the development of strategies for future implementation in this and similar resource-limited settings in LMICs.

The perceived barriers of insufficient time and resources are consistent with perspectives articulated in other studies across a range of contexts (Alatawi et al., 2020; Cooke et al., 2019; Geerligs et al., 2018; Leonard et al., 2020; McNeely et al., 2018). The PennCNB can serve as an alternative to traditional neurocognitive screening tests that require multiple hours to administer via paper and pencil, so implementation of this tool will streamline assessments substantially. Modifications to the tool to shorten the administration time may be possible, but they will require rigorous assessments to ensure validity. Previous modification of the core version of the PennCNB involved the administration of the battery on a tablet (Basner et al., 2015), so future research could explore similar adaptations to increase accessibility and mitigate concerns over time and shared computer resources. Further, institutional-level support for designated time for implementation (e.g., specific day of the week) or a phased approach to integration may help address the barrier of time (Geerligs et al., 2018). The PennCNB does not require a psychologist to administer the tool, so task-shifting to personnel currently working in the setting may be the most efficient and effective strategy. Both the medical stakeholders and literature emphasize integrating interventions into the current workflow (Geerligs et al., 2018; Perry et al., 2019) and task-shifting (Benjamin Wolk et al., 2018; Murray et al., 2014; Patel, 2009). Extensive research has demonstrated success of task-shifting in similar low-resource settings and LMICs (Mdege et al., 2013; Seidman & Atun, 2017).

To address the expressed concern about healthcare workers being overworked, incentive-based implementation strategies could be explored. Respondents also recommended both schools and clinics as implementation locations, which may alleviate time constraints and personnel burden in one setting. Future research will elicit perspectives from educational stakeholders.

The successful implementation of the PennCNB in Botswana will offer promise for uptake in other resource-limited settings. The government of Botswana invests heavily in its medical system. Historically, this has allowed for the implementation of innovative programs that, subsequently, surrounding countries adopt after demonstration of their effectiveness (e.g., universal HIV testing and prevention of mother-to-child transmission services (Centers for Disease and Prevention, 2004; Creek et al., 2007)). Further, the successful translation of the PennCNB into Setswana (as well as Xhosa (Campbell et al., 2017)) suggests feasibility of translation into other Bantu languages. Thus, results from this research may influence integration in other countries in Sub-Saharan Africa.

This research has limitations. First, the interviews were conducted concurrently with local validation, so participants' responses reflected their beliefs about implementation rather than experience with implementation. However, some of the respondents (35%) had prior exposure to the PennCNB through research collaboration or participation in the stakeholder group that completed the in-depth cultural adaptation process, and the PennCNB was described in detail before conducting the interviews to increase familiarity with the tool. Further, this research helps address the research-to-practice gap (Lane-Fall et al., 2019) by engaging in pre-implementation inquiry and

designing for implementation. Second, social desirability bias and interviewer bias may have existed. The interviewer's impartiality and lack of involvement in the development of the PennCNB was communicated to encourage honest responses. Third, sampling occurred in the capital city, Gaborone, which may limit the generalizability of the findings to more rural locations. However, initial rollout of the PennCNB is targeted for the greater Gaborone area, and stakeholders were recruited from the public sector. Fourth, the sample comprised few policy makers, but some of the clinician stakeholders had previous government experience.

This is the first effort to understand how to plan for implementation of the PennCNB into practice. Results will inform the development of specific implementation strategies to maximize the likelihood of successful integration of the PennCNB into clinical settings in Botswana, ultimately providing access to cognitive screening for a high-need pediatric population.

Table 5.1. Participant Characteristics

Variable	N (%)
Total	20
Median Age, (range)	40 (26-62)
Sex	
Female	10 (50)
Male	10 (50)
Stakeholder Group	
Leadership	4 (20)
Mental Health Clinicians†	7 (35)
Non-Mental Health Clinicians‡	9 (45)
Occupation by Training	
Nurse	6 (30)
Physician	6 (30)
Psychologist	4 (20)
Social worker	4 (20)
Prior Exposure to CNB	
Yes	7 (35)
No	13 (65)

†2 participants are head of department

‡2 participants described history of leadership in government and health policy

Table 5.2. Interview Themes by CFIR Domain

CFIR Domain	Supporting Quotes
Outer Setting	"So, at our clinic we [Botswana], unfortunately, don't have the capacity or the resources to identify any cognitive dysfunction [...] We don't have any measures or any validated tests or anything that would identify any cognitive impairment."
	"Basically, if you have cognitive difficulties that equates to insanity or stupidity. Yeah. There's a lot of stigma- a lot of stigma."
	"So, there's really great need in the country."
	"But there are not enough psychologists- we will refer a patient, but the patient will have to wait- will be booked maybe two years from now because those psychologists, they're seeing inpatients in the hospitals, their families, and they're also seeing outpatients from clinics. So, it's quite a long queue."
Intervention Characteristics	"I think the beauty about it is that you train somebody to be able to administer it, and that person doesn't need the high level of training in terms of being a neuropsychologist..."
	"...the fact that it's computerized, it makes the job easier for us. You just have the child doing it and then you just collect the data and interpret it."
	"It's more like a game-like assessment that they are more used to playing games in the phones, so this time they will be more like playing games in the computer. I think they'll love and enjoy using it."
Inner Setting	"Guidelines are generally followed. From experience, you'll find your healthcare workers refusing to implement something in which they have not seen in writing [...] So once it's in the guidelines level, it should be possible."
	"From experience, when you train someone to do something, you train their mentor and then you follow up. That's the usual structure."
	"Maybe in some of the private schools you might be able to find computers, but in a lot of places- like even in the hospitals, there

	might not be a computer that is readily available to be used by patients."
Characteristics of Individuals	"Because, as you know, there are few health workers. Sometimes someone is supposed to consult, someone's supposed to do certain things, then they will end up skipping some things if it takes more time or if there are a lot of patients." "And I think it will be exciting for people who work in the clinical setting who think they are not resourced to do this; but they do feel that it's important to be able to assess children."
	"I think the perception of the healthcare workers thinking that probably [implementation of the PennCNB will] put so much work into their program. That could be a barrier."
	"The other problem would be the patients themselves. If it takes long to administer the test- complaints- so many complaints. They will be complaining that this person has been here for over an hour now."
Implementation Process	"So we've got a school health program which is supposed to be running, and it's got its strategies, but something like this begins to create a bridge between the schools and the health systems [...] So it would work out well from both ends in terms of linking the two systems."
	"But generally, when you're implementing something into care it can -in the HIV setting it can be in the form- it can be part of the guidelines for example [...] Through the guidelines it can be possible. So, you can for example, when we are writing the guidelines we have section of neurology, we'll just say when you're assessing the child if possible send for neurocognition assessment."
	"[...] we already have an integration of the child growth in the HIV care [...] So if CNB would be integrated, it would just be one of the tools- okay- one of the kind of screening tool that should be added to the existing ones."
	"I would look at the health promotion and the health education team simply because while the tool has clinical components in it, it doesn't always require a clinician to do it. And this cadre is well placed within the health education space. And just the whole task-sharing bit just makes it easier."

	"I think involving stakeholders is the most important thing, because if you just involve your healthcare worker and your client [...] once you have this neurocognitive assessment, you might have a flood of patients who need action."
	"I think for children, a brief review of the history. If they're having learning problems, for example, then those would be the ideal candidates, or if they have delayed milestones. But ideally since it takes longer, I don't think it would be ideal to give it to every child, but so there should be a quick screening of either a few simple questions to determine that this might be an impaired child rather than subjecting every child to this."

Table 5.3. Barriers and Facilitators to Implementation

	Key Themes	Supporting Quotes
Barriers		
Time	PennCNB takes too long to complete	"So in a clinic setting where a healthcare auxiliary does other things in the clinic [..] I think having to do four or more assessment a day would take a significant amount of time, and that [...] would just weigh down on the operations of the clinic."
	Too many patients for duration of assessment	"We know that the healthcare system is really overwhelmed [...] there's long waiting lines. People are always waiting for service [...] I think the only difficulty that they might be in this being acceptable within practice is people actually having time to complete it or to use it."
Human resources	Shortage of HCWs	"[...] within nursing and doctors here there's serious staff shortage."
	Limited mental health clinicians	"And like I said, psychologists are scarce, they're rare."
Physical resources	Limited computer and space availability in some settings	"One of the barriers that I see […] is lack of computers in the- in the clinics or even the primary hospitals [...]"
Stakeholder pushback	Reluctance from HCWs due to overwork	"I think the biggest barrier is mindset, the attitude of, is this more work? Why should we be spending time doing this when we could do other things?"
	Patients complain about time	"...If patients see that somebody went into a room and they took one and a half hour, then they might start complaining..."
Facilitators		
Physical resources	Computers and space available in some settings	"Well the resources are there, the computers are there, the infrastructure is there, the patients are there."
Procedures	Follow MoHW guidelines	

	SOPs for new interventions	"[...] if there's a directive from the Ministry as in it's an implemented guidelines that when a child presents with a referral about cognitive impairment, then you must assess them using at least this tool, then they have that best practice to- to use. " "But again, when something new comes, the Ministry makes sure that we do workshops [and receive training on] how a particular thing is to be done."
Acceptability	HCWs satisfaction and high acceptability	"Well, I think it would be a great thing. It would be very, very acceptable, I mean especially to the healthcare workers because it will be something new to help in assessing kids."
	Desire for cognitive screening	"We might not know the magnitude of the problem in terms of children having those neurocognitive issues [...] So I would be very excited to see this going forward and implementing this because definitely is going to help us understand the magnitude of the problem that we may have in that field."

Table 5.4. Recommended Strategies per Expert Recommendations for Implementing Change

Strategy	Stakeholder Recommendations
Use evaluative and iterative strategies	Develop team to monitor ongoing use of PennCNB Improve implementation over time Target selection of initial implementation sites
Provide interactive assistance	Use existing IT support in clinics
Adapt and tailor to context	Leverage existing roles as implementers
Develop stakeholder interrelationships	Achieve buy-in from stakeholders
Train and educate stakeholders	Demonstrate administration of PennCNB Provide written guidelines for implementation Facilitate train-the-trainer workshop Educate stakeholders on value of tool and cognitive impairment (community, implementers, policy makers)
Support clinicians	Revise professional roles to distribute responsibilities to non-specialists via task-shifting
Engage consumers	Utilize media to increase awareness about cognitive impairment
Change infrastructure	Designate specific room for PennCNB administration Designate specific computer for PennCNB Decorate room with kid-friendly colors

CHAPTER 6. CONCLUSIONS

“Notice me”

Summary of Findings

This body of research yielded many overarching conclusions. Through the confirmatory and exploratory factor analyses, Chapter Two offered insights into the psychometric properties of the adapted PennCNB and provided evidence of convergent and discriminant validity. These findings supported the theoretical design of the battery measuring the intended neurocognitive domains: executive functioning, episodic memory, complex cognition, and sensorimotor/processing speed. By examining the classification accuracy and utility of the PennCNB against professional consensus classifications of impairment, chapter three provided evidence of criterion validity, which further supported the validation of the tool for this setting. The last two empirical chapters detailed pre-implementation inquiry to plan for future integration of the PennCNB into practice. Chapter Four highlighted the high acceptability of the PennCNB among children and adolescents, which offers promise for successful implementation in this setting. Finally, through key stakeholder interviews, Chapter Five underscored the need for neurocognitive screening, identified anticipated barriers and facilitators to using the battery, and suggested strategies for implementation. These findings will inform the development of specific implementation strategies to maximize the likelihood of successful integration of the PennCNB into clinical settings in Botswana.

Future Directions

The conclusions from this work identified several new directions for future research. It is important to note that this dissertation research evaluated only three constructs of validity. Ongoing research is exploring additional measures of reliability

and validity (e.g., internal consistency and retest reliability) for comprehensive validation of the Botswana version of the PennCNB (Scott et al., 2020).

Potential Adaptations of PennCNB

Results highlighted potential adaptations for the PennCNB that may increase the appropriateness for the local context and evaluation of school-aged children in Botswana. To begin with, investigators could modify the instructions or provide additional practice time for specific modules considered difficult by participants to increase the acceptability of the tool among pediatric populations. To alleviate the time constraints articulated by stakeholders, future research could explore the development of a shortened version of the PennCNB. This work would require a systematic approach for modifying or deleting specific tests and a reassessment of the validity of the shortened battery. In addition, future research could investigate the acceptability of the battery in alternative formats to address the limited computers in resource-limited settings. For example, a previous study administered a version of the PennCNB on a tablet (Basner et al., 2015).

Implementation Strategies

Overall, this research provided robust data and inspired several next steps for future implementation of the PennCNB in Botswana. First, Chapter Three demonstrated the PennCNB's acceptable discrimination across a range of cut-points. Implementation will require finalizing the cut-point for determining impairment based on data from a larger cross-section of a local non-clinical population and the development of data interpretation guidelines. Future analyses could develop norms from the full cohort enrolled in the Ntemoga study to assess for differences in classification accuracy.

Some of the medical stakeholders recommended implementing the PennCNB in the educational sector. Ongoing research is eliciting perspectives from educational stakeholders to elucidate factors likely to impact the successful implementation of the battery in that setting. Upon conclusion of these interviews, future work could utilize approaches such as implementation mapping to operationalize the input to design implementation strategies for both the medical and educational sectors. A future study could implement the PennCNB in both settings and measure implementation outcomes to determine the most effective setting for implementation.

Further, findings suggested the need for increased awareness of cognitive impairment in Botswana. Successful adoption and uptake of the PennCNB will require an understanding of the importance of cognitive screening and, therefore, the need for the PennCNB. Forthcoming work utilizing data from the medical stakeholder interviews will describe how the lack of understanding of neurocognitive impairment manifests in the community as a way to provide clarity and articulate the importance of understanding cognitive impairment among children and adolescents.

Finally, implementation of the PennCNB in Botswana requires ethical considerations. For instance, the target population already experiences HIV-related stigma, and the medical stakeholder interviews described stigma associated with cognitive dysfunction. Future work could explore the integration of stigma-reducing strategies during the administration of the PennCNB to minimize further stigmatization from being identified as having neurocognitive impairment. Further, after identifying neurocognitive deficits, the individual should be referred for cognitive support. Previous research evaluated interventions for children with neurocognitive impairment in resource-

limited settings (Van Pelt et al., 2020). Future research could leverage the findings from this systematic review to package the implementation of the PennCNB with support strategies.

Public Health Implications

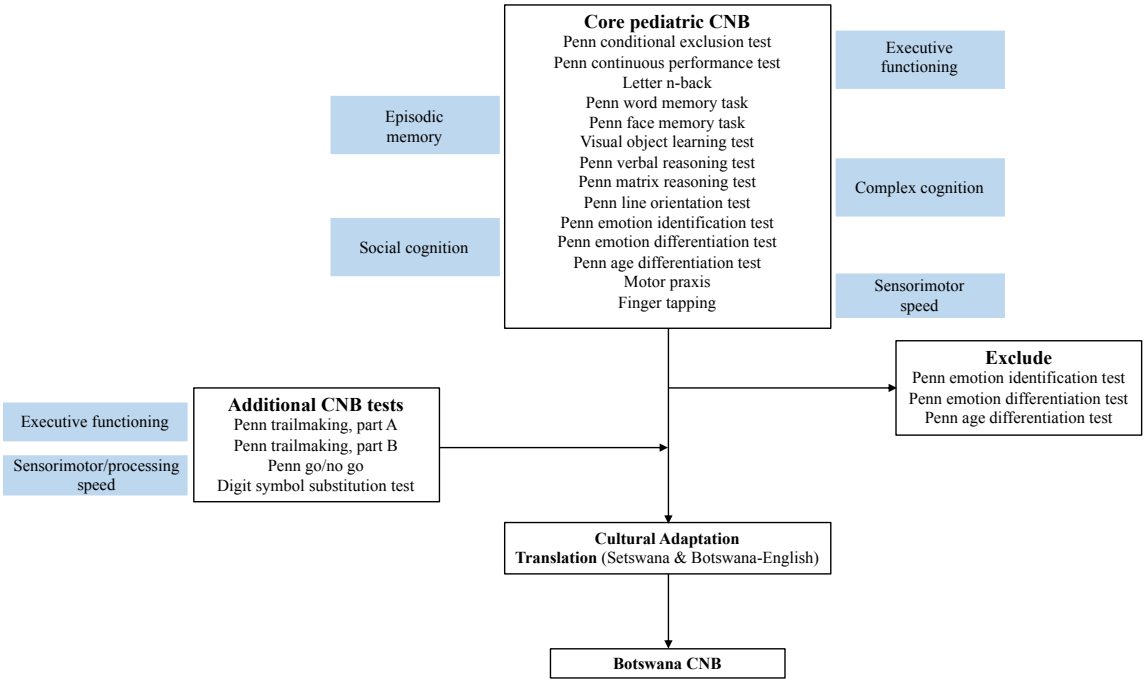
This body of work advances the research agenda for providing access to neurocognitive assessments and related support in high HIV-prevalent, resource-limited settings. Successful implementation of the PennCNB will provide access to cognitive screening for a high-need pediatric population in Botswana. The nature of the computerized battery has the potential to streamline assessment of cognitive functioning and help reduce the burden on the limited mental health capacity. The identification of neurocognitive impairment will facilitate the provision of appropriate support for children and adolescents struggling in school and daily life. Further, identifying impairment will allow for an understanding of the epidemiology of neurocognitive deficits in this population, which will better inform the development of neurocognitive interventions and future research questions on the topic. Finally, successful implementation of the PennCNB in Botswana will likely influence uptake in surrounding regions, which will expand the reach of the tool and resulting public health implications.

APPENDIX

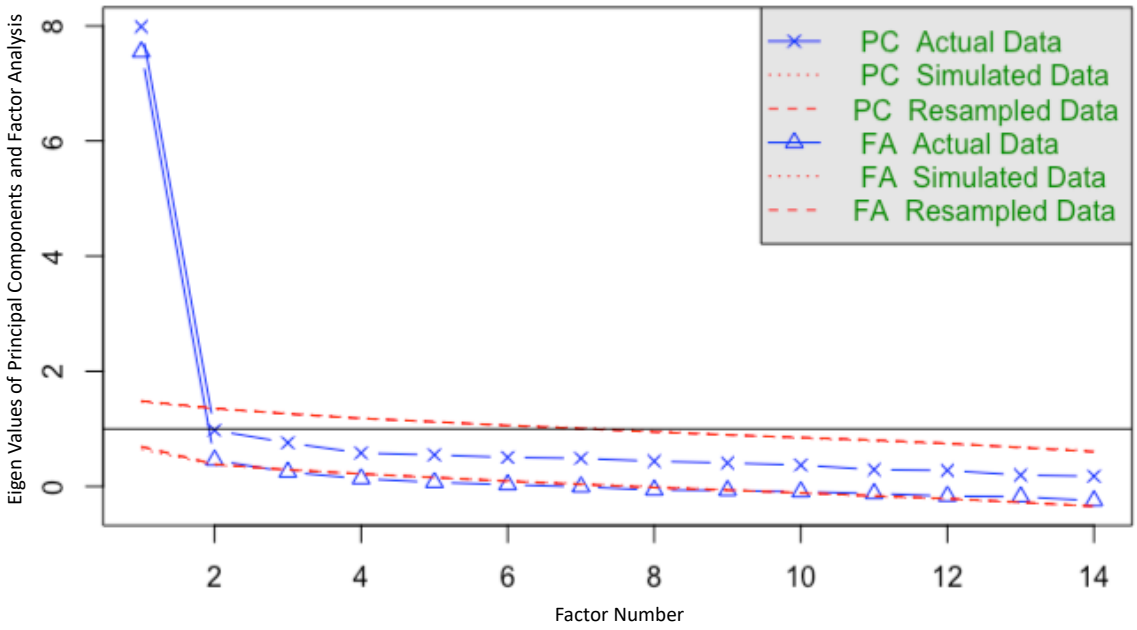
Appendix Table 2.1. Fit Indices from Sensitivity Analyses for Confirmatory Factor Analyses on PennCNB Efficiency Score

			Fit Indices			
Sample	**N**	**Factors**	**CFI**	**RMSEA**	**SRMR**	**BIC**
No HEUs	173	4	0.964	0.067	0.036	5523.569
No English CNB	189	4	0.967	0.063	0.035	6075.749
No HEUs or English CNB	157	4	0.969	0.061	0.036	5080.762

Appendix Figure 2.1. Schematic of Adaptation Process for Botswana PennCNB

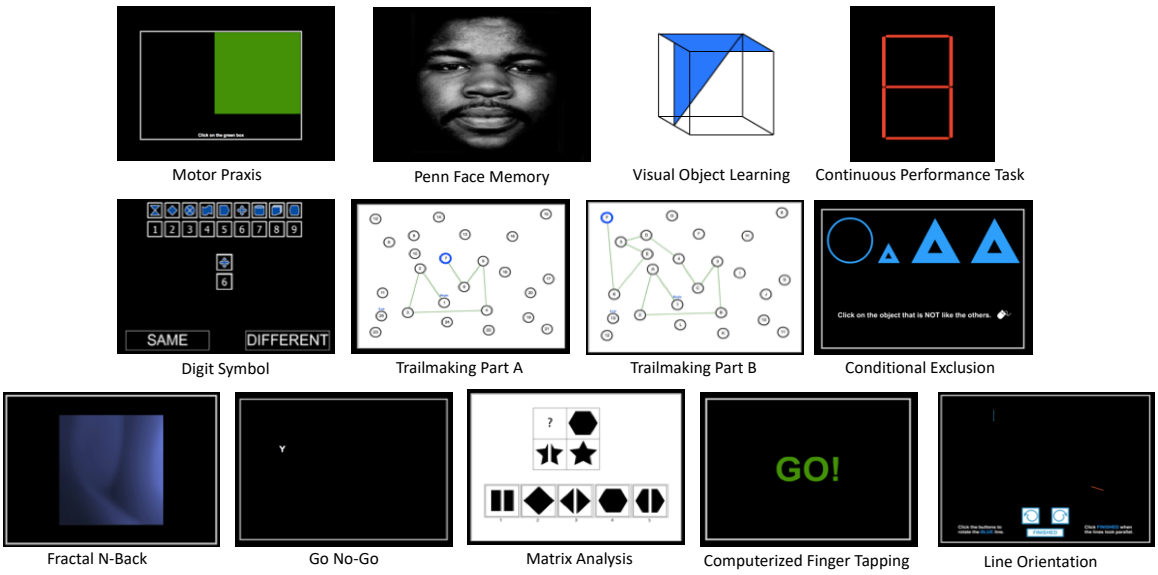


Appendix Figure 2.2. Parallel Analysis Scree Plot from Exploratory Factor Analysis on PennCNB Efficiency Scores



PC= principal components model; FA= factor analysis model
This analysis was completed to assist in the determination of the most optimal number of factors for the model.

Appendix Figure 4.1. PennCNB Modules Administered to Participants



Appendix Material 5.1. Questions from Semi-Structured Interview Guide

Part 1: Introduction Question

1. **To begin, please tell me your job title.**
    a. **What do you do in that position?**
    b. Identify the stakeholder's job "setting" (e.g. clinic, school, health post) and utilize the language throughout the rest of the interview.
    c. Probe for the interviewee's experience in other jobs.
        i. Have you worked in any other settings?
2. **How are children with cognitive difficulties currently identified in your "setting"?**
    a. Cognitive difficulties refer to the way children are learning, concentrating, remembering information, and solving problems, for example. Cognitive delays can manifest as "special educational needs" or "attention issues".
3. **What screening methods to detect neurocognitive difficulties among children are currently used in your "setting"?**
    a. Probe for the interviewee's thoughts on the effectiveness of the current methods.
        i. Who requests the evaluation of a child (e.g. teacher, parent, doctor)?
        ii. Who does the screening?
        iii. How does the screening happen in your "setting"?
        iv. What are the strengths of the current screening methods?
        v. What are the limitations of the current screening methods?

1. How accurate are the current methods at classifying impairment?
2. Can the current methods detect mild/moderate impairments?

4. **How acceptable would it be to use the CNB in your "setting"?**
    a. Probe for reasons why the CNB would or would not be acceptable.

Part 2: Consolidated Framework for Implementation Research Questions

(Text in purple indicates possible CFIR constructs related to each question, but it will not be read aloud by the interviewer.)

Considering the available resources and context in the "setting", I will now ask you questions about your thoughts on how the CNB could best be integrated into the current workflow.

For participants who are in leadership or academic positions without experience interacting with patients/students, frame the questions to ask about their thoughts on where the CNB would best be implemented. Start the questioning with the following question:

Where would be the best place to use the CNB?

5. **Who would be responsible for making the decision on whether or not to use the CNB in your "setting"?**

(Process of Implementation, Inner Setting)

6. **How would you determine which children should be screened with the CNB?**
    a. Reworded: How will you select *patients/students* to take the CNB?

    (Process of Implementation)

7. **Who would be involved in implementing the CNB in your setting?**
    a. Probe for specific roles to administer and maintain the CNB.
        i. Who would administer the CNB to *patients/students*? If you cannot think of a specific person, which position, such as a *nurse/teacher*, would administer the CNB?
        ii. Who would be responsible for maintaining the CNB in your "setting"? If you cannot think of a specific person, which position, such as an administrator, would be responsible for maintaining the CNB?

(Process of Implementation, Inner Setting)

8. **Where would you administer the CNB in your "setting"?**
    a. Probe for necessary resources.
        i. Would the infrastructure in your "setting" support the implementation of the CNB?
            1. Is there a private space in which the CNB could be administered to *patients/students*?

(Process of Implementation, Inner Setting)

9. **What resources would you need to successfully use the CNB in your "setting"?**
    a. Probe for provider and organizational level factors.
        i. What physical resources, such as computers, would be needed to effectively implement the CNB in your "setting"?

1. Physical resources refer to tangible items or things that you can actually touch, such as a table.

ii. The training for the administration of the CNB is standardized. What additional education would be needed to get individuals, such as *providers/teachers*, to use the CNB?

iii. What standard operating procedures would need to be created at your "setting" to get *providers/teachers* to use the CNB?

(Process of Implementation, Inner Setting, Individual Characteristics)

10. **What facilitators for the use of the CNB exist in your "setting"?**

a. Facilitator refers to anything that will make using the CNB in your setting easier, such as the resources that currently exist in your "setting".

b. Probe for facilitators related to the components of the CNB as well as provider, organization, or system level factors.

i. What features of the CNB may help with the successful implementation in your "setting"?

ii. What infrastructure or procedures that currently exist in your setting may help with the implementation and maintenance of the CNB?

iii. What is the attitude about neurocognitive impairments among children in your community?

1. How do parents or caregivers of children discuss neurocognitive challenges with *medical providers/teachers*?

2. Tell me about stigma against children with cognitive delays.
3. How do parents or caregivers who recognize that their child is struggling in school ask for help from their *medical providers/teachers*?

iv. How commonly do you encounter children with neurocognitive impairments in your community?

(Intervention Characteristics, Inner Setting, Individual Characteristics, Outer Setting)

Now that we have discussed elements that will help with the successful implementation of the CNB in your setting, I will ask you about factors that may make implementing the CNB in your "setting" difficult.

11. **What barriers may prevent the use of the CNB in your "setting"?**
    a. Barrier refers to anything that may make using the CNB in your "setting" difficult.
    b. <u>Probe</u> for barriers related to the components of the CNB as well as provider, organizational, or system level factors.
        i. Are there any features of the CNB that will make using it in your "setting" difficult?
        ii. What standard operating procedures in your "setting" may make the implementation of the CNB difficult?
            1. What standard operating procedures in your "setting" may make the maintenance of the CNB difficult?

iii. What staff characteristics (e.g. self-efficacy or beliefs about the CNB) may make the use of the CNB in your "setting" difficult?

1. Self-efficacy refers to an individual's belief in his or her ability to complete a task.

iv. What policies outside of your "setting" may prevent you from implementing the CNB in your "setting"?

(Intervention Characteristics, Inner Setting, Individual Characteristics, Outer Setting)

Part 3: General Questions

Now, I will ask you a couple of questions about what is likely to happen after a child completes the CNB. Once the CNB identifies a child with a cognitive delay and the possible area affected, such as attention or memory, the child should be referred for support. We want to understand the current availability of support strategies and alternative support that might work well in your "setting".

12. **What support strategies are currently being used for children with neurocognitive difficulties?**

    a. Probe for where and how the interventions are being employed.

        i. Where do children currently go for these "treatments" or interventions?

        ii. Who is currently recommending the support strategies for children with neurocognitive difficulties?

        iii. Who is currently administering the support strategies for children with neurocognitive difficulties?

13. **How would you and other *medical/school* staff determine which support strategy is appropriate for a child?**

    b. Probe for the inclusion of the CNB.

        i. How will you use the results from the CNB assessments?

14. **How does the school assess if a support strategy is working for a particular child?**

    c. Probe for the method of measurement and the individuals responsible for the assessment.

        i. What methods will you use to measure "improvement"?

            1. Would you conduct a formal assessment?
            2. Would the review occur in an educational support team meeting?

        ii. Who would be responsible for conducting the assessment?

15. **What additional type of assessment would be helpful to introduce to see if a child is getting better after using a support strategy?**

Part 4: Conclusion Question

16. **Is there anything else that you would like to add before we conclude the interview?**

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