NEUROPSYCHOLOGICAL ASSESSMENT FOR FIRST-EPISODE PSYCHOSIS PATIENTS IN LOW RESOURCE SETTINGS.

by

STUDENT: Dr. Emmanuel Kiiza Mwesiga

Registration: MWSEMM001

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SUPERVISORS	AFFILIATION
Prof Dan Stein; BSc (Med) MBChB *UCT*, FRCPC PhD DPhil *Stell*	Department of Psychiatry and Mental Health; University of Cape Town
Dr. Dickens Akena; MBChB *MUK*, MMED (Psych) *MUK*, PhD *UCT*	Department of Psychiatry, College of Health Sciences; Makerere University
Dr. Nastassja Koen; MBChB *UCT*, PhD *UCT*	Department of Psychiatry and Mental Health; University of Cape Town
Associate Prof. Noeline Nakasujja; MBChB *MUK*, MMED (Psych) *MUK*, PhD *MUK*.	Department of Psychiatry, College of Health Sciences; Makerere University

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ABSTRACT

Introduction: Cognitive impairment is the most significant predictor of long-term outcomes in psychotic disorders, and neuropsychological assessment is therefore recommended in first-episode psychosis patients. However, the literature on neuropsychological assessment for first-episode psychosis patients in low resource settings is limited, the clinical utility of such assessments are unclear, and lengthy assessments may not be practicable in these contexts. This thesis therefore investigated 1) which brief neuropsychological assessment measures researched in patients with psychotic disorders from low and middle-income countries are appropriate for cognitive screening, 2) the differences in prevalence and profile of cognitive impairment between first-episode psychosis patients and healthy peers in one low resource setting, 3) the association of clinical variables with impairment in different cognitive domains in first-episode psychosis patients from one low resource setting, and 4) the validity of the NeuroScreen (a collection of brief neuropsychological test delivered via smartphone) for neuropsychological assessment in first-episode psychosis patients in this setting (as determined by comparison with a gold standard evaluation).

Methods: First, a systematic review of articles in which brief neuropsychological assessments were researched in patients with psychotic disorders from low and middle-income countries was performed. The 2014 Working Group on Screening and Assessment (WGSA) guidelines were used as a benchmark of the appropriateness for cognitive screening for the neuropsychological assessment measures employed. Second, first-episode psychosis patients and matched healthy peers were recruited into an observational study at the National mental referral hospital in Uganda. Clinical variables were collated (including sociodemographic characteristics, dietary history, previous childhood trauma and illness severity), and after the resolution of psychotic symptoms, a neuropsychological assessment was performed using the gold standard MATRICS consensus cognitive battery. Student t-tests and chi-square tests were used to determine differences in the prevalence and profile of cognitive impairment in patients with psychosis and healthy peers. Multiple linear regression analyses were used to determined associations between clinical variables and cognitive domains while controlling for potential confounders. Finally, Pearson's rank correlation

coefficients and receiver operating curves were computed to examine the validity of the NeuroScreen against the MATRICS consensus cognitive battery**.**

Results: In the 29 articles reviewed, none of the neuropsychological measures researched in patients with psychotic disorders of low and middle-income countries was appropriate for cognitive screening according to the Working Group on Screening and Assessment (WGSA) guidelines. Neuropsychological assessment with the MATRICS consensus cognitive battery found the burden of cognitive impairment in first-episode psychosis patients six times that of healthy peers. The largest cognitive impairment burden was in the visual learning and memory domain. Increased age was associated with impairment in the domains of the speed of processing (p=<0.001) and visual learning and memory (p=0.001). Cassava rich diets had a negative association with cognitive impairment in the visual learning and memory domain (p=0.04). There were no significant associations between sex, history of childhood trauma or illness severity with any of the seven cognitive domains. A composite score from five cognitive domains of the NeuroScreen had a moderate accuracy of 0.79 compared to the MATRICS consensus cognitive battery.

Conclusion: There is need for further research on appropriate measures for neuropsychological assessment in low resource settings. As demonstrated here, the use of such assessments may reveal modifiable risk factors for such impairment; appropriate nutrition may be a particularly important intervention for individuals with psychotic disorders in poorly resourced settings. The NeuroScreen may be useful for neuropsychological assessment of patients with psychotic disorders in low resource settings but needs modification to improve its accuracy.

FOREWORD

This doctoral thesis is dedicated to Myra, Aubrey, Cornelius and Kyra who stood by me all these years without complaining.

ACKNOWLEDGMENTS AND DEDICATION

Four years is a long time to spend on one project. When I started this journey, social distancing was frowned upon, and I had only read about a pandemic in fiction novels. In a few years, I will look back and say it was worth it. I have learnt a lot and it would be foolhardy to name all the people who were instrumental to this thesis. Still, I will attempt to recognize a handful of those who have walked this journey with me.

The department of Psychiatry at Makerere University held my hand and helped to understand the intricacies of the mind while I was still a postgraduate student. I am especially grateful to Prof, Seggane Musisi, Prof. Noeline Nakasujja and Dr. Dickens Akena who introduced me to psychiatric research. Prof. Dan Stein and Dr. Nastassja Koen from the department of Psychiatry and mental health at the University of Cape Town were patient with me even during the times when I struggled as a doctoral student. The NeuroGAP study headed by Dr. Karestan Koenen was kind enough to provide unlimited resources to complete this thesis. I am also indebted to the GINGER program that gladly provided access to facilities at Harvard University that were unavailable in my home country. Special mention goes to Prof. Lori Chibnik who ensured that I remain focused on my doctoral studies. My research team of Angel, Lawrence, Anne, Joy, Shubaya and Wilber are forever my superheroes. The staff of Butabika hospital, especially Dr. Juliet Nakku; who made me feel at home are deeply appreciated. To the patients, I hope this thesis reveals ways to treat you better. It would be a small token of appreciation for the hours you spent answering the questions. Finally, I need to thank my family that stood by me while I spent hours poring over articles and reviews. My wife has been one of my greatest cheerleaders on this journey. I dare not forget Mummy, Daddy, Aunt Phillipa, siblings, in-laws, nephews and nieces who have encouraged me over the years in small and big ways. I am truly thankful and hope that my appreciation will be deeply felt by each one of you. May God truly bless you.

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LIST ABBREVIATIONS AND GLOSSARY

CPZeq	Chlorpromazine equivalents.
CTQ	Child Trauma Questionnaire
DALY`	Disability Adjusted Life Years
DUP	Duration of untreated psychosis
FEP	First-episode of Psychosis
HIC	High income country.
LMIC	low- and middle-income countries
MCCB	MATRICS consensus cognitive battery
PANSS	positive and negative signs and symptoms of Schizophrenia.
SSA	sub-Saharan Africa
WHOOQL-BREF	World Health Organization Quality of life tool - Brief version
YLL	Years of Life Lost
GINGER	Global Initiative for Neuropsychiatric Genetics Education in Research

OPERATIONAL DEFINITIONS

Psychosis: A confirmed diagnosis of any DSM-5 Schizophrenia-spectrum and related psychotic disorder(s) or a bipolar mood disorder on the Mini International Neuropsychiatric Interview (MINI) for mental illnesses (2).

First-episode of psychosis: Antipsychotic-naïve patients or patients who had been on antipsychotic medication for less than six weeks' duration at the time we identified them for recruitment into the study (3).

General cognitive impairment: When assessed using the MATRICS consensus cognitive battery a person had scores two standard deviations below the mean in any one cognitive domain or scores of one standard deviations below the mean in any two cognitive domains (4).

Psychosis resolution: Adapted from the definition by Andreasen et al (2005) that defines resolution as scores of 2 or less on the positive and negative signs and symptoms of Schizophrenia scale in the domains that assess for delusions, unusual thought content, hallucinatory behavior, conceptual disorganization, mannerisms, blunted affect, social withdrawal and lack of spontaneity (5).

High income country versus Low and middle-income country: Low-income economies were defined as those with a GNI per capita, calculated using the World Bank Atlas method, of $1,035 or less in 2019; lower middle-income economies are those with a GNI per capita between $1,036 and $4,045; upper middle-income economies are those with a GNI per capita between $4,046 and $12,535; high-income economies are those with a GNI per capita of $12,536 or more (https://datahelpdesk.worldbank.org/knowledgebase/articles/906519#High_income)

CHAPTER ONE:

This chapter will introduce the key gaps in the literature on neuropsychological assessment in first-episode psychosis patients from low resource settings. After a brief introduction, this section will highlight the main research questions and conceptual framework of the study.

Introduction

Current clinical guidelines for managing psychotic disorders recommend neuropsychological assessment as part of routine care (6). Difficulty performing everyday functions such as planning, arithmetic, and problem-solving characterize cognitive impairment which is a core feature of psychotic disorders (7-12). Neuropsychological assessment must be performed early at the first episode of psychosis and continue throughout the course of the illness (13-15). Neuropsychological assessment in first-episode psychosis patients is important, as cognitive impairment is a greater predictor for psychosis disease burden than behavioral, positive or negative symptoms of psychosis (16-23). The impairment is associated with inferior quality of life and poorer long term functional outcomes (24, 25).

Neuropsychological assessment guidelines developed in high income countries for patients with psychotic disorders may not easily be extrapolated to low resource settings. First, it is notable that there are a wide range of neuropsychological assessment measures which assess different domains, using different tests, and taking different times. These measures may also be used in various settings such as clinical or research settings, and by different levels of health care professionals. In low-resource settings there may be far fewer specialized neuropsychologists in clinical settings (20). Therefore, it is essential to determine if brief measures used in patients with psychotic disorders from low resource settings are appropriate for brief neuropsychological assessment.

Secondly, knowledge of the prevalence and profile of cognitive is important for determining testing procedures and the validity of tests used for neuropsychological assessment (26). Neuropsychological assessment for psychotic disorders covers the seven cognitive domains of i) working memory, ii) attention/vigilance, iii) verbal learning and memory, iv) visual learning and memory, v) reasoning and problem-

solving, vi) information processing speed, and vii) social cognition (4, 27). In high-income countries, up to 80% of first-episode psychosis patients have cognitive impairment primarily in the domains of speed of processing and verbal learning and memory (28-30). The few studies that have assessed the burden and profile of cognitive impairment in this population did not use standardized measures for assessment (31-33). Also, in high-income countries, cognitive scores for first-episode psychosis patients were found to be 2SD below scores of their healthy peers in all the domains (34). Literature comparing the clinical presentation of cognitive impairment in first-episode psychosis patients and healthy peers in low resource settings is limited. There are also few studies that have determined differences in test scores between first-episode psychosis patients and their healthy peers in low resource settings (35, 36).

Furthermore, first-episode psychosis patients from low-income countries differ from those of high-income countries in patient characteristics (illness severity, duration of untreated psychosis, drug dosages, diagnostic categories) (32-39), environmental exposures (diets, trauma exposure) (40, 41) and social characteristics (sex, age and welfare) (32). These characteristics may impact on the performance of neuropsychological assessment measures, and it is important to determine whether they need to be controlled for during assessment (42). However, few studies have determined the clinical variables associated with cognitive impairment in first-episode psychosis patients from low resource settings (10). Even fewer studies have determined if the clinical variables associated with impairment vary across the seven different cognitive domains. Therefore, determining the association of clinical variables with impairment in different cognitive domains in patients with psychotic disorders in low resource settings is required.

Finally, to facilitate neuropsychological assessment in first episode psychosis patients from low resource settings, there might be benefit in using mobile health applications (37, 38). Mobile health applications (mHealth apps) are beneficial for neuropsychological assessment in populations with a limited human resource as they automate testing and scoring processes (39-41). mHealth apps are already in use for neuropsychological assessment in HIV/AIDS and elderly populations in low resource settings (37, 42). These mHealth apps have not been used extensively for neuropsychological assessment in first-episode psychosis patients from low resource

settings (43, 44). It is unclear if these mHealth applications have prerequisite sensitivity and specificity for neuropsychological assessment in first-episode psychosis patients from low and middle-income countries. It is also unclear what impact different clinical variables would have on test performance of these mHealth applications for neuropsychological assessment.

This thesis aimed to identify gaps that may limit extrapolation of neuropsychological assessment of first-episode psychosis patients to routine care in low resource settings. Specifically, it investigated 1) if the measures researched in studies of patients with psychotic disorders from low and middle-income countries are appropriate for brief neuropsychological assessment, 2) the differences in the prevalence and profile of cognitive impairment between first-episode psychosis patients and healthy peers in one low resource setting 3) the association of clinical variables with impairment in seven cognitive domains in this low resource setting, and 4); the validity of a mobile health application, NeuroScreen, for neuropsychological assessment in first-episode psychosis patients from this setting.

Research questions

The four specific research questions addressed by this dissertation are:

a) Are the measures researched in studies of patients with psychotic disorders from low and middle-income countries appropriate for brief neuropsychological assessment?
b) Are there differences in the prevalence and profile of cognitive impairment in first-episode psychosis patients and healthy peers from low and middle-income countries?
c) What is the association between clinical variables and impairment in specific cognitive domains in first-episode psychosis patients from a low and middle-income country?
d) What is the validity of the NeuroScreen (a collection of brief neuropsychological test delivered via smartphone) for neuropsychological assessment in first-episode psychosis patients from a low and middle-income country?

Conceptual framework

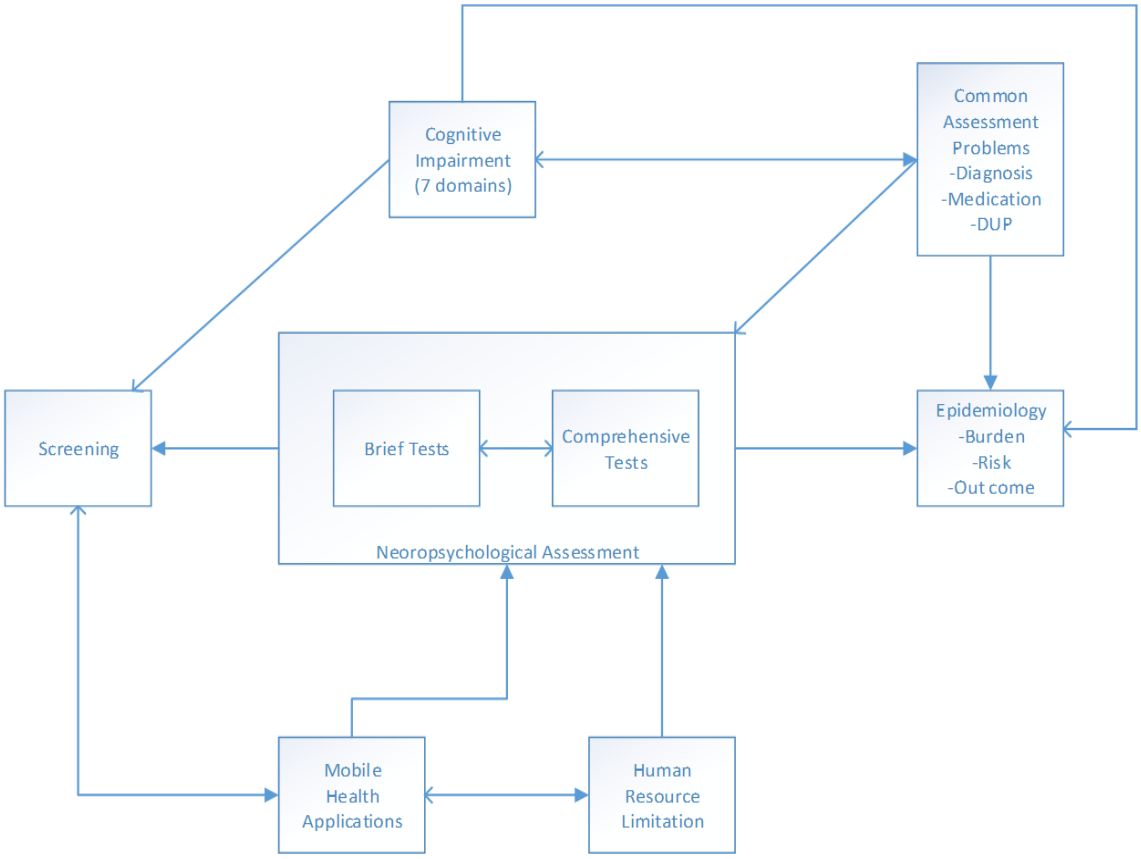

Figure 1: Conceptual framework based on Lezak's description of neuropsychological assessment.

Essentially there are several gaps in the existing literature on neuropsychological assessment in first-episode psychosis patients from low resource settings. When performing neuropsychological assessments, the domains to be assessed, neuropsychological assessment procedures to employ, personnel to administer the tests, and clinical, environmental, and social factors of the participants must be pre-determined (26). Comprehensive batteries like the MATRICS consensus cognitive battery that assess for impairment in all seven domains are ideal for determining the burden of impairment, common domains impaired, mean differences between domain scores, and clinical variables associated with cognitive impairment. However, comprehensive batteries are rarely used in low resource settings which limits our understanding of cognitive impairment to improve neuropsychological assessment. Brief measures that assess for impairment in a few domains are often developed from comprehensive batteries. They are preferred for their brevity and utility even by non-specialized staff. Mobile health applications delivering these brief neuropsychological

measures could improve neuropsychological assessment for first-episode psychosis patients (45). The NeuroScreen is one such application that delivers brief neuropsychological test using a smartphone (39). The validity of the NeuroScreen for use in first-episode psychosis patients from low resource settings has not been determined to ensure it has the desired sensitivity and specificity. Also, Lezak defined "*common assessment problems with brain disorders"* as clinical, environmental, and social factors of the participants that might impact tests' performance. The impact of these "*common assessment problems with brain disorders"* on the NeuroScreen need to be determined.

CHAPTER TWO: LITERATURE REVIEW

This chapter will review the literature on neuropsychological assessment in patients with psychotic disorders. The review will give an overview of the specific challenges of neuropsychological assessment in psychotic disorders that are specific to low resource settings.

Neuropsychological assessment in psychotic disorders

Early in the 1900s, limited availability of neuropsychological tests impeded descriptions of cognitive impairment in psychotic disorders (26). Bleuler, for example, believed that patients with schizophrenia did not have memory impairments and that forgetfulness was due to disorganization (46). At the time, there were no standardized tests to prove this assumption. Around the middle of the 19th century, neuropsychiatrists such as Carl Wernicke began to develop procedures for assessing more specific components of mental functioning like cognitive functioning (47).

In the early 1960s, the first neuropsychological tests were developed and revolutionized cognitive neuroscience (20). Initial test batteries designed by Halstead–Reitan and Luria–Nebraska were able to determine differences in cognitive impairment between patients with neurological disorders and healthy peers (48). Maintaining set or "set" was the first clear description of a cognitive domain (49). Set referred to the ability to respond to a stimulus situation appropriately. Patients with Schizophrenia had difficulties maintaining set and responded to irrelevant aspects of the situation (50). Nevertheless, difficulties in maintaining set were not limited to psychotic disorders and these early neuropsychological tests were therefore unable to differentiate cognitive impairment across various disorders (51). A better understanding of neural systems in the late 1960s contributed to further advances in neuropsychological assessments' (52). Various tests for different sub-populations of patients could now be developed. Initial tests developed were primarily for assessing traumatic brain injury, but later; neuropsychological tests for mental illnesses like Schizophrenia were developed (53-55). Studies in patients with psychotic disorders

like Schizophrenia then highlighted how cognition was not a unitary construct and that different domains were impaired in the disorder (56).

The MATRICS initiative

The Measurement and Treatment Research to Improve Cognition in Schizophrenia (MATRICS) initiative was undertaken in 2002 to build consensus on which domains and tests were crucial for research in psychotic disorders (40). The aim of the initiative was to "*stimulate the development of drugs to treat the cognitive deficits of Schizophrenia, to clarify requirements for regulatory approval, and to facilitate the development of appropriate methods for collecting data to present to the FDA when requesting regulatory approval (27)."* Funded by the National Institutes of Mental Health, the initiative was based on the following premises 1) cognitive deficits are core features of psychotic illness, 2) these deficits are common, 3) the cognitive deficits are associated with functioning more than positive and negative symptoms and 4) performance of the cognitive function can be improved (56).

The Initiative's core task was to determine the critical cognitive domains for assessing cognitive function in patients with psychotic disorders and identified seven cognitive domains impaired in patients with psychotic disorders (27). The domains selected included i) working memory, ii) attention/vigilance, iii) verbal learning and memory, iv) visual learning and memory, v) reasoning and problem-solving vi) information processing speed, and vii) social cognition (4, 27). These different cognitive domains may be broadly classified into social or non-social cognition (See figure 2) (20). Social cognition is related to but distinct from neurocognition (other six cognitive domains) and negative symptoms even though it is involved with social processing. The other

six domains constitute non-social cognition (neurocognition) because they are necessary irrespective of the ongoing social processes (20).

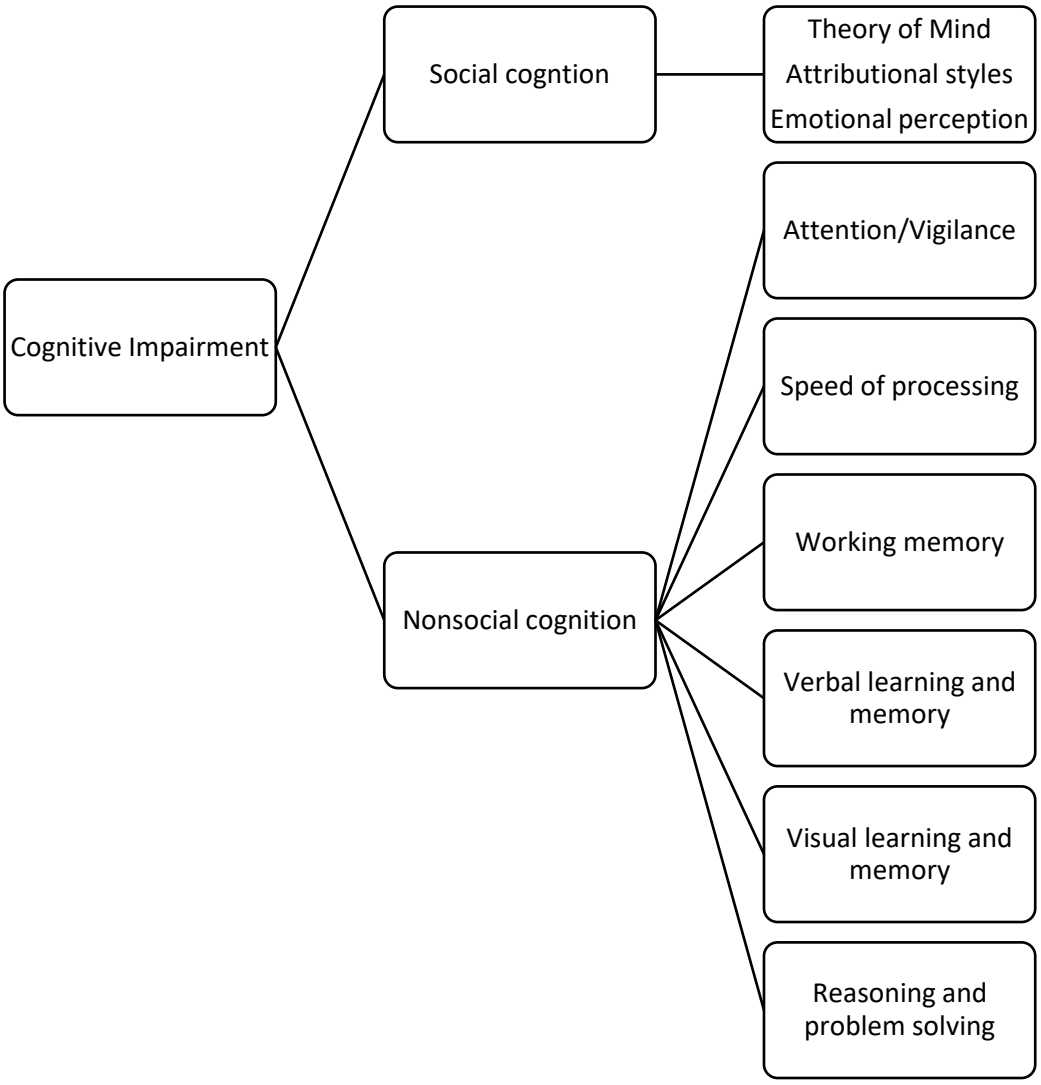

Figure 2: Classification of cognition in psychotic disorders

The MATRICS initiative also validated a standardized neuropsychological battery called the MATRICS consensus cognitive battery (27, 57). This battery is the gold standard for assessing cognitive impairment in psychotic disorders (4, 27, 58). It assesses cognitive impairment in the seven key domains selected by the MATRICS initiative. Neuropsychological assessment for psychotic disorders is categorized as "complete" if all seven domains are assessed or as "brief" if an assessment is limited to some domains only (6). Comprehensive neuropsychological tests such as the MATRICS consensus cognitive battery are broader in scope with superior reliability

and validity. These tests have been used infrequently in low resource settings (58, 59). The MATRICS consensus cognitive battery, for example, has no normative values for any African country, although there have been validation studies in low and middle-income countries such as Brazil and China (58, 60).

Various brief neuropsychological assessment measures have been developed for neuropsychological assessment in psychotic disorders (61). These brief assessments are typically used for screening before referral for comprehensive neuropsychological testing (59, 62). They differ from a comprehensive neuropsychological assessment in that they do not always assess for impairment in all the seven cognitive domains. While the brevity of such neuropsychological assessments is advantageous, their validity as screening measures is unclear (4, 27, 63-66). Brief neuropsychological assessments may vary in the tests administered, modes of administration, domains assessed, duration of assessments and psychometric properties (67). Many of these brief assessments like the Brief Assessment of Cognition in Schizophrenia (BACS) were developed according to the MATRICS initiative guiding principles (61). They assessed some of the seven key cognitive domains and used similar tests to the MCCB (68). Few of these brief tests have been validated for use in low resource settings (43).

Neuropsychological assessment for psychotic disorders in low resource settings

In selecting the seven cognitive domains and appropriate tests, consensus was built between experts from academia, pharmaceutical companies and science funders such as the National Institutes of health (69, 70). Unfortunately, there were few experts and limited literature from low and middle-income countries like Africa; where most patients with psychotic disorders reside (22, 71). To date there has also been limited use of the MATRICS battery in low resource settings. As such it is not clear if the domains commonly impaired in high income countries are similarly impaired in low resource settings. The psychometric properties of the MATRICS battery are not well described in low resource countries (35, 43, 58). Below the seven domains are reviewed while describing factors that may be important to consider while performing neuropsychological assessments in low and middle-income settings.

a) Speed of processing

Speed of processing domain refers to performing simple perceptual and motor tasks, quickly and efficiently, like adding up change (56, 72). Neuropsychological assessment of processing speed is critical because many other cognitive operations, such as encoding, and retrieval of memories are affected by this domain's impairments. Speed of processing is not related to intelligence and therefore is an important domain to assess for populations with low literacy levels like low-income countries. In literature from high-income countries, processing speed is the largest single cognitive domain impaired in psychotic disorders (73). It is also the cognitive domain most impacted by increased dosages of antipsychotic medication (74). This is important for low and middle-income countries as patients present late with severe illness often requiring higher antipsychotic dosages (66, 75). In neuroimaging studies of healthy individuals, speed of processing is closely related to the structural integrity of white matter tracts. For Schizophrenia, abnormal microstructure integrity of the white matter tracts of the left inferior longitudinal fasciculus and left inferior fronto-occipital fasciculus ae associated with deficits in processing speed (76). Genetic factors are associated with white matter integrity thus may have different presentation in low resource settings (77).

b) Attention/vigilance.

Attention/vigilance may be the foundation of other higher cognitive skills as attention deficits often impact other cognitive domains. Attention is the ability to detect relevant information, maintain focus on this crucial stimulus while ignoring irrelevant competing stimuli (26, 78). Attention comprises of two different constructs that comprise two domains. Selective attention is the process of attending to relevant and vital information while ignoring non-important information (79). Vigilance, also called sustained attention, involves maintaining concentration over prolonged periods like sitting through a school lecture (56, 78). The MATRICS consensus cognitive battery measures sustained attention/vigilance.

Neuroanatomical areas for selective attention and vigilance differ (80). Vigilance for example is controlled by the brain stem arousal systems while selective attention is controlled by networks in the parietal areas of the brain; both of which are linked to executive functions of the midline frontal/anterior cingulate cortex. While vigilance

requires adrenergic neurotransmitters the selective attention component is comprised mainly of cholinergic neurons (81). Psychotropic medication therefore plays a big role on neuropsychological performance of sustained attention/vigilance. Anticholinergic and benzodiazepines are frequently used in low and middle-income countries to manage antipsychotic side effect and aggression (82). Blocking the release of acetylcholine in the forebrain with GABAergic compounds like benzodiazepines impacts vigilance performance by acetylcholine efflux in the basal forebrain (83, 84). With often older (typical) antipsychotics used in low resource settings the impacts of these drugs and anticholinergic medications need to be considered during neuropsychological assessments. In healthy individuals, age may not impact attention/vigilance performance (85), but this is not the same in patients with psychotic disorders (78). It is vital to determine the impact of age on this domain in low resource settings as patients often present late, yet the illness begins early in late adolescence (15, 86).

c) Working memory

Working memory domain involves temporarily holding information over a brief period, for example, remembering the floor directed to by a receptionist (56, 87, 88). Working memory differs from episodic or long-term memory in that the stimuli is not transferred to long-term storage. Baddeley described four essential processes involved in working memory, and these included i) a short term buffer for visual information ii) a short term buffer for verbal information iii) manipulation and transformation of information in storage buffers (central executive) and iv); the episodic buffer which involves the integration of different types of information into a story (89). Visual and verbal short term buffers are controlled from occipital to temporal cortex supporting object recognition while the manipulation is controlled by a dorsal stream connecting the occipital with parietal cortex enabling spatial operations. The episodic buffer relies on the inferior parietal cortex, Broca's area, the supplementary motor association area and possibly the cerebellum (90). Atypical antipsychotic drugs, notably risperidone, and persistent memory exercises, improve working memory tasks (91, 92). These are not commonly available in low resource settings.

d) Verbal learning and memory

Verbal learning and memory domain refers to the ability to initial encoding and subsequent recall and recognition of words and other abstractions (e.g., stories, word pairs) involving language (56, 93). In recent literature, impairment in this domain in the psychosis prodrome has been associated with progression to overt psychotic disorders (94). In line with the Baddeley and Hitch model, verbal learning and memory are distinct working memory types (6). In literature from high-income countries earlier age of onset, more negative symptoms and higher doses of anticholinergic medication impact neuropsychological test performance in this domain (95). The impact of these factors on neuropsychological test performance in low resource settings is not well described. There are also sex differences in verbal learning and memory with females performing better than males in both healthy peers and patients with psychosis (96). With greater burden of psychosis in males in this setting (66), the burden of impairment in this domain would be important to determine to see if it differs from literature of high income countries.

e) Visual learning and memory

Visual learning and memory domain involves the initial encoding and subsequent recall and recognition of non-verbal information such as color, shape, movement and location (56, 97-99). It is also a distinct type of working memory. The literature on visual learning and memory in psychotic disorders as a distinct domain is limited (100). However, there are no associations between visual working memory deficits and age, diagnoses gender, duration of disease or positive syndrome in high-income countries while there are associations with low-educational level, and negative symptoms (91, 100, 101). Also, this is the domain that shows least improvement over the course of a psychotic illness (102).

f) Reasoning and problem-solving.

Reasoning and problem-solving refer to logical and strategic thinking to solve problems and attain goals like figuring out the shortest way to get through traffic when late for work (56). The prefrontal cortex (specifically the rostrolateral and right dorsolateral PFC) is responsible for reasoning and problem solving (103). The literature on reasoning and problem solving is scarce as it includes executive

functioning, which also involves working memory and attention vigilance. Reasoning and problem solving is associated with older age which is more prevalent in low resource settings given patients often present late for care. (104, 105).

g) Social cognition

Social cognition domain includes mental operations needed to perceive, interpret and process information for adaptive social interactions (20, 21, 106). It may present difficulties in identifying emotions, feeling connected to others, inferring people's thoughts and reacting emotionally to others (107). Social cognition has four main sub-domains of emotion processing, social perception, Theory of Mind and attributional style (108, 109). The neurocircuitry for neurocognition (six lower order domains) is different from social cognition, implying that it may require different treatment strategies. It is, therefore, an ideal domain to assess for in low and middle-income countries.

Emotion processing is the ability to perceive and use emotions. At a lower level lies emotion perception which refers to identifying emotions in voice or facial expressions. At a higher level, one must understand these emotions and manage these emotions or respond correctly to these emotions (106). Social perception is the ability to understand social cues. It involves understanding social norms and is essential to functioning in society (110). Theory of Mind refers to an individual's ability to make inferences about another person's intentions (111). Attributional style refers to the explanations people generate after positive or negative events in their lives (112). It is the ability to make sense of social events and interactions correctly.

Different brain regions are involved in the four social cognition networks. The dorsal anterior cingulate cortex and the anterior insula are involved in emotion processing (113, 114). The posterior superior temporal sulcus, the fusiform face area and the amygdala are responsible for social perception (115). The dorsomedial prefrontal cortex and the temporoparietal junction are responsible for theory of mind domains (116). The orbitofrontal cortex and ventromedial prefrontal cortex are responsible for attributional styles (117). Injuries in these different brain regions are responsible for the impairment in social cognition (113). Also, factors like infections, diets and childhood trauma may impact the functioning of these regions. For example, changes in the posterior superior temporal sulcus are associated with neglect (118).

Neuropsychological assessment in low resource settings.

Neuropsychological assessment is uncommon in first-episode psychosis patients from low resource settings. The few available studies had many methodological flaws. Most studies dis not assess for cognitive impairment in first-episode psychosis patients but rather in chronic psychosis patients (28, 64, 119, 120). In some studies, standardized measures were not employed to describe cognitive impairment. For example, a study among 100 participants with Schizophrenia in South Africa described self-reported clinical symptoms of cognitive impairment like poor memory and poor concentration (31). Another by Nakimuli et al in Uganda used the mini mental status exam which is more suited for screening for dementia in the elderly (33). The few studies that used standard neuropsychological measures had small sample sizes (121). They were also not designed to describe the burden of impairment which are crucial for driving policy interventions (122). Most studies were brief and assessed for impairment in selected domains so there is limited literature on studies in social cognition and visual learning and memory domains (123-125). There are few studies that have used the MATRICS consensus cognitive battery but many were limited by sample size (35). Finally, studies of normative values for low resource populations are lacking (126-128).

In studies using comprehensive batteries from high income countries, mean scores of healthy peers are two standard deviations higher than patients with psychotic disorders in both the general cognitive impairment and various domain scores (20). The impairment is often most significant in the speed of processing and verbal learning and memory (28, 29). The domains most impaired, the difference in mean scores to healthy peers in literature from low-income countries is lacking (125). It is possible there might be differences in low resource settings due to different social factors (level of education, wealth), genetics driven by different environmental exposures and clinical factors like greater illness severity. Limited literature from low resource settings limits planning for neuropsychological assessment as it is challenging to determine cut-offs, sensitivity and specificity of tests and what assessments to prioritize.

Importance of the first-episode of psychosis in neuropsychological assessment.

Patients with psychotic disorders often present at the first-episode of psychosis (129). Three main operational definitions for first-episode psychosis include 1) the first presentation at psychiatric services, 2) the first presentation of symptoms or 3) having

been on antipsychotic medication for less than six weeks duration (2). The latter definition is often preferred since antipsychotic medication is still the best treatment of choice for psychotic disorders (130, 131). In Uganda, most studies in Uganda have defined first-episode psychosis as the first presentation at psychiatric services (132, 133). The few studies that assessed for cognitive impairment in patients with psychotic disorders were in chronically ill patients and not first-episode psychosis patients (119) . However, an integrated socio-development cognitive model of psychosis (Figure 3) posits that multiple non-diagnostic symptoms including cognitive impairment may precede the clinical presentation of frank psychotic symptoms at the first-episode of psychosis (134).

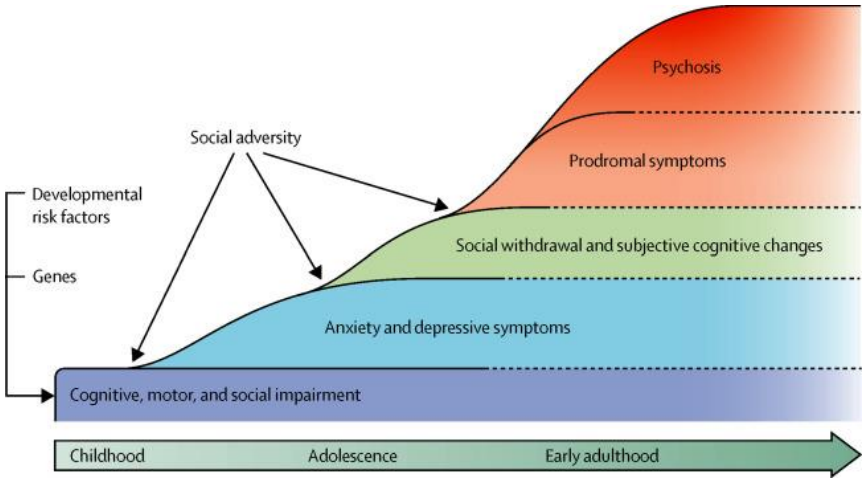

Figure 3: Change in cognitive symptoms across the lifespan (134)

Also, the course of cognitive impairment in psychotic disorders is such that there is little change in the burden and profile of impairment after the first-episode of psychosis (See figures 4).

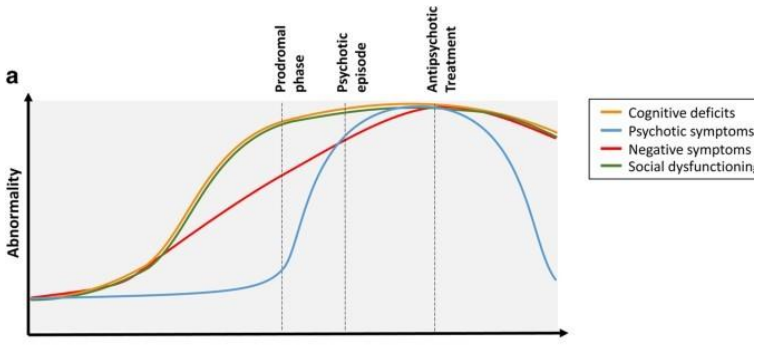

Figure 4: Cognitive deficits across the lifespan (1)

It is recommended that neuropsychological assessments are performed early at the first-episode of psychosis. Cognitive impairment in patients with a first episode of psychosis has been found to be a key predictor of functional outcomes and likelihood of recovery (14, 16, 135-137). Cognitive impairment also adversely affects long-term educational

achievement, work functioning and quality of life (138-140). However, in low resource settings there are high rates of disengagement from care (141, 142). Therefore, neuropsychological assessments must be performed early at the first episode of psychosis.

Patient factors affecting neuropsychological assessment.

Lezak described various factors in a population that might affect the performance of neuropsychological measures used in assessment (26). Most literature on environment and clinical factors that might affect test performance have been performed in high income countries (143-146). Below, I have reviewed a few of the factors that have been shown to impact neuropsychological assessment in high income countries. Assumptions on how they may affect test performance in low resource settings is made.

a) Childhood trauma and cognitive impairment

About 25% of children experience a traumatic event before the age of 18 years (147). These children who experience a traumatic event are more at risk of developing a psychotic disorder than their peers who did not experience a traumatic event (148). These traumatic events include sexual abuse, emotional abuse, physical abuse, emotional neglect, physical neglect, parental abuse and bullying (147, 149). Among patients with psychotic disorders who reported previous trauma, there were higher cognitive impairment rates (147, 150, 151). The literature of childhood trauma and cognitive impairment in patients with psychotic disorders is inconsistent (143, 152). A systematic review by Dauvermann et al. found that in 9 studies, specifically in patients with psychotic disorders, childhood trauma was associated with impairment in the social cognition domain (143). The association is more marked in patients with chronic psychosis illnesses than first-episode psychosis patients (153, 154). Previous childhood trauma may have an impact on neuropsychological test performance. In one study, lower trauma intensity was associated with high response inhibition on the Stroop test in patients with first-episode psychosis (155). However, the authors did not assess the impact of different trauma types and did not assess the impact of the trauma on different cognitive domains. This study was also not performed in a low resource setting where childhood trauma rates are higher compared to high-income countries (156).

b) Cognitive impairment and diet.

There is growing evidence to suggest that diet quality may be a modifiable risk factor for mental illness (157, 158). Diets rich in fruit and vegetables are associated with decreased pro-inflammatory cytokines and antioxidant and increased brain plasticity (159-161). Although the initial literature has primarily been in dementia and mood disorders, there is also increasing evidence for the impact of diet as an intervention for psychotic disorders (162). Specific to psychotic disorders, there is evidence to show that omega-three fatty acids may be associated with better cognitive performance (163, 164). For example, Mediterranean diets and green tea have been associated with better cognitive functioning (165), while carbohydrate-rich foods and especially cassava are associated with worse cognitive function. To our knowledge, no study has determined the association between specific diets and cognitive function in patients with the first-episode of psychosis from low and middle-income countries.

c) Antipsychotic dosages and neuropsychological test performance

In previous studies from high-income countries, antipsychotic medication was associated with more unsatisfactory neuropsychological test performance (166). This negative association was more in typical antipsychotics compared to atypical antipsychotics (167, 168). However, patients from low and middle-income countries often present late with severe illness requiring higher antipsychotic doses (75). There is also a larger proportion of patients on typical antipsychotics than atypical antipsychotic drugs (66). Literature from high-income countries has also highlighted that the impact of antipsychotic medication varies across the different cognitive domains. For example, Verdoux et al. showed that neuroleptics impact test performance of the digit symbol and Stroop colour naming tests but not the Wisconsin card sorting test (167). Literature that takes into account low resource setting contexts are required.

d) Illness severity and neuropsychological test performance

The presence of positive symptoms positively influences the timing of assessments of cognitive function. Assessments are performed when the active psychosis has resolved between the second and third months after initiation of treatment for psychosis (169, 170). Delaying assessment in patients who are already characterized

by poor health-seeking behavior and limited resources, may lead to a missed assessment. Current literature suggests that psychosis resolution may occur earlier in low resource settings like Africa (169). It is therefore useful to determine if doing the assessments earlier would affect neuropsychological test performance.

Health system factors affecting neuropsychological assessment.

Human resource shortages are common in mental health care (171). Even in high-income countries, neuropsychological assessment is not routine practice in care. Belgaied et al. assessed 61 psychiatrists in Europe and North America to assess their cognitive assessment knowledge for various severe mental illnesses, including Schizophrenia. This study found that few psychiatrists followed neuropsychological assessment guidelines, used patient histories rather than neuropsychological tests, and the tests used were not appropriate (172). The most considerable burden for psychotic disorders is in low and middle-income countries, yet there are few qualified mental health staff (22, 173). For example, Uganda currently has less than 50 qualified psychiatrists for a population of almost 50million people (174). The bed occupancy rate at the National psychiatric hospital of Uganda in 2018 was 149% (66). In this context with limited human resource and large patient numbers, it might not be feasible to perform a complete neuropsychological assessment. Novel ways to overcome human resource challenges for neuropsychological assessment are required.

The increasing use of mobile technologies worldwide offers an excellent opportunity for mental health practitioners to improve cognitive assessment in patients with psychotic disorders (38). Mobile health (mHealth) apps may ultimately improve standardization of neuropsychological assessments in patients with psychotic disorders (41, 175). These mHealth apps can overcome health system challenges like low numbers of qualified staff and large patient volumes that limit the assessment for cognitive impairment (66, 174, 176).They are also easy to use and would easily be adapted by the next generation clinical practitioners who are accustomed to working online. In high income countries, mHealth apps are already in use for symptom screening, assessment, and monitoring of symptom severity (37, 38, 177). These assessments are a means of providing health-related information, enhancing community support and facilitating early treatment (45). These mHealth applications are an emerging method of assessment for cognitive impairment and are already in use in settings like HIV/AIDS clinics (178).

Currently, there is limited use of mobile technologies for neuropsychological assessment in patients with psychotic disorders (179). A systematic review of 120 studies in both high and low income countries assessing verbal memory found that only 04 studies used digital technology for assessment (44). Studies validating these mHealth applications for neuropsychological assessment in patients with psychotic disorders are required (37, 45). mHealth apps may ultimately improve standardization of neuropsychological assessments (45, 178) as they may circumvent many of the inherent limitations of paper-based assessments. Some of the limitations of paper-based assessments include the human error in data collection, the time required to score the assessments and the burden of transporting and storing hard-copy questionnaires. Evidence suggests that mHealth apps are more efficient, accurate, accessible, and interactive than assessments delivered via pen and paper (38). The initial cost of acquiring mHealth applications are also affordable, and they generally require fewer financial and human resources than do computerized tests and comprehensive assessments (180). The collection of diverse data, including sociodemographic and phenotype characteristics, and cognitive performance variables such as reaction times is more straightforward with mHealth apps. mHealth applications may also be highly automated with standardized instructions and administrative procedures such as the neuropsychological tests scoring, enabling their use by less specialized research staff.

CHAPTER THREE: METHODOLOGY

In the previous chapter, existing literature on neuropsychological assessment for cognitive impairment in patients with psychotic disorders was reviewed. This chapter describes the general methodology used to answer the four aims of the thesis.

Study aims and hypotheses.

This thesis sought to address four specific aims.

Aim 1: To determine if the measures researched in patients with psychotic disorders from low and middle-income countries are appropriate for brief neuropsychological assessment.

> Hypothesis: The measures researched in patients with psychotic disorders from low and middle-income countries are inappropriate for brief neuropsychological assessment.

Aim 2: To compare the prevalence and profile of cognitive impairment between patients with a first-episode of psychosis and healthy peers in a low and middle-income country.

> Hypothesis: A large burden and differing profile of cognitive impairment would not be evident in the study sample. It is anticipated that the prevalence and profile of impairment will be like that seen in chronically medicated psychosis patients since in this setting patients often delay in initiating antipsychotic medication and have long durations of untreated psychosis (181-183).

Aim 3: To determine the association between clinical variables and impairment in specific cognitive domains in patients with psychotic disorders from a low and middle-income country.

> Hypothesis: No associations exist between clinical variables and impairment in different cognitive domains.

Aim 4: To determine the validity of the NeuroScreen (a collection of brief neuropsychological test delivered via smart phone) for brief neuropsychological assessment in patients with psychotic disorders.

Hypothesis: The NeuroScreen will not have the prerequisite sensitivity and specificity to identify CI in this study sample.

Methods for Aim 1:

To determine if measures researched in patients with psychotic disorders from low and middle-income countries are appropriate for neuropsychological assessment as defined by the Working Group on Screening and Assessment (WGSA).

Study design: A systematic review and meta-analysis was undertaken. The study protocol was first registered in the open-access online registry, PROSPERO, University of York, York, United Kingdom, registration number CRD42018047872. http://www.crd.york.ac.uk/PROSPERO/display_record.php?ID=CRD42018047872 .

Study selection: Exclusion and inclusion criteria were determined using the PICOSS (Population, Intervention, Comparator, Outcomes, Study design, Setting) framework (184). We considered articles written in English with no time limit on when the studies were conducted. The population of interest were participants with psychosis. Psychosis was defined as Schizophrenia spectrum and related psychotic disorders, bipolar affective disorder and depression with psychotic features. We selected these disorders, given the current literature that highlights their shared genetic and neurobiological underpinnings (185, 186). Although the thesis is primarily on first-episode psychosis patients, I wanted to compare assessments used in FEP and chronic psychosis patients to determine if they differ. The intervention included any study in which brief neuropsychological assessment was performed, i.e., assessed for cognitive impairment in less than seven cognitive domains. The comparator were healthy peers. Our outcomes included the measures used, whether they were validated against a gold standard, the domains they assessed, duration of assessments, cadres performing the assessments and if the assessments were performed early in the course of the illness. All study designs irrespective of sample size were included in the review. The review was limited to the low and middle-income country setting defined by the World Bank criteria (https://data.worldbank.org/region/sub-saharan-africa). We did this given the disparity in care between high income and low-income countries.

Data management: Data sources included (a) electronic search of databases, (b) search for grey literature (conference proceedings, clinical trial registers) and (c) using the reference bibliography of full-text articles to identify potentially relevant studies. The electronic search strategy followed the PICOS approach (Population, Intervention, Comparator, Outcome and Study design/setting), and was conducted in three databases, including PubMed, Embase and PsychINFO. The complete search strategy can be found in the appendices. The search strategy used Boolean logic to combine terms in the PICO framework. Full-text articles were saved into Endnote (187) and two authors screened the titles to determine which articles were eligible for the review in parallel. Consensus was applied to arbitrate in the event of disagreement. For each study, we abstracted the participants' clinical characteristics, including diagnosis, sex, and age. For each measure we then abstracted the name of the test, the domains assessed, duration of the assessment, mode of delivery (Paper, Computer, and Mobile App) and whether the measure had been validated against a gold standard. Studies with poor-risk of bias assessment were not excluded from the final analysis as we used statistical analyses (trim and fill method) to determine the extent of the bias.

Data Synthesis: Data were analyzed using Stata version 14 (188). Meta-analysis was not performed, and the review was limited to a narrative synthesis where words and text are used to summarize and explain the findings of the review (189). The criterion (a) of a measure being able to identify early on individuals at high risk for impairment was assessed by abstracting the clinical diagnosis to determine which measures were performed early at the first-episode of psychosis. The criterion (b) of a measure needing to be sensitive enough to determine those who need further review was assessed by determining if the measures had been validated against a comprehensive neuropsychological battery. The criterion (c) of a measure being brief and narrow in scope was assessed by the number of domains assessed and the assessment duration. The criterion (d) of a measure administered as part of a routine clinic visit was assessed by determining the setting (inpatient versus outpatient) in which the measure was performed. These settings were chosen since neuropsychological assessments are performed only on the resolution of psychotic symptoms which is often in outpatient, not inpatient settings (6). The criterion (e) of a measure being administered by clinicians or support staff with electronic devices was assessed by

determining the mode of delivery of the test (pen and paper versus computerized) and the person administering it. Finally, the criterion (f) of a measure able to monitor progress and outcomes was assessed by determining the studies that employed a longitudinal study design and those that assessed the quality of life in participants.

Methods for Aims 2-4

After the systematic review, an observational study was performed to answer aims 2-4. The observational study methods are discussed in general before specific data analysis plans for each aim are detailed.

Study site

Figure 5: Entrance to Butabika hospital.

The study was performed at the National Psychiatric Teaching and Referral Hospital of Uganda (Butabika Hospital) (Fig. 5). This 600-bed facility is in the central region of Uganda and serves both in-patients and outpatients. It has four acute admissions wards and a convalescent ward, in which patients with clinical resolution of symptoms are managed before discharge. On average, each ward has 150 beds with a bed occupancy rate of 149% (66). As a national referral hospital, it receives patients from various regions of the country. The hospital also provides care for non-psychiatric illnesses through outpatient clinics for antenatal care, HIV/AIDS, dental treatment and common infections like malaria. Approximately 200 patients are seen each day in the outpatient units the majority with psychotic disorders (66).

Study tools for sociodemographic, clinical and phenotypic variables

i) **Sociodemographic questionnaire:** Collected variables such as age, gender, the minimum level of education attained, diet, housing and employment status. Additional phenotypic data like ethnicity was also collected.
ii) **Mini-International Neuropsychiatric Interview (MINI) version 7.0 (190):** This is a semi-structured interview guide for DSM-5 diagnoses. It is validated for use in settings such as ours (33, 119, 191). Module A (major depressive episodes)

module C (mania and hypomania), Module K (psychotic disorders and mood disorder with psychotic features) confirmed the psychotic diagnosis. Modules I (alcohol use) and module J (other substances) excluded substance use disorders.

iii) **Child Trauma Questionnaire (CTQ) (192):** This 28-item questionnaire provides a quick screening method for childhood abuse and neglect that is administered in approximately 15 minutes (192). The abuse category describes sexual abuse, emotional abuse and physical abuse. The neglect category describes emotional neglect and physical neglect. It also includes a minimisation/denial scale for detecting individuals who may be underreporting traumatic events. This tool has previously been used in low resource settings like Nigeria, Swalziland and South Africa and the five domain structure has also been validated (193-195).

iv) **Positive and Negative Syndrome Scale (PANSS) (196):** This is a 30-item clinician-rated scale designed by Kay et al. to assess dimensions of the severity of both Schizophrenia and bipolar psychotic symptoms. Items are grouped into scales for Positive Symptoms (7 items), Negative Symptoms (7 items), and General Psychopathology (16 items). For our purposes, the tool determined if psychosis symptoms had resolved before administering the neuropsychological batteries. Only nine items of the PANSS describe symptom resolution, i.e. those assessing for delusions, conceptual disorganisation, hallucinatory behaviour, blunted affect, social withdrawal, lack of spontaneity, mannerisms and unusual thought content (14, 16, 197). The PANSS has been previously used in Uganda and has also been validated for use in low resource settings (198, 199).

v) **Additional clinical data:** Blood for HIV/AIDS and syphilis testing was collected by venepuncture into vacuum tubes containing ethylene diamine tetraacetic acid (EDTA). For HIV testing, a standard algorithm of three tests (Determine, Stat Pack and Tiebreaker) was used. At Butabika hospital, nurses screen all patients for HIV/AIDS at admission. This is done due to a high prevalence of HIV/AIDS in patients with severe mental illnesses (133). Counselling is done before returning the results to the patients. If a patient is HIV positive the clinician is also informed to begin care. Both the rapid plasma reagent and the venereal disease research laboratory (VDRL) were used to test acute and

chronic syphilis infection. Patient charts were reviewed to collect data on medication regimens and dosages.

Study tools for neuropsychological assessment

1.1 MATRICS consensus cognitive battery

The MATRICS consensus cognitive battery is recommended as the gold standard for assessing cognition in patients with psychosis (4) . It assesses for CI in all the seven cognitive domains of i) working memory, ii) attention/vigilance, iii) verbal learning and memory, iv) visual learning and memory, v) reasoning and problem-solving vi) information processing speed, and vii) social cognition (4, 27). The complete battery takes ninety minutes to administer, excluding the time needed to score. The MATRICS consensus cognitive battery was pretested and piloted for use in our study population before commencing the study.

The MATRICS comprises ten different neuropsychological tests that assess for impairment in seven different cognitive domains. The ten neuropsychological tests of the MATRICS were administered in the same order as described by Neuchterlein et al. (2008) and as listed in the procedure below. This order ensures that 1) start the battery with less cognitively taxing activities that are relatively straight forward and easy to understand, in order to facilitate participants' optimal test-taking performance; and 2) alternate verbal with nonverbal measures, thus aiming to alleviate processing burden and minimise interference among tests (4).

Tests of the MATRICS consensus cognitive battery (listed in the order performed)

1.1.1 Trail Making Test (TMT): Part A

This test is a brief, timed pen-and-paper test of visual tracking that involves connecting consecutive numbers arranged in different locations. During the test, the participant draws lines from one number to the next without lifting the hand from the paper. The primary score is computed as the time to completion of the test. The test is discontinued after 300 seconds (five minutes). Higher scores imply more unsatisfactory performance; thus, scores are reversed when calculating the domain

scores. Items required to perform this test include a stopwatch, respondents form, and pencil for the participant.

The trail making test has been used broadly through out Africa in neuropsychological assessment research especially in HIV/AIDS studies (200, 201). In Uganda, it has primarily been used in HIV/AIDS populations but also in patients with psychotic disorders (32, 202). The trail making test has not been validated for use in patients with psychotic disorders but in African patients with traumatic brain injury from urban centers, it has been shown to discriminate between patients and healthy peers .(203) Trail making tests are dependent on motoric speed and therefore extrapyramidal drug side effects may affect perfomance (26).

1.1.2 Brief Assessment of Cognition in Schizophrenia (BACS): symbol coding

This is a pen-and-paper test of processing speed that involves writing numbers that correspond to nonsense symbols as quickly as possible. A key shows which symbols correspond to which numbers. The participant is given random symbols and instructed to use the key to determine the corresponding numbers as quickly as possible within 90 seconds. The outcome measure is the total number of symbols that have been correctly corresponded to their numbers. Items required to perform this test are similar to TMT: Part A, above. The Brief Assessment of Cognition in Schizophrenia: symbol coding has not been used extensively in Africa except in SouthAfrica where it was used in studies using the MATRICS consensus cogntiive battery(36, 204). In these studies however it was able to discriminate the cognitive function between patients and helathy peers .

1.1.3 Hopkins Verbal Learning Test-Revised (HVLT-R)

This test is a measure of learning word lists (only the immediate recall component of the HVLT-R is included in the MATRICS). The assessor reads a list of words to the participant (from the test booklet), who must remember as many of the words as possible. This participant is allowed three trials with the total number of words recalled over the three trials the final score. The Hopkins Verbal Learning Test-Revised has been adapted for use in many langauges in many low and middle-income countries (205). In Africa, it has been used primarily in neuropsychological assessment in

research studies of HIV/AIDS with few studies in patients with psychotic disorders (128, 205, 206).

1.1.4 Wechsler Memory Scale-Third Edition (WMS-III): Spatial Span

The WMS-III: Spatial Span tests for working memory, assessing the participant's ability to remember the blocks' locations on a spatial span board (Fig. 6) to which the assessor points. The board has ten different cubes with one side of the cube numbered and the opposite side blank. The assessor positions the board facing him-/herself and the blank side is facing the participant.

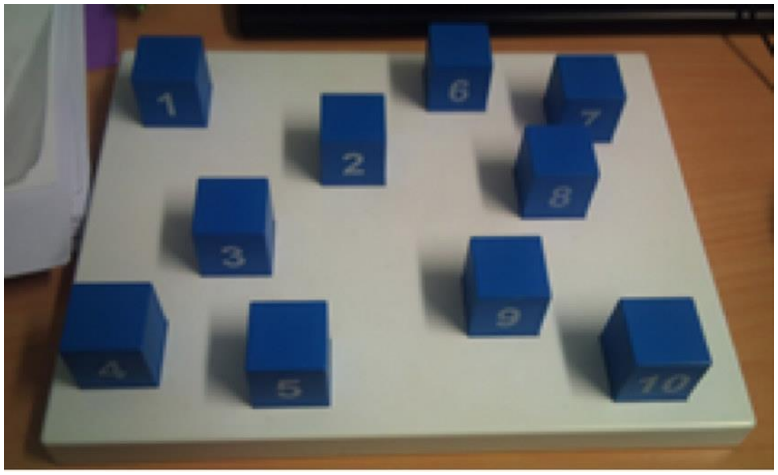

Figure 6: Spatial span board

For the spatial span forward test, the assessor indicates a predetermined sequence that the participant is required to reproduce. The number of cubes included is increased with each attempt until the participant fails to reproduce the sequence. The spatial span backwards test then commences. A similar process is followed, but participant is now required to indicate the cubes in a reverse sequence. The WMS-III: Spatial Span is discontinued if the participant fails trials of both the forwards and backwards spatial span. The primary score is the sum of raw scores on the forward and backward tests. The Wechsler Memory Scale-Third Edition (WMS-III): Spatial Span has extensively been used in African settings in patients with psychotic disorders (43, 119, 122, 126, 207-214).

1.1.1 Letter-Number Span (LNS)

This working memory task assesses both maintenance and manipulation of working memory and requires a mental reordering of orally presented lists and numbers. In the letter number span test, the assessor reads a list of numbers and letters to the participant. The participant is then required to recite the numbers from the smallest to the largest; followed by the letters in alphabetical order. The lists increase in the length of numbers and letters until a participant fails a sequence after four trials. The outcome

score is the total number of correct sequences. Most studies in low resource countries like Uganda have used the digit span test rather than the letter number span to assess for working memory (215). Although the tests are similar, the letter number span offers greater insights into the contributions of the various buffers of the working memory domain especially the visuospatial buffer (89, 216). The letter number span test has been used in a few studies on the African continent and was able to differentiate memory impairments between different diagnostic categories (125).

1.1.2 Neuropsychological Assessment Battery (NAB): Mazes

The Mazes is adapted from the NAB; and tests reasoning and problem-solving by assessing foresight, planning and impulse control. A participant is provided with several mazes, which should be completed as quickly as possible. There are seven mazes of increasing difficulty that the participant must complete within a set time. Each maze has a score awarded on completion within the set time. Failure to complete the maze within the set time, a score of zero for that maze is assigned. The seven individual maze scores are summed for the total raw score. Although the MATRICS consensus battery uses the mazes subtest, it has been found to be less sensitive than the Stroop test in patients with the first-episode psychosis (217). It was chosen as it easier to administer in clinical settings (4). Therefore, the mazes subtest has not been extensively used for assessment in patients with psychotic disorders.

1.1.3 Brief Visuospatial Memory Test-Revised (BVMT-R)

This test assesses immediate recall of six geometric shapes. The participant is given 10 seconds to look at the six shapes before drawing them from memory. This process is repeated over three trials and scored as follows.

-score of 2 if the shape is accurately drawn and accurately placed

-score of 1 if the shape is accurately drawn but incorrectly placed

-score of 1 if the shape is inaccurately drawn (though recognizable) and correctly placed

-score of 0 if the shape is not drawn or unrecognizable and incorrectly placed

The primary raw score is the total recall score over the three trials.

The Brief Visuospatial Memory Test-Revised has primarily been used in high income countries for psychosis research. Also, standardized norms for various populations are found for high income countries (127). Gender but not age impacted the

performance of BVMT-R in some high income countries (218). In settings like Uganda, the Brief Visuospatial Memory Test-Revised has not been used extensively in patients with Schizophrenia but rather in HIV/AIDS populations (128).

1.1.4 Category Fluency: Animal Naming (Fluency)

This test evaluates the spontaneous production of words from a specific category, thus assessing information processing speed. The participant names as many animals (domesticated and wild) as possible within a 60-second window. The primary score for this test is the number of animals mentioned in 60 seconds. The category fluency test has been used before in studies of patients with psychotic disorders (119, 182, 219). However, none of these studies validated its use in these populations. Two validation studies from Egypt among different populations produced inconsistent results. In one study among 79 healthy peers and 32 elderly patients, age and level of education had no effect on test scores (220). In another study among 139 healthy subjects, category fluency was influenced by age and education.

1.1.5 Mayer-Salovey-Caruso Emotional Intelligence Test (MSCEIT): Managing Emotions (D & H)

This test is a social cognition test that assesses emotions and solving emotional problems (8). Ten different scenarios test the participant's ability for emotional control. Scoring of the test requires computer software that outputs raw scores, adjusted and standard scores. For this study, raw scores were collated and later standardized using healthy peers (See Data Analysis, below).

Scores on this managing emotions subtest have been associated with positive symptoms of psychosis and quality of life (221, 222) Studies on the social cognitive domain have found positive correlations with processing speed, attention/vigilance and working memory (221).

1.1.6 Continuous Performance Test- Identical Pairs (CPT-IP), MATRICS International Version 2

This test is a computerized test that assesses for impairment in the attention/vigilance domain. The participant is required to press a computer mouse each time identical digits follow each other. There are three different tasks involving two digits, three digits and four digits. The test requires a computer running current operating systems and

software for the test that is purchased. This test has been used before in low resource settings (207, 212, 223). It has been validated for use in high income country settings and normative values are available for comparison (224). In one study from Japan, age, chlorpromazine-equivalent dose, and negative symptom score were associated with scores of patients (145).

1.2 NeuroScreen

This is a collection of brief psychological screening tests administered using a smartphone application (225). It assesses six cognitive domains - learning and memory, working memory, processing speed, motor speed and executive function. The NeuroScreen was also pretested and piloted for use in our study population before commencing the study. It has previously been used to assess for cognitive impairment in HIV/AIDS populations in South Africa and this was the first time validating it for use in patients with psychotic disorders (39, 42). Specific tests of the NeuroScreen are discussed below.

The NeuroScreen does not require extensive support from the research assistant or clinician. The research assistant is primarily an observer to ensure that the participant is doing the assessment rather than administering the tests. In some instances, however, the research assistant/ clinician handles the tablet to ask the test questions while other sections require the participant to answer the tests as shown on the NeuroScreen.

In this study assessment of the NeuroScreen was performed by non-specialized staff. These were research assistants (psychiatric clinical officers) who had received training in the administration of the NeuroScreen. The version used for this study had English and Luganda versions. Participants would decide if they preferred the assessment in English or Luganda.

The participant was introduced to the NeuroScreen by the research assistant. A brief overview included how the assessment is performed and the research assistant's role. The research assistant then registered the participant in the app by taking the participants biodata. The research assistant selected the tests to administer and the language before handing the tablet over to the participant.

1.2.1 Learning and memory: Five-word list

Verbal learning and delayed memory are assessed by a 5-item word list with two learning trials and a 5-minute delayed recall. For this test, the research assistant holds the phone and press play for the word list to be broadcast. After the app broadcasts the list, the research assistant asks the participant to mention the words he/she remembers and scores those that are correct. Scoring of the test was performed by the application automatically. Learning is scored by totaling the number of correctly recalled words across both learning trials. The minimum score for this assessment is 0, and the maximum score is 10. After five minutes, the NeuroScreen prompts the participant to recite as many of the words they remember. Again, the research assistant scores those remembered correctly. Scoring is also performed automatically by the app. It totals the number of correctly recalled words. The minimum score is 0, and the maximum score is 5.

1.2.2 Working memory: Number span test (forwards and backwards)

Working memory is assessed via a number span test (forwards and backwards). The application reads a pre-recorded string of digit. After, the patient is supposed to repeat the string mentioning as many numbers as they remember. The application starts with a string of 3 digits that increase up to a maximum of 9 digits. After two incorrect responses of any length of string, the task moves on to the number span backwards portion. The backwards span also starts with three-digit spans but has a maximum of 8 digit spans. A similar process followed is like the forward's test with the test ending after two-digit span failures. Scoring is done automatically by summing the longest forward and backward spans correctly to give a test score.

1.2.3 Processing speed: Visual discrimination and number input tests

The participant holds the tablet. The tasks include two timed visual discrimination tasks and a number input test. The first visual discrimination task has 61 items that require the participant to match a target shape to its correct number by tapping the number on the screen. The second visual discrimination task has 150 items and requires patients to determine if one of two symbols matches an array of symbols. Before the tests, the participants can practice once, and the research assistant ensures that they have understood the instructions. Each test is scored by summing the total number of

correctly answered items. The number input test involves participants entering sets of numbers as quickly as possible into a keypad on the NeuroScreen. As they enter the numbers, they turn green if correct and red if wrong. There are six trials in total, starting with a five-digit number that keeps increasing with each trial till the last trial with a ten-digit number. In the back end, the NeuroScreen records the completion time for each trial and the number of errors made while inputting the number. This test is scored by summing the completion times (in seconds) for each of the five trials. The maximum completion time allowed is 75-seconds.

1.2.4 Reasoning and problem solving: Trail making tests

Executive functioning is assessed two trail making type tests. Trail 1, participants use their finger to draw a line between numbered circles (1 – 8). The NeuroScreen automatically times how long it takes to complete the trial and systematically records any errors. The participant goes back to the last correct circle on making an error. The test is discontinued at 35-seconds with all discontinued tests recorded as the maximum completion time. Trail 2, the participant draws a line between numbered and lettered circles in ascending order. Again, the NeuroScreen automatically times how long it takes to complete and records any errors. Scores for this test are completion times (in seconds). The test is discontinued at 40-seconds with all discontinued tests recorded as the maximum completion time. Table 1 highlights the tests assessing for impairment in different cognitive domains across the two different neurocognitive batteries.

Table 1: A comparison of the tests used in the MCCB and the NeuroScreen.

Domain	MCCB	NeuroScreen
Verbal Learning and Memory	HVLT-R scores	5 word list (immediate and 5min recall)
Working memory	WMS®-III: Spatial Span Letter-Number Span	Number span forwards and backwards
Reasoning and problem solving	NAB mazes score	Trail making paradigm and number speed
Attention	Continuous performance tasks	Trail making paradigm
Processing speed	BACS: Symbol Coding Category Fluency: Animal Naming Trail Making Test: Part A	Symbol matching

Social cognition	MSCEIT	N/A
Visual learning and memory	BVMT-R scores	N/A

Translation procedures

Research tools were translated from English to Luganda, the commonest language in Uganda's central region (226). The central region is also the economic hub of Uganda and as such people from other regions are also often fluent in Luganda. Following translation to Luganda, tools were then back-translated to English to capture the correct constructs. For the NeuroScreen, specific terms required further adaptation, e.g. modifying "pear" to "mango" (a more common fruit in this study setting);" ocean" to "lake" (as Uganda is landlocked); and" scarf" to "cloth."

SAMPLE SIZE CALCULATION

Aims 2 and 3: Prevalence, profile and associated factors.

Sample size was calculated using Leslie Kish formula (227) for determination of sample size for descriptive studies of single proportions as follows:

$$N = \frac{Z^2pq}{D^2}$$

Where Z= Standard deviation at 95% confidence interval (1.96), P= Expected proportion of patients with both cognitive impairment at the first episode of psychosis, D= Precision of the estimate (5%), Q= 1-p and N= Sample size. P was 80% based on a study by Keefe and colleagues (9). We calculated a sample size of two hundred and forty five (245) participants.

The minimum sample size for associated factors by multiple regression was estimated using the A priori sample size estimation formula using fifteen predictors including age, gender, DUP, previous childhood adversity, handedness, level of education, alternative and complimentary treatment, welfare status and mean dosages. The anticipated effect size was 0.15 (228) with desired statistical power of 0.8 and a probability level of 0.05. This gave a minimum sample size of one hundred and thirty-nine (139) participants.

Aim 4: Validation of the Neuroscreen

Using Buderer's formula for estimating sample sizes in validation of medical tests (229) we estimated the prevalence of CI among patients with psychosis to be 80% (9). Precision was set at 10%, at 95% confidence intervals. The desired sensitivity of 80% and desired specificity of 90% were chosen because CI is common at FEP. The sample size calculated was 77 participants for sensitivity analyses and 173 for specificity analyses. The final sample size was 173 participants.

STUDY PROCEDURE

a) Recruitment and enrolment

In-patients in the four acute admission wards with a confirmed first-episode of psychosis were eligible for participation. Additional inclusion criteria were ages 18-60 years, able to give informed consent, HIV-negative status, and absence of syphilis or substance abuse. A cut-off age of 18 years for the first-episode of psychosis was applied to mitigate the challenges of CI assessment in adolescents versus adults. In Uganda, patients older than 60 years are deemed elderly (230) . Thus, these individuals were excluded from participation to eliminate potential effects of normal ageing and dementia. Participants with illnesses requiring urgent medical attention and those with physical deformities inhibiting their hands and fingers while performing the neuropsychological tests were also excluded.

b) Questionnaire administration

At Butabika hospital, all in-patients with a diagnosis of psychosis were eligible for recruitment. A study nurse assessed these patients to determine further eligibility for enrollment. Those found to be eligible were informed of the study before obtaining informed consent. A diagnosis of psychosis was confirmed using the MINI version 7.0. The MINI was also used to exclude substance use disorders; and sociodemographic characteristics and clinical symptoms assessed using the sociodemographic questionnaire and the (PANSS), respectively. Blood was drawn to test for HIV and syphilis, and participants with a confirmed diagnosis of psychosis and meeting no exclusion criteria included in the study. This initial assessment was completed within 72 hours of admission. After the initial assessment, patients were reviewed weekly for psychosis symptom severity using the PANSS until symptom resolution. Symptom resolution was defined as scores of 2 or less on nine selected items of the PANSS

(14, 16, 197). These patients then had additional data on previous adverse life events using the childhood trauma questionnaire (CTQ) obtained. Patients also underwent a neuropsychological assessment using the MCCB and NeuroScreen. Neuropsychological assessments were performed before 10am in the morning before administration of any medications by the nurses. For half of the patient group, the MCCB was administered first; with the NeuroScreen being administered first for the other half. Participants could train with the NeuroScreen for up to three times before formal assessment began. This training avoided bias due to some participants' having never used a smartphone. Finally, chart abstraction documented participants' medication regimen and dosages.

Neurocognitive assessments of healthy peers were also undertaken. These participants were recruited from the outpatient dental department at Butabika Hospital and assessed on the day of recruitment. Inclusion criteria for control participants were 1) no evidence of current or lifetime psychosis or substance use, as assessed by the MINI; and 2) no evidence of HIV/AIDS or syphilis. Healthy peers were matched according to age, gender and level of education with the FEP patients. Cases and controls received the same study tools except for the PANSS (administered to cases only).

DATA CURATION

a) MCCB scores.

Raw scores of the ten tests of the MCCB were first tested for normality. Scores of the mazes sub-test of the Neuropsychological Assessment Battery (NAB-mazes) and trail making test deviated from normal and were log-transformed. The trail making test was also reverse-scored, with lower scores suggesting more inferior cognitive function. Composite scores were generated for each of the seven domain scores by summing the raw scores of individual tests per domain. These composite scores were then transformed to z scores, using the means and standard deviations of the control group. Standardization was done based on age and level of education of the healthy peers as follows:

$$\text{Standardized score} = \frac{\text{(domain score - mean score of controls)}}{\text{standard deviation of the controls}}$$

Cognitive impairment throughout the thesis was categorized in different ways:

i) For aim 2, a global cognitive score was calculated. It was a categorical variable in which impairment was defined as mean standardized scores of 2SD below the mean in one domain or 1SD below the mean in more than one domain.

ii) For aim 3, domain specific impairment scores were calculated. These were continuous variables in which higher scores implied better cognitive functioning.

iii) For aim 4, a composite score of both the NeuroScreen and the MCCB were determined. They were summations of standardized scores for the domains of verbal learning and memory, attention/vigilance, speed of processing, working memory and reasoning and problem solving.

b) Diagnostic categories

For the patient diagnoses, participants with a diagnosis of Schizophrenia, Schizophreniform or Schizoaffective disorder were classified as having non-affective psychosis. Patients with diagnoses of bipolar mood disorder (irrespective of the phase) or with depression with psychotic features were classified as having affective psychosis.

c) Childhood trauma

For previous childhood trauma, negatively framed questions of the CTQ were recoded to positively framed questions (reverse scoring) so that higher scores implied higher trauma rates. Scores of the five domains of sexual abuse, physical abuse, emotional abuse, physical neglect and emotional neglect were computed. A minimization/denial score was also computed. Scores for the five abuse/neglect domains are categorized as low moderate and severe as low moderate and severe. For the minimization domain any score above 1 is classified as presence of minimization (149). This is shown in Table 2 below.

Table 2: Cut off scores for the various childhood trauma domains.

	Physical neglect	Emotional neglect	Sexual abuse	Physical abuse	Emotional abuse	Minimization/Denial
None	5-7	5-9	5	5-7	5-8	0
Low	8-9	10-14	6-7	8-9	9-12	1-3 categorized as presence of minimization or denial
Moderate	10-12	15-17	8-12	10-12	13-15	
Severe	13+	18+	13+	13+	16+	

d) NeuroScreen data

The NeuroScreen calculates raw scores in the backend. These results are then uploaded onto a secure server when the smartphone has an internet connection. These raw scores of the different tests of the NeuroScreen were downloaded. Where standardized scores were required the means and standard deviations of the control group were used basing on the on age and level of education.

DATA ANALYSES

Data was analysed using Stata version 14.0 (188). Detailed methods for data analysis for aim 2-4 are described below.

Aim 2: To compare the prevalence and profile of cognitive impairment between patients with a first-episode of psychosis and healthy peers in a low and middle-income country.

To determine the burden of impairment, participants with mean domain scores 2 standard deviations (SD) below the mean in one domain of the MCCB; or as 1SD below the mean in two or more domains (231) were classified as impaired. Descriptive statistics were employed for the prevalence and profile of CI for both a general cognitive impairment and in each cognitive domain. To determine the impairment in a specific domain, standardized scores of 2SD below the mean were defined as signifying CI. Student t-tests were used to determine if mean cognitive domain scores differed across the patients with psychosis and healthy peers. The level of significance for all analyses was set at 0.05.

Aim 3: To determine the association between patient variables and impairment in specific cognitive domains in patients with psychotic disorders from a low and middle-income country.

Composite scores were generated for each of the seven domain scores by summing raw scores of individual tests specific to each domain. Means and standard deviations of the domains were then calculated for the control group which was used to standardise the participant scores according to different age and gender categories of the health controls. After, regression coefficients for the various exposures with the seven different cognitive domains in patients with FEP were calculated while controlling again for gender and level of education.

Aim 4: To determine the validity of the NeuroScreen (a collection of brief neuropsychological test delivered via smart phone) for brief neuropsychological assessment in patients with psychotic disorders.

Standardized scores for the MCCB and NeuroScreen were calculated using the means and standard deviations of the healthy peers. Two composite scores for NeuroScreen and the MCCB were then computed. The composite score comprised of standardized scores for the domains of verbal learning and memory, attention/vigilance, speed of processing, working memory and reasoning and problem solving. To examine sensitivity and specificity of NeuroScreen, Receiver Operating Curve (ROC) scores at various cut-offs were computed using the standardized and categorized MCCB scores as the gold standard. The MCCB was our dependent variable. Scores less than 2sd below the mean (SD <-2) in a particular domain of the MCCB were categorized as impaired and categorized as 1 while those not impaired (SD>-2) were categorized as 0. Thereafter, positive predictive and negative predictive values, as well as sensitivity and specificity for the optimized NeuroScreen cut-off score were calculated. Multiple regression analyses were conducted to determine the impact of greater prevalence of affective psychoses (66), longer duration of untreated psychosis (129, 232-234), greater illness severity (235), higher antipsychotic dosages (236, 237), and more childhood trauma (148, 238) on the test scores of the NeuroScreen. To determine the discriminant validity Wilcoxon sign ranked tests were calculated for the difference of NeuroScreen test scores between cases and controls.

Concurrent validity was determined by calculating the Spearman's correlation coefficients between NeuroScreen and MCCB scores for each test.

Ethical considerations

Ethical approval was sought from the Human Research Ethics Committee (HREC) of the Faculty of Health Sciences, University of Cape Town (UCT) (#574/2017), the Ugandan National Council of Science and Technology (UNCST) (#HS142ES) and the School of Medicine Research and Ethics committee (SOMREC) (#REC REF 2017-153) of the College of Health Sciences, Makerere University. Institutional permission to carry out the study was also received from the administration of Butabika hospital. All approvals have been attached in the appendices.

Description of risks and benefits

Potential risks: Participants may have experienced distress when disclosing details of exposure to traumatic events or quality of life. However, we emphasized during the consenting process that participants were free not to answer questions that caused them distress or unease. In cases when this occurred the distress was managed by the clinical psychologists.

Benefits: There were no direct benefits to participant. Participants however had cognitive assessments done which are not part of routine care at the hospital.

Informed consent

Initial information about the study was provided by the attending psychiatrist and inpatient nurses. The consenting process was carried out by a study nurse. It was done in a private room and began with the study nurse explaining the aims of the study and re-iterating that enrollment is entirely voluntary, and consent may be withdrawn at any stage. Participants had an opportunity for questions, discussion and clarification during the consenting process. All study documents were translated into Luganda, which is commonly spoken in this region. Two consent forms were signed by each participant using a pen or a thumbprint for those unable to read or write. Participants were given one copy of the consent form on discharge and the other was stored as a study record. All research procedures were undertaken after the clinical psychiatric consultation so as not to disrupt the clinic routine.

Privacy and confidentiality

All study questionnaires were administered in a private room at Butabika Hospital. Participants were allocated a unique identification number that was linked to the clinical file number. Only the principal investigator (PI) had access to the identification code and the clinical file number simultaneously. All other study staff only had access to separate, de-linked identification information. All standardized data including sociodemographic variables, phenotypes, and assessment scores were collected using pen and paper records. These were stored under lock and key in a file cabinet in the research office provided for the study. NeuroScreen data was captured on a smart phone. This captured data was automatically deidentified and immediately synced to a password-controlled electronic database that was only accessible to the PI .

Storage and transportation of biological specimens

Blood drawn for HIV and syphilis diagnostic testing was managed by the National Reference Laboratories at Butabika Hospital. The laboratories were responsible for the storage and disposal of specimens. Only the test results of the participants were provided to the PI.

Participant reimbursement

Patients were reimbursed $3 (approximately ZAR 40) for their time, either on completion of the full study assessment or when consent was withdrawn. This amount was approved by the UNCST for reimbursement.

Funding Support

This PhD study was funded by the Neuro-GAP psychosis study (191). The NeuroScreen was provided by Professor Reuben Robbins of the University of Columbia, New York, USA.

Role of the PhD candidate

According to the Contributor Role Taxonomy (CRediT) guidelines (239), the following were my contributions to the thesis

a) ***Conceptualization***: Together with the supervisors developed the concept for the study.

b) ***Methodology***: I received formal data methodology training from the Global Initiative for Neuropsychiatric Genetics Education in Research (GINGER) program https://ginger.sph.harvard.edu/. With support from the program, I learnt how to select the appropriate research methods for the study.

c) ***Validation***: I checked the original data entered at the end of each clinic day. I also validated the data entry and results.

d) ***Formal analysis:*** I performed the systematic review analysis following training from the Africa Centre for Systematic Reviews & Knowledge Translation https://chs.mak.ac.ug/afcen/center-team . I received formal data analysis training from the GINGER program. The skills garnered allowed me to perform all bivariate analyses unaided. I was assisted by a statistician in building statistical models for regression analyses. Staff in the GINGER program was also consulted on data analysis methods.

e) ***Investigation:*** Data collection was performed by research assistants and clinical psychologists. My role was to confirm the study participant diagnoses using the MINI International Neuropsychiatric Inventory. I also confirmed severity of patient illness weekly prior to formal cognitive testing.

f) ***Data Curation:*** I supervised the data curation process that led to the dataset used for analysis.

g) ***Writing - Original Draft***: I wrote the original first draft of the thesis.

h) ***Writing - Review & Editing:*** After changes suggested by the supervisors, I edited the first draft till this final draft was developed.

i) ***Visualization:*** Figures and Tables were created with the help of a statistician.

j) ***Supervision:*** I supervised research activities like participant enrollment, chart abstraction and participant reimbursement.

k) ***Project administration:*** I was responsible for ensuring the project run smoothly and according to ethical guidelines.

l) ***Funding acquisition*** was done by the supervisors.

m) ***Software development*** was through collaboration with Dr. Reuben Robbins of the HIV Center for Clinical and Behavioral Studies, New York State Psychiatric Institute and Columbia University Medical Center.

In chapter 3, the methods of the thesis were described. This next four chapters (4-7) present the research studies undertaken to achieve the study aims. Each of these chapters will address a particular aim. The chapters will include a background and an abridged methods section before presenting the results and a discussion.

CHAPTER 4: A SYSTEMATIC REVIEW OF NEUROPSYCHOLOGICAL ASSESSMENT MEASURES FOR PSYCHOTIC DISORDERS IN LOW RESOURCE SETTINGS.

This chapter has already been published in the journal of Schizophrenia Research: Cognition *(Schizophr Res Cogn. 2020 Aug 24;22:100187. doi: 10.1016/j.scog.2020.100187. eCollection 2020 Dec.)*. It is a systematic review that examined the measures researched in studies of patients with psychotic disorders from low and middle-income countries to determine if they are appropriate for brief neuropsychological assessment. It highlights previous research on neuropsychological assessment in patients with psychotic disorders. This helps highlight the shortcomings for neuropsychological assessment in low resource settings.

Introduction

The Working Group on Screening and Assessment (WGSA) in 2014 described guidelines for a measure to be appropriate for brief neuropsychological assessment (59). Briefly the guidelines state that the measure must be: a) able to identify early on individuals at high risk for impairment, b) be sensitive enough to determine those who need further review; c) be brief and narrow in scope d) be administered as part of a routine clinic visit; e) be administered by clinicians or support staff or with electronic devices and; f) may be used to monitor progress and outcomes (59). Many measures in use have primarily been selected for brief neuropsychological assessments due to their brevity (4, 27, 63-66). While this is an added advantage, it is not enough to justify them as appropriate for use (40).

To our knowledge, there is no review of the literature that has summarized the measures researched in studies of brief neuropsychological assessment in patients with psychotic disorders from low and middle-income countries to determine if they are appropriate (65, 240). It is unclear if the measures used have been compared against a gold standard to assess their sensitivity and specificity. The domains assessed and the duration of assessment of these measures is also unclear (67). For example, while the brief neuropsychological assessment (BNA) test assesses for impairment in the domains of working memory and processing speed (62, 241), the Brief Cognitive Assessment Tool for Schizophrenia assesses for impairment in the domains of reasoning and problem solving as well as memory and processing speed

(241). There has been no review to determine if the measures researched in studies of brief neuropsychological assessment in patients with psychotic disorders from low and middle-income countries are appropriate. As such there is lack of clarity on who, where and how these measures are administered as well as if they can be used in long term follow up assessments.

The available literature addressing neuropsychological research in psychotic disorders in low- and middle-income countries was systematically reviewed to determine if the measures used in this research meet the WGSA guidelines. Standard systematic review methods were used to determine the characteristics of the patients receiving the measures, whether the measures had been validated against a gold standard, the domains they assessed, duration of assessments, cadres performing the assessments and if the assessments were repeatedly performed.

Methods

These were previously described in chapter 2 of the methods. Briefly the **study design** was a systematic review and meta-analysis that was registered before beginning the review http://www.crd.york.ac.uk/PROSPERO/display_record.php?ID=CRD42018047872

Study selection was determined using the PICOSS(Population, Intervention, Comparator, Outcomes, Study design, Setting) framework (184). We considered articles written in English with no time limit on when the studies were conducted in which the p**opulation** of interest were participants with psychosis. The i**ntervention** included any study in which brief neuropsychological assessment was performed i.e., assessed for cognitive impairment in less than seven cognitive domains. The **comparator** were healthy peers. Our **outcomes** included the measures used, whether they had been validated against a gold standard, the domains they assessed, duration of assessments, cadres performing the assessments and if the assessments were performed early in the course of the illness. All **study designs** irrespective of sample size were included into the review. The review was limited to low and middle-income country **setting** as defined by the World Bank criteria (https://data.worldbank.org/region/sub-saharan-africa).

Data management involved searching three data bases including PubMed, Embase and PsychINFO. The search strategy used Boolean logic to combine terms in the PICO framework. Full text articles were saved into Endnote (187) and two authors screened the titles to determine which articles were eligible for the review in parallel. For each study we abstracted the clinical characteristics of the participants including diagnosis, sex and age. For each measure we then abstracted the name of the test, the domains assessed, duration of assessment, mode of delivery (Paper, Computer, and Mobile App) and whether the measure had been validated against a gold standard. Studies with poor risk of bias assessment were not excluded from the final analysis as we used statistical analyses to determine the extent of the bias. The complete search strategy can be found in the appendices.

Data Synthesis involved determining whether a measure met the WGSA criteria. The criterion (a) of a measure being able to identify early on individuals at high risk for impairment was assessed by abstracting the clinical diagnosis to determine which measures were performed early at the first-episode of psychosis. The criterion (b) of a measure needing to be sensitive enough to determine those who need further review was assessed by determining if the measures had been validated against a comprehensive neuropsychological battery. The criterion (c) of a measure being brief and narrow in scope was assessed by the number of domains assessed and the duration of the assessment. The criterion (d) of a measure administered as part of a routine clinic visit was assessed by determining the setting (inpatient versus outpatient) in which the measure was performed. The criterion (e) of a measure being administered by clinicians or support staff with electronic devices was assessed by determining the mode of delivery of the test (pen and paper versus computerized) and the personnel administering it. Finally, the criterion (f) of a measure able to monitor progress and outcomes was assessed by determining the studies that employed a longitudinal study design as well as those that assessed quality of life in participants.

Results

A search was made in three databases on the 18th of October 2018. After removal of duplicates, eligible titles and abstracts were screened according to the inclusion criteria until a final list was agreed upon. The process is highlighted in figure 7.

29 studies were included into the final analysis. The articles were published between 1994 and 2018 with the majority (14/29) published between the years 2000 and 2010. Six (06) studies were from Central and South American countries, twelve (12) were from Asian countries and eleven (11) were from African countries. South Africa had the highest number of individual studies making up 7 of the 29 studies.

Results of individual studies.

a) Study setting and population.

In total, the review included 3,184 participants with psychosis and 1,261 controls. 23 studies were conducted in an outpatient population, 05 carried out among in-patients and 01 in both outpatient and inpatient populations. Three studies were carried out in first-episode psychosis participants. The different diagnostic characteristics of the participants are shown in Table 3.

PRISMA 2009 Flow Diagram

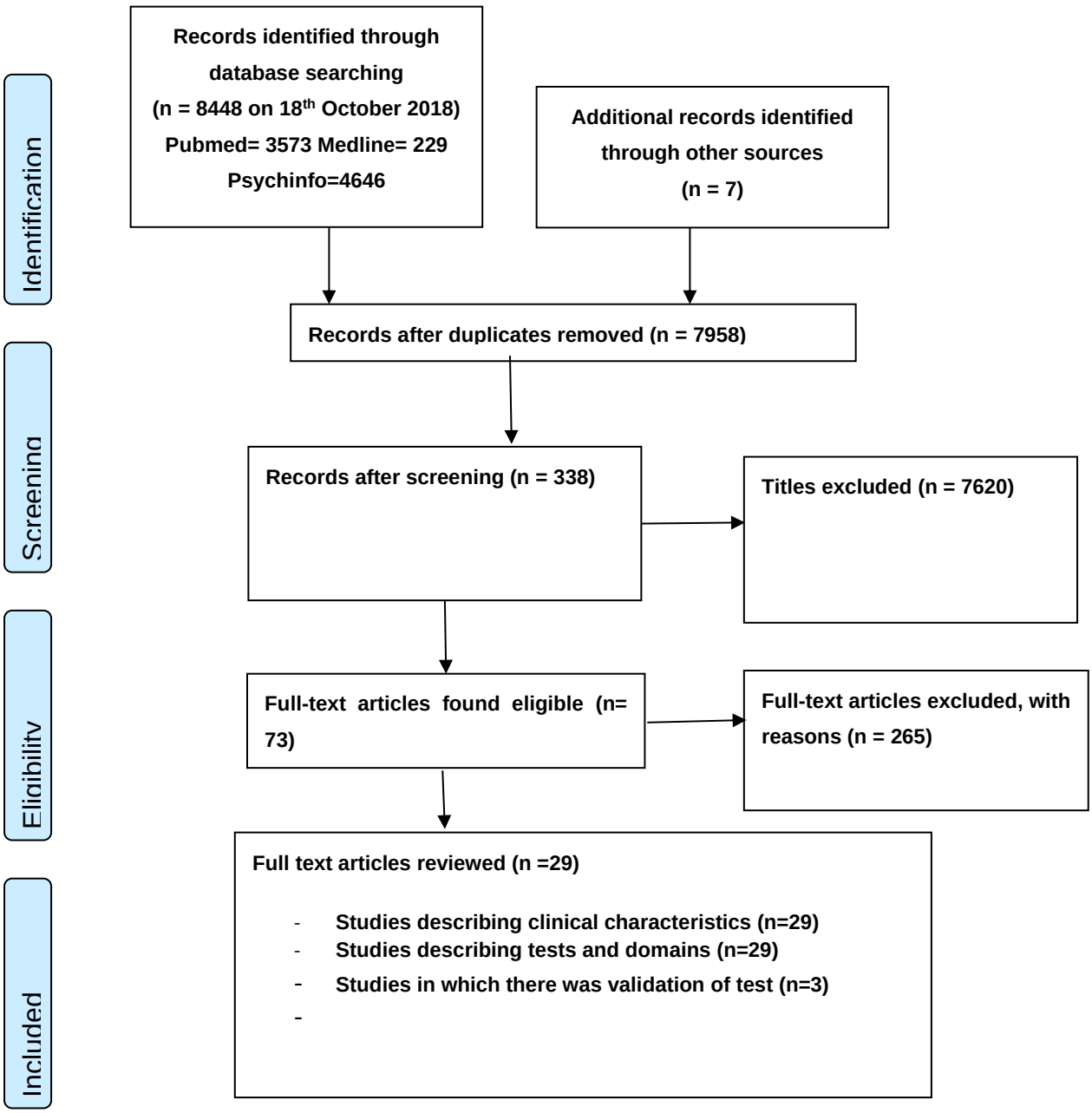

Figure 7: Article selection using PRISMA guidelines.

Table 3: Summary of studies included in the review.

Year	Author	Country	Study Design	Population	race	Total number of participants	Diagnostic type	Number
2009	Savitz	South Africa	CS	Outpatient	Caucasian	110	BPD with Psychosis	25
							BPD without psychosis	24
							HC	61
2017	Hendricks	South Africa	CS	Inpatient	Caucasian	29	Alcohol induced psychosis	13
							Alcohol use	16
1994	Gureje	Nigeria	CS	Inpatient	Black	128	Schizophrenia	43
							Mania	32
							HC	53
1997	Mattson	South Africa	CS	Outpatient	Caucasian	40	Schizophrenia positive symptoms	20
							Schizophrenia negative symptoms	20
2009	Ngoma	Democratic Republic of Congo	CS	Inpatient	Black	341	HC	153
							Brief Psychotic Disorder	68
							Schizophreniform	50
							Schizophrenia	70
2002	Harvey	South Africa	CS	Outpatient	Caucasian	29	Schizophrenia English speaking	5
					Black		Schizophrenia Afrikaans speaking	24
2008	Leppanen	South Africa	CS	Outpatient	African	81	Psychosis	36
							Siblings	23
							HC	22
2006	Leppanen	South Africa	CS	Outpatient	Black	84	Schizophrenia	44
							HC	40
2012	Nakasujja	Uganda	Longitudinal	Inpatient	Black	483	Mania	312
							Psychosis NOS	16
							Schizophrenia	100
							Depression	55
2008	Savitz	South Africa	CS	Outpatient	Caucasian	230	HC	65
							BPD I	49
							BPD II	19

2018	Sagar	India	Longitudinal	Outpatient	Oriental	178	BPD depressed	36
							BPD manic	41
							BPD euthymic	52
							HC	49
2005	Aleptekin	Turkey	CS	Outpatient	Caucasian	69	Schizophrenia	38
							HC	31
2015	Arau´ jo	Brazil	CS	Outpatient	Caucasian	174	Schizophrenia	116
							HC	58
2007	Ayres	Brazil	CS	Outpatient	Caucasian	553	Schizophrenia	98
							BPD	41
							Depression with psychosis	31
							HC	383
2010	Cabral-Calderin	Cuba	Longitudinal	Outpatient	Caucasian	68	Schizophrenia	34
							HC	34
2017	Charernboon	Thailand	CS	Outpatient	Oriental	72	Schizophrenia	36
							HC	36
2009	Ayres	Brazil	CS	Outpatient	Caucasian	160	Schizophrenia	56
							Affective psychosis	34
							HC	70
2002	Ertugrul	Turkey	Case control	Outpatient	Caucasian	90	Schizophrenia	60
							HC	30
2011	Guo	China	Longitudinal	Outpatient	Oriental	698	Schizophrenia	578
							Schizophreniform	120
2014	Heeramun-Aubeeluck	China	Longitudinal	Outpatient	Oriental	101	FEP	101
2016	Hou	China	CS	Outpatient	Oriental	80	FEP	40
							HC	40
2011	Mehta	India	CS	Outpatient	Oriental	18	Schizophrenia	9
							HC	9
2014	Okasha	Egypt	CS	Outpatient	Black	90	BPD	60
							HC	30
2008	Pradhan	Brazil	CS	Outpatient	Caucasian	103	BPD	48
				Inpatient			Schizophrenia	32
							HC	23
2013	Santosh	India	CS	Outpatient	Oriental	100	Schizophrenia	100
2008	Schneider	Brazil	CS	Outpatient	Caucasian	94	BPD	66
							HC	28
2016	Tang	China	CS	Outpatient	Oriental	148	Schizophrenia	94
							HC	54
2007	Trivedi	India	CS	Outpatient	Oriental	45	BPD	15

							Schizophrenia	15
							HC	15
2017	Zhou	China	Longitudinal	Inpatient	Oriental	49	FES	32
							HC	17

FES=First-episode Schizophrenia, **HC**= Healthy peers, **BPD**=Bipolar Affective Disorder, **FEP**= First-episode Psychosis, **NOS**= Not Otherwise Specified

a) Characteristics of the patients.

The mean age for participants was 34.4 years (SD 9.25) which was not statistically different from the mean age of the healthy peers of 35.0 years (SD 0.74). Most of the participants had at least 11.99 years (SD 3.25) of education compared to 12.71 years (SD 3.82) in the healthy peers [Mean difference -0.74 (95%CI -0.8206999-1.6007; p-value 0.06]). The mean age of illness onset was 26.3 years (SD 7.6). The mean intelligence score on Wechsler Adult Intelligence scale was 92.43 (SD 10.6) for the participants and 105.5 (SD 13.8) for the healthy peers. On the Positive and Negative Signs and symptoms of Schizophrenia scale the mean severity total score was 65.96 (SD 13.98). The mean antipsychotic dosage of the participants was 588. 8 CPZeq (SD 347.1).

For the studies that reviewed participants early at the first-episode of psychosis the mean age of the participants was 26.3 years (SD7.2). Other sociodemographic and clinical measures are shown in Table 4.

Table 4: Clinical and sociodemographic characteristics of participants and controls.

Author	Psychosis severity Rater	Psychosis severity [MEAN (SD)]	Age of participants (Mean/SD)	Age of healthy peers (Mean/SD)	Age of onset of illness (Mean/SD)	Female gender in participants (%)	Female gender in healthy peers (%)	Number of years of education in participants (MEAN)	Number of years of education in healthy peers (MEAN/SD)	Intelligence test	Intelligence Score in participants (MEAN/SD)	Intelligence score in healthy peers (MEAN/SD)
Savitz,2009	ASRM	3.45 (3.6)	48 (14.9)	50.7 (18.9)	27.3 (11.1)	48	46	15.3 (2.3)	15.6 (3.7)	Wechsler Adult Intelligence Scale - General Knowledge subtest	11.3 (1.5)	11.1 (1.7)
Hendricks,2017	NR	NR	37.07	37.5	35.7	7.7	12.5	8.08	11.81	NR	NR	NR
Gureje, 1994	PANSS	NR	28.5	27.1	24.6	36	53	12.3	14.6			
	BPRS	NR								NR	NR	NR
Mattson, 1997	PANSS	36.19	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR
Ngoma, 2009	PANSS	60.14 (14.3)	28.14 (7.1)	28 (7.1)	27.3 (6.7)	54.7	57	-	-	NR	NR	NR
Harvey, 2002	NR	NR	26.3 (4.6)	-	-	46				NR	NR	NR
Leppanen, 2008	NR	NR	38.9 (11.7)	40.9 (10.3)	NR	46.5	50	5.9 (3.0)	6 (3.1)	NR	NR	NR
Leppanen, 2006	SAPS	3.8 (4)	36.4 (11)	37.1 (9.6)	22.5 (5.5)	32.4	17.5	NR	NR	NR	NR	NR
Nakasujja, 2012	YMRS		30.31 (8.33)			42.3					NR	NR
	BPRS											
	BPRS											
	PHQ			-	-		-	-	-	NR		
Savitz, 2008	ASRM	2.72 (2.93)	47.75 (15.3)	50.11 (19.5)	26.8 (13.12)	-	-	14.8 (3.4)	15.19 (3.77)	South African Wechsler Adult Intelligence Scale (SA-WAIS) General Knowledge subtest	11.2 (1.7)	11.13 (1.7)

Sagar, 2018	YMRS (Median)	23.5	33.81 (12.1)	27.31 (4.47)	22.7 (8.06)	24.4	10.2			Verbal adult intelligence scale	91.54	99.52
	BPRS (Median)	6.67										
	HDRS (Median)	5.3										
Aleptekin, 2005	PANSS	66.28 (14.83)	37 (10.3)	38.13 (13.9)	24.96 (7.56)	39.5	58.1			NR		
Arau´ jo, 2015			38.5	39.1		48.3	55.4	8.02	7.62	NR		
Ayres, 2007			32.2 (11.4)	32.1 (11.3)	30.1 (11.8)	52	52.7			NR		
Cabral-Calderin	PANSS	66.41	34.97	34.97	25.74	44.2	47.06	12.7	12.85	NR		
Charernboon, 2017	PANSS		37.1 (11.2)	37.1 (12.1)		55.6	72.2	13.8 (3.7)	13.8 (4.2)	NR		
Ayres, 2009			29.6 (8.4)	31.76 (8.7)	26.6 (8.7)	35.7	45.7	9.95 (3.3)	11.2 (4.2)	Wechsler Abbreviated Scale of Intelligence	-0.36	
Ertugrul, 2002	PANSS	60.9 (17.2)	34.4 (11.1)	34.4 (10.6)	23.2 (6.4)	46.7	46.7					
Guo, 2011	PANSS	44.9 (14.7)	26.18 (7.4)			46.5		12.5 (2.81)				
Heeramun-Aubeeluck, 2014			26.4 (7.0)			51		12.8 (3.1)				
Hou, 2016	PANSS	76.1 (9.6)	26.4 (6.5)	24.4 (5.1)		40	52.5	26.4 (6.5)	24.4 (5.1)			
Mehta, 2011			30 (1.2)	29 (1.0)		33	33	9.9	10.3			
Okasha, 2014	YMRS		27.0 (5.7)	25.8 (3.9)		66.7	33.3	12.8 (3.2)	13.9 (2.7)	Wechsler Adult Intelligence Scale	97.3 (7.0)	112.5 (11.5)
Pradhan, 2008	PANSS	37.0 (4.63)	35.4 (10.7)	37.4 (12.3)	28.2 (10.5)	31.3	43.5	13.6 (2.4)	15.5 (2.7)	Wechsler Adult Intelligence Scale	93.5 (15.0)	106.0 (15.3)
Santosh, 2013	PANSS	2.6 (0.7)										
Schneider, 2008	YMRS	3.01 (2.6)	43.7 (11.9)	35.1 (14.1)		72.7	42.9	10.6 (3.6)	12.2 (3.0)	Wechsler Adult Intelligence Scale	86.5 (9.8)	98.6 (14.6)
Tang, 2016	BPRS	29.2 (3.7)	47.6 (6.4)	47.6 (10.1)	22.2 (2.74)			8.8 (2.2)	10.1 (3.2)			
	SAPS	9.8 (4.7)										
	SANS	41.6 (13.3)										
Trivedi, 2007			34.7 (10.5)	34.3 (11.2)		20	20	11.7 (3.7)	10.8 (2.5)			
Zhou, 2017	PANSS	41.8 (5.9)	26.2 (8.1)	25.5 (5.6)		31.6	23.5	13.5 (2.2)	12.6 (2.3)			

b) Measures used, duration of assessments, domains assessed and personnel providing tests.

Briefly, most assessments were performed by a neuropsychologist; or by trained research assistant/ graduate trainee. Only three studies (Savitz et al, 2009; Savitz et al, 2008; and Harvey et al, 2002) used nonspecialised health professionals like nurses. The average time taken to complete the assessments was 1.8 hours. Only four out of the 29 studies used computerised assessments. More results in Table 5 below

Table 5: Summary of tests used, domains they assess, duration and who performed test.

Author	Subtest/Scale/Battery	Domains assessed	Administration Time (Hours)	Mode of Delivery	Person administering test	Training received
Savitz, 2009	Digits span	WM, AV, VLM, RP, IP	1	Pen and paper	Neuropsychologist	NR
	Controlled Oral Word Association Test (COWAT)				Psychiatric nurse	Yes
	Rey Complex Figure (RCF)				Graduate students	Yes
	Stroop Colour and Word Test					
	Rey Auditory Verbal Learning Test (RAVLT)					
	Wisconsin Card Sorting Test (64 card version)					
Hendricks, 2017	Controlled Oral Word Association Test (COWAT)	VLM, AV, IP, WM, VSM, RP	NR	Pen and paper	Neuropsychologist	NR
	Trail Making Test					
	Rey Auditory Verbal Learning Test (RAVLT)					
	Visual Reproduction Trails					
	Rey Complex Figure (RCF)					
	Rey 15 Item					
	Wechsler Adult Intelligence Scale (WAIS) (South African)					
	clock drawing test					
Gureje, 1994	Verbal memory	VLM, RP, WM, AV	NR	Pen and paper	Neuropsychologist	NR
	Verbal fluency					
	Design fluency					
	Wechsler Adult Intelligence Scale (WAIS) (Performance subtests)					
	Wechsler Adult Intelligence Scale (WAIS) (Verbal subtests)					
Mattson, 1997	Rey Auditory Verbal Learning Test (RAVLT)	VLM, RP, IP, AV	NR	Pen and paper	Clinical psychologist	NR
	Wisconsin Card Sorting Test (Modified)					
	Austin Maze					
	Rey Complex Figure (RCF)					
	Controlled Oral Word Association Test (COWAT)					
	Trail making test					
	Stroop Colour and Word Test					
Ngoma, 2009	Rey 15 Item	VLM, VSM, WM, AV, MS, RP	NR	Pen and paper	Clinical psychologist	NR
	Rey Complex Figure (RCF)					
	Letter number sequence task					
	Test of attention					
	Trail making test					

	Motor speed					
	Controlled Oral Word Association Test (COWAT)					
	Stroop Color and Word test					
	Wisconsin Card Sorting Test (256 version)					
	Trail making test					
Harvey, 2002	Wechsler Memory scale (revised)	WM, VLM, AV, IP, RP	NR	Pen and paper	Research assistants	YES
	Rey Auditory Verbal Learning Test (RAVLT)					
	Continuous performance test (IP version)					
	Verbal fluency					
	Wechsler Adult Intelligence Scale (WAIS)					
	Wisconsin Card Sorting Test					
Leppanen, 2008	Facial affect recognition	social cognition	NR	Computer	NR	NR
Leppanen, 2006	Facial affect recognition	social cognition	NR	Computer	NR	NR
Nakasujja, 2012	WHO UCLA Auditory verbal learning test	VLM, AV, WM, RP, IP	NR	Pen and paper	NR	NR
	Symbol digit modalities test					
	Verbal fluency					
	Wechsler Adult Intelligence Scale version III (WAIS)					
Savitz, 2008	Wechsler Adult Intelligence Scale (WAIS)	AV, WM, VLM, VLM, IP, RP	1	Pen and paper	Neuropsychologist	NR
	Controlled Oral Word Association Test (COWAT)				Nurse	
	Rey Complex Figure (RCF)				Graduate students	
	Stroop Color and Word test					
	Rey Auditory Verbal Learning Test (RAVLT)					
	Wisconsin Card Sorting Test (64)					
Sagar, 2018	Post graduate institute memory scale	AV, WM,RP, VLM	1	Pen and Paper	Neuropsychologist	NR
	National Institute of Mental Health and Neuro-Sciences neuropsychology battery					
	Verbal working memory					
Aleptekin, 2005	Wechsler Adult Intelligence Scale (WAIS)	AV, WM, RP	NR	Pen and paper	NR	NR
	Controlled Oral Word Association Test (COWAT)					
Arau´ jo, 2015	Rey Auditory-Verbal Learning Test	VLM, WM, IP, VSM, AV, RP, TS	0.68	pen and paper	NR	NR
	Wechsler Adult Intelligence Scale (WAIS) (Version III)					
	Trail Making test					
	Controlled Oral Word Association Test (COWAT)					
	Wisconsin Card Sort Test (128 cards)					
Ayres, 2007	Controlled Oral Word Association Test (COWAT)	VSM, AV, WM	NR	pen and paper		NR
	Wechsler Adult Intelligence Scale (WAIS)					
Cabral-Calderin, 2010	Emotional Expression Multimorph task	social cognition	NR	NR	NR	NR
Charernboon, 2017	Emotion perception	SC	NR	NR	NR	NR
	Theory of mind					
	Social knowledge					
Ayres, 2009	Short Cognitive test.	IP, AV, VLM, VSM, WM, RP	2	Pen and paper	NR	NR
	Wechsler Memory Scale (Version III)					
	Short Cognitive test.					
	Controlled Oral Word Association Test (COWAT)					
	Hayling and Brixton test					

Ertugrul. 2002	Wechsler Memory Scale Revised	AV, WM, RP, VSM	2	Pen and paper	NR	NR
	Wisconsin card sorting test					
Guo, 2011	Wechsler Adult Intelligence Scale (WAIS) (Revised)	IP, RP, WM, VSM	NR	Pen and paper	Neuropsychologist	NR
	Wisconsin card sorting test					
	Wechsler Adult Intelligence Scale (WAIS) (Revised)					
	Wechsler Memory Scale (Revised)					
Heeramun-Aubeeluck, 2014	Paced Auditory Serial	WM, IP, VLM, VSM	NR		NR	Yes
	Wechsler Memory Scale					
	Wechsler Adult Intelligence Scale (WAIS)					
	Trail making					
	Hopkins Verbal Learning Test (Revised)					
	Brief Visuospatial Memory Test (Revised)					
Hou, 2016	Trail making	IP, AV, VLM				
	Stoop colour word test					
	Hopkins Verbal Learning Test-Revised (					
Mehta, 2011	Social cognition rating scale in Indian Settings	social cognition				
Okasha, 2014	Weschler memory scale	WM, VSM, VLM, AV, RP,	3.5	pen and paper	Research assistants	
	Continuous performance tests					
	Wisconsin Card Sorting test					
Pradhan, 2008	Wisconsin Card Sorting Test	RP, VLM, WM, IP, AV	3.5	pen and paper		
	Trail B					
	Controlled Words Association Test					
	PGI Memory scale					
	Bender Visual Motor Gestalt Test					
	Trail A					
Santosh, 2013	Trail making test part B	RP, IP, AV, WM, VLM				
	Trail making test part A					
	Stroop test					
	Digit span					
	Verbal fluency test					
Schneider, 2008	WAIS III	VSM, WM, IP				
Tang, 2016	Facial emotional recognition task	SC				
Trivedi, 2007	Wisconsin Card Sorting Test	RP, AV		computer		
	Continuous performance test					
Zhou, 2017	The Hopkins Verbal Learning Test-revised	WM, VLM, AV, RP		Computer		
	The Verbal Fluency Test, Chinese version					
	The Color Trails Test					
	Stroop Color Word Test Chinese version					
	Cambridge PM Test (C-CAMPROMPT					

WM = working memory, AV = attention/vigilance, VLM = verbal learning and memory, VSM = visual learning and memory, RP = reasoning and problem solving, IP = information processing speed, and SC = social cognition.

The choice of number of domains assessed differed in different publications with publications 20% (6/29) of the publications assessing only one domain and 17%

assessing for six domains. The proportions of domains assessed is shown in the bar graph (figure 8) below

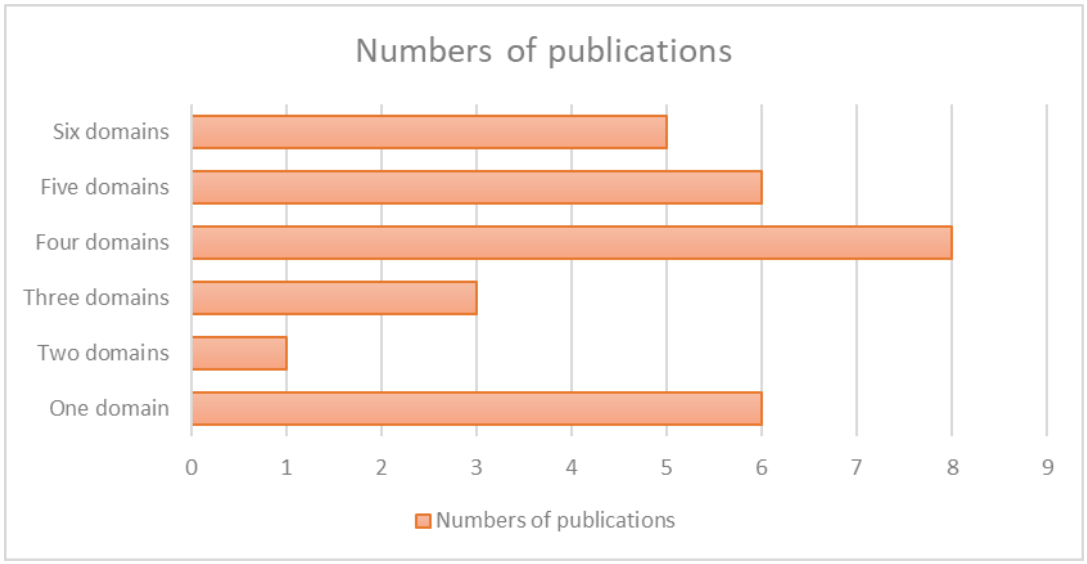

Figure 8: Bar graph showing number of domains assessed in the publications.

Most measures used were specific for assessment of impairment in the reasoning and problem solving domain accounting for 24.64% of all tests in the studies. Figure 9 highlights the proportions of tests that assessed the other domains.

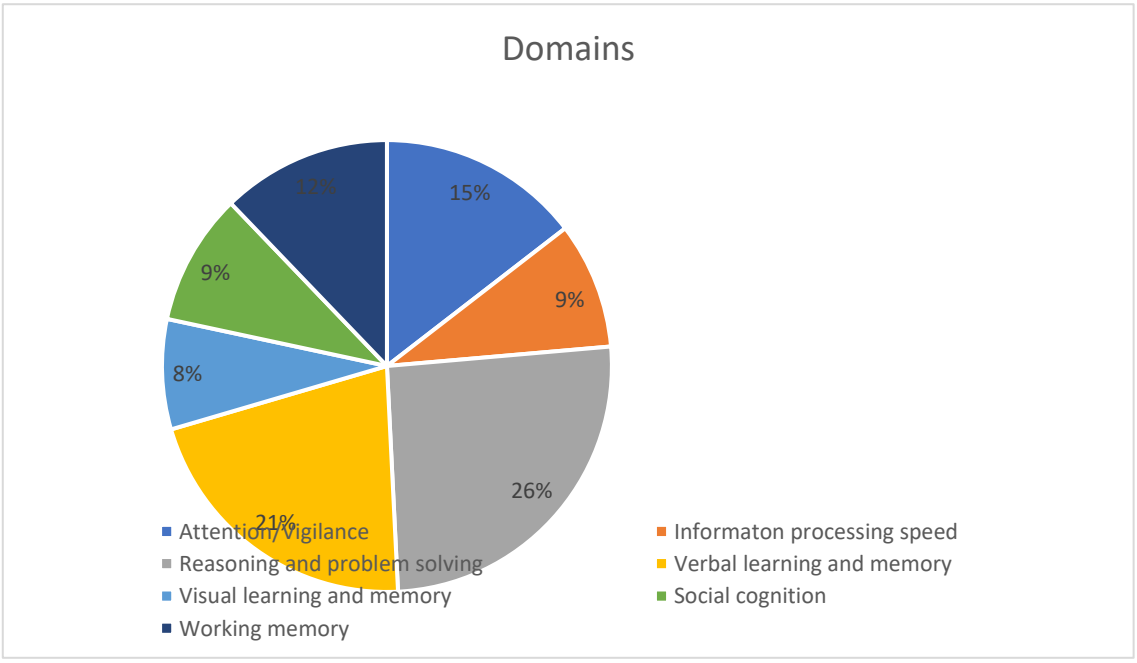

Figure 9: Pie chart showing the proportion of domains assessed.

c) Validation of measures

No study attempted to validate the measures for brief neuropsychological assessment against the gold standard (MATRICS cognitive consensus battery). In only three studies was the sensitivity and specificity of the measure determined. A summary of the publications is shown in Table 6.

Table 6: Studies in which a brief test was compared to a complete battery.

Author	Validated	Comparison group-selection criteria	Comparison group-size	Comparison tool	Sensitivity	Specificity	reliability	concurrent validity
Arau´ jo, 2015	YES	HC	58	BACS-French	NR	NR	0.874	0.625
Mehta, 2011	YES	NR	NR	NR	84.2	81	0.71	NR
Xao, 2014	YES	HC	130	MOCA	68.8	81.5	0.905	0.902

6 studies however used at least 1 test that found in the gold standard and these are highlighted in the Table 7.

Table 7: Studies that used tests also found in the MCCB.

Author	**Year**	**Country**	**Subtest/Scale/Battery**
Hendricks	2017	South Africa	Trail Making Test
Mattson	1997	South Africa	Trail making test
Ngoma	2009	DRC	Trail making test
Harvey	2002	South Africa	Wechsler Memory scale (revised) Continuous performance test (IP version)
Ayres	2009	Brazil	Wechsler Memory Scale (Version III)
Ertugrul	2002	Turkey	Wechsler Memory Scale Revised

Risk of bias across studies

There was extensive publication bias (p=<0.005) as shown in the funnel plot (Fig. 10). Published studies (circles) and unpublished studies (squares) in the funnel plot were estimated from the trim-and-fill method. The solid line corresponds to adjustments for the impact of publication bias summary effect and the dashed line to

the unadjusted summary effect.

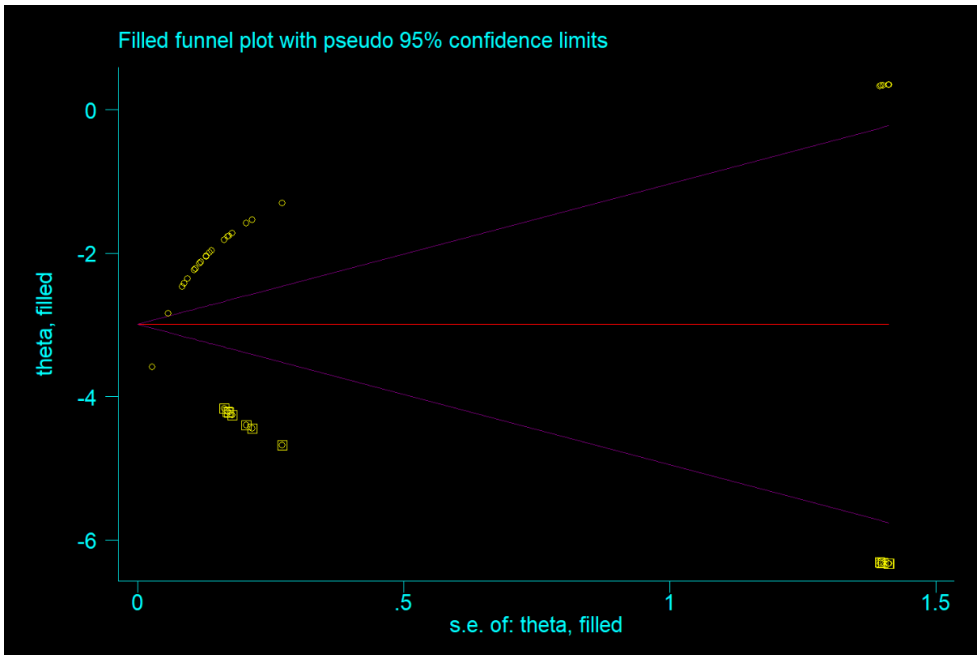

Figure 10: Filled funnel plot with pseudo 95% confidence limits.

Discussion

Our main finding was that the measures researched for brief neuropsychological assessment in patients with psychotic disorders in low and middle-income countries are 1) not used early at the first-episode of psychosis 2) not validated against comprehensive batteries 3) take long to perform 4) are not used in the clinical setting 5) not performed by non-specialised staff and 6), not used for follow-up of patients. Below we discuss our findings according to the WGSA criteria.

a) Ability of tests to identify early on individuals at high risk for impairment.

Only three studies were performed early at the first-episode of psychosis. It is recommended that cognitive assessments be performed when psychotic symptoms have resolved. This might be particularly challenging in first-episode psychosis patients given the higher rates of patient disengagement from care when compared to other mental illnesses (242-244). This disengagement has been shown to be higher in low and middle-income countries than high income countries (244).

Second, the mean age of participants (34.4years) compared to the mean age of illness onset (26.6 years) also suggest that these assessments were not performed early in the course of the illness. This is not uncommon for low and middle-income countries

were patients with psychotic disorders often present late with longer durations of untreated psychosis (105, 245).

Finally, the mean psychosis severity scores with the PANSS and mean dosages also point to these assessments having been performed later in the course of the illness. In low and middle-income countries, it has been shown that patients often use alternative and complimentary therapies before presenting for care with antipsychotic medication (246, 247). They therefore often present with high levels of illness severity and greater psychopathology often necessitating higher dosages (75). The mean chlorpromazine equivalent of 588.8 was higher than that reported in literature among patients also from low and middle-income countries (248, 249).

b) Sensitivity of the measures

The MATRICS consensus cognitive battery has been suggested as the gold standard for assessment for cognitive impairment among patients with psychotic disorders (27, 250). Its development came out of the need to standardize assessments of cognitive function during clinical trials (251). It is a collection of ten neuropsychological tests that have been validated for use in many diverse settings. The developers selected these tests for the final battery given their short administration times, good psychometric properties and practicability (4, 27). Only eight studies used any of the neuropsychological tests found in the MCCB. Only 02 of the 10 tests were used across all studies. In the three studies in which the measures were validated, none used the MCCB as a comparison tool. There is need to validate these measures for brief neuropsychological assessment against the MCCB.

c) Brevity and scope of the measures.

On average most tests took 1.8 hours which is not appropriate. Low and middle-income countries are often characterized by large patient volumes with minimal mental health staff (174, 252). Measures which take a shorter time to administer and score are needed.

d) Utility in routine care.

We found limited use of these measures in clinical settings and primarily in the outpatient rather than inpatient setting. Given that many of the patients in low and middle-income countries present late with severe illness as alluded to in (a) above there might be more benefit for these measures to be use in inpatient settings as well.

e) Use by non-specialized personnel with support of electronic devices.

Many of the studies used highly skilled staff that might not easily be available for most providers in low resource settings (173). Only three studies used lower cadre staff to perform the neuropsychological assessments. In low resource settings, these lower cadre staff are usually at the forefront of care (253). There is therefore an urgent need to develop capacity of lower health cadres to perform neuropsychological assessments. We suggest future trials on the benefit of short courses in improving the ability of lower level staff to perform cognitive assessments. Short courses have been associated with high levels of satisfaction and led to improvements in knowledge across target groups (173, 252, 254).

Additionally, most measures were performed by pen and paper and were not computerised. Some of the limitations of paper based assessments include human error in data collection, the time required to score the assessments and the burden of transporting and storing hard-copy questionnaires (225). There might be benefit in using technological advances in delivering the assessments. Evidence suggests that mHealth apps are more efficient, accurate, accessible and interactive than assessments delivered via pen and paper (255). mHealth apps improve standardization of assessments for CI as they may circumvent many of the inherent limitations of paper-based assessments (45). The initial cost of acquiring mHealth applications are also affordable and require less financial and human resources than computerized tests and comprehensive assessments (255). mHealth applications may also be highly automated with standardized instructions and administration procedures such as scoring of the neuropsychological tests, giving them the ability to be used by less specialized research staff. Electronic assessments using mobile technology (mHealth applications, or “apps”) for smartphone and Tablet devices are already in use for assessing cognitive function among persons living with HIV/AIDS(PLWHA) (37, 39, 42).

f) Monitoring progress and outcomes.

Despite including all study designs into the review only two studies were longitudinal. Given the lack of longitudinal data, it is difficult to argue that these brief tests can be used as follow up measures. The limited validation of the tools also prevented us from determining the ability of the tests to perform consistently over repeated assessments

(test-retest measures). There is therefore need for further research on these neuropsychological tests as tools for monitoring progress and outcomes.

Strengths and limitations: Our search that only included English language studies is a major limitation and may explain the large publication bias. Also, the WGSA criteria is not entirely specific on what characteristics constitute the threshold for meeting a criterion. The systematic review study design enabled us to review many studies to summarize the literature on the appropriateness of measures researched in studies of brief neuropsychological assessment in patients with psychotic disorders from low and middle-income countries.

Conclusion:

In this review, we found that many of the measures researched in studies of patients with psychotic disorders from low and middle-income countries are inappropriate for brief neuropsychological assessment according to the WGSA guidelines. Several candidate assessments are, however, attractive in terms of their scope and duration, and at least one of these, the Brief Assessment of Cognition in Schizophrenia; has been validated in high-income settings (256-260). Further work on the administration of measures performed by non-specialized staff using mHealth apps is recommended in low and middle-income contexts.

CHAPTER 5: COMPARISON OF COGNITIVE IMPAIRMENT IN FIRST-EPISODE PSYCHOSIS PATIENTS AND HEALTHY PEERS IN A LOW RESOURCE SETTING

Chapter 4 highlighted how many of the measures researched in studies of brief neuropsychological assessment in patients with psychotic disorders from low and middle-income countries are inappropriate. The literature on the burden and profile of impairment could not be summarized due to limitations of the brief measures used. Comprehensive batteries are most suited for describing the burden and profile of impairment. In Chapter 5 and 6, I utilized a comprehensive battery to describe the burden, profile and associated factors for cognitive impairment in first-episode psychosis patients from one low resource setting.

Introduction

In order to carry out any neuropsychological assessment, it is important to have an idea of the cognitive performance in patients and healthy peers in a particular setting (26). This is important because it prevents wrongly assigning a disease status to otherwise healthy patients (6). The MATRICS consensus cognitive battery (MCCB) that assesses for impairment in all seven domains is an ideal test to compare cognitive performance between first-episode psychosis patients and healthy peers (27, 56). In studies from high income countries in which the MATRICS consensus cognitive battery has been used, the prevalence of cognitive impairment has been found to range from 36% to 78% (251, 261). At the first-episode of psychosis, the impairment is most often in the domains of processing speed and verbal learning and memory (28). Notable differences (as large as 2SDs) have also been found between the mean domain scores of patients with first-episode psychosis versus scores of healthy peers (20, 136, 262).

Comparisons of cognitive performance between first episode psychosis patients and healthy peers in low resource settings like Uganda are scarce. The available literature in such settings has not used comprehensive batteries like the MATRICS consensus cognitive battery to describe the prevalence and profile of cognitive impairment at the first-episode of psychosis (35, 125, 204). In addition, work to date has been limited by small sample sizes (35, 125, 207, 263) and diminished power to detect statistically

significant differences in cognitive impairment between cases versus healthy peers (35, 40).

To address these gaps in the current literature, I investigated the prevalence and profile of cognitive impairment in first-episode psychosis patients (versus health controls) in a resource-limited setting. Specifically, I compared the burden of impairment in first-episode psychosis patients and healthy peers when assessed using the MATRICS consensus cognitive battery. I also determined whether the profile of impairment and mean cognitive scores varied between first-episode psychosis patients and healthy peers.

Methods

Study design and setting

A comparative cross-sectional study was undertaken at the Butabika National Referral Mental Hospital in Uganda. As a national referral hospital, the hospital primarily offers mental health services, as well as selected non mental health services such as antenatal care, HIV/AIDS care, and dental services.

Sample size

The Leslie Kish formula (71) was used to calculate the target sample size for determining the burden and profile of impairment in the study sample:

$$N = \frac{Z^2pq}{D2}$$

Where Z = Standard deviation at 95% confidence interval (1.96); P = Expected proportion of patients with cognitive impairment at the first-episode of psychosis, D = Precision of the estimate (5%); Q= 1-p and N = Sample size. Based on recent work by Keefe and colleagues (37), the expected proportion of patients with cognitive impairment at the first-episode of psychosis was 80%. Thus, the target sample size for this study was calculated as two hundred and forty five (245) participants.

Instruments

i) **Sociodemographic questionnaire:** This was designed to collect variables such as age, gender, minimum level of education attained, diet, housing and

employment status. Additional phenotypic data such as self-reported ethnicity was also collected.

ii) **Mini International Neuropsychiatric Interview (MINI) version 7.0 (190):** This is a semi-structured interview guide for DSM-5 diagnoses. It has been validated for use in low resource settings (33, 119, 191). Only modules D (mania), J (alcohol use), K (other substances) and L (psychotic disorders) were administered for our purposes. Participants with diagnoses of Schizophrenia, Schizophreniform or Schizoaffective disorder were classified as having non-affective psychosis. Patients with a diagnosis of bipolar mood disorder (irrespective of the phase or type) as well as depression with psychotic features were classified as having affective psychoses.

iii) **Positive and Negative Syndrome Scale (PANSS) (196):** This is a 30-item clinician rated scale that assesses dimensions of severity of both Schizophrenia and bipolar psychotic symptoms. This tool was primarily used to determine if psychosis symptoms had resolved before administering the neuropsychological batteries.

iv) **MATRICS consensus cognitive battery:** This is the gold standard for assessment of cognition in patients with psychosis (4). It assesses for CI in the seven cognitive domains of i) working memory, ii) attention/vigilance, iii) verbal learning and memory, iv) visual learning and memory, v) reasoning and problem solving, vi) information processing speed, and vii) social cognition (4, 27). The complete battery can usually be completed in approximately 90 minutes, excluding time needed to score.

Research participants

Adult in-patients with a confirmed first-episode of psychosis on the MINI international neuropsychiatric inventory were eligible for inclusion in the study. Additional inclusion criteria included never having been treated with antipsychotic medication or having been on medication for less than six weeks' duration. This cut-off of six weeks (as opposed to twelve weeks) was informed by prior evidence that psychosis may resolve faster in low- and middle-income countries (LMICs), versus high income countries (169, 170, 245, 264). Patients with HIV/AIDS, syphilis and substance use were

excluded from participation, as these are common clinical presentations in this setting; and may each also be associated with cognitive impairment (33, 119, 265). For the healthy peers, adults who consented to participate in the study were eligible for inclusion. Exclusion criteria were a positive diagnosis of psychosis on the MINI, and/or a history of substance use, HIV/AIDS and syphilis.

Research procedure

First-episode psychosis patients were enrolled into the observational study; After obtaining informed consent, the diagnosis was confirmed using the MINI. Illness severity was assessed using the PANSS and sociodemographic information was compiled using a standard questionnaire. Patients were then followed up weekly with the PANSS until resolution of psychotic symptoms at which point the MATRICS consensus cognitive battery was administered. Consenting healthy peers (matched for age and level of education) were also then recruited from the dental wards of the hospital; and were administered the MATRICS consensus cognitive battery.

Data analysis

Raw scores of the ten tests of the MCCB were first tested for normality. Scores of the mazes sub-test of the Neuropsychological Assessment Battery (NAB-mazes) and trail making test deviated from normal and were log transformed. The trail making test was also reverse scored, with lower scores suggesting poorer cognitive function. Composite scores were generated for each of the seven domain scores by summing the raw scores of individual tests per domain. These composite scores were then transformed to z scores, using the means and standard deviations of the control group. Standardization was done based on age and level of education of the healthy peers as follows:

$$\text{Standardized score} = \frac{(\text{domain score} - \text{mean score of controls})}{\text{standard deviation of the controls}}$$

In order to determine the burden of impairment, participants with mean domain scores 2 standard deviations (SD) below the mean in one domain of the MCCB; or as 1SD below the mean in two or more domains were classified as impaired (231). Descriptive statistics were employed to describe the prevalence and profile of CI for both a general cognitive impairment and in each cognitive domain. To determine the impairment in a

specific domain, standardized scores of 2SD below the mean were defined as signifying cognitive impairment. Student t-tests were used to determine if mean cognitive domain scores differed across the patients with psychosis and healthy peers. The level of significance for all analyses was set at 0.05.

Results

At the end of the data cleaning process, the final sample included 129 first-episode psychosis patients and 52 healthy peers. The median age of the sample was 29 years (IQR 22-34). Most participants were female [108/181, 64%], single [75/181, 45%] and in non-formal employment [64/181, 38%]. Among the first-episode psychosis patients, the median age for first seeking help for psychosis was 26 years [IQR 21-32]. The mean time between onset of symptoms and presenting to the hospital was 0.932 years [SD 2.798, Range (0-18)years]. Most participants [76/120; 63%] were presenting with symptoms for the first time, while 95/113 (84%) were presenting to a hospital for the first time. Those who had previously presented to a hospital largely used the regional referral hospitals [8/13, 61.5%]. There were 15/116 (13%) participants who had previously received antipsychotic medication but for less than 6 weeks' duration. Additional sociodemographic characteristics of the study sample are noted in Table 8.

Table 8: Sociodemographic characteristics of the study sample.

Variable		FEP (129)	Healthy peers (52)	p-value
Age	Median (IQR)	26(27.3;30.5)	31.8(29.1;34.5)	0.063
gender	Male Female	43(35.8%) 77(64.2%)	18(36.7%) 31(63.3%)	0.912
Handedness	Right Left	116(96.7) 4(3.3)	43(93.5) 3(6.5)	0.360
Marital Status	Single Married Divorced	63(53.4) 36(30.5) 19(16.1)	12(24.5) 28(57.1) 9(18.4)	0.002
Current Employment Status(?)	Student Formal Non formal Unemployed	7(5.9) 16(13.6) 47(39.8) 48(40.7)	0(0.0) 22(44.9) 17(34.7) 10(20.4)	P<0.001
Highest level of education	No school Primary Secondary Diploma University	3(2.6) 44(37.6) 56(47.9) 12(10.3) 2(1.7)	1(2.0) 15(30.6) 26(53.1) 6(12.2) 1(2.0)	0.932
Ethnicity	Bantu Nilotic NiloHamites Sudanic Hamites	86(73.5) 8(6.8) 4(3.4) 6(5.1) 13(11.1)	34(70.8) 6(12.5) 6(12.5) 1(2.1) 1(2.1)	0.041
Current living arrangements	Renting Own house Living with family No housing	23 (19.5) 25 (21.2) 69 (58.4) 1(0.9)	30(61.2) 9(18.4) 10 (20.4) 0	<0.001
Main source of income in the household	Self Father Mother Relative/ guardian Nonrelative/ organization	43(36.4) 17(14.4) 18(15.2) 28(23.7) 12(10.2)	28(58.3) 3(6.2) 3(6.2) 10(20.8) 4(8.3)	0.087

FEP= First Episode Psychosis

Comparison of the burden of cognitive impairment in patients and healthy peers

As shown in figure 11, 80/129 (62%) of the first-episode psychosis patients and 6/52 (11.5%) of the healthy peers were classified as having a general cognitive impairment (scores two standard deviations below the mean in any one cognitive domain or scores of one standard deviations below the mean in any two cognitive domains) (4). There were no statistical differences in the proportions of participants with a general cognitive impairment across sex [prevalence ratio (PR)=1.151 (p=0.79)], age [PR=0.46 (p=0.19)] or diagnosis [PR=1.17 (p=0.76,].

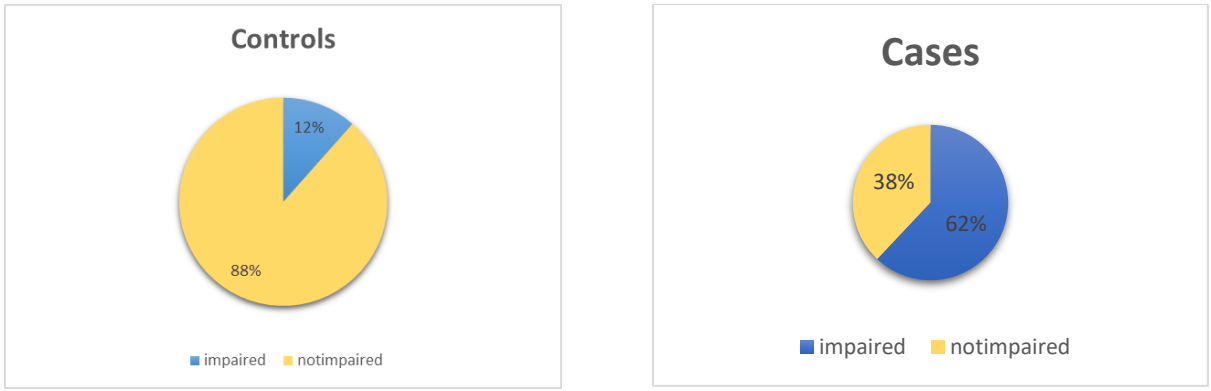

Figure 11: Proportion of participants with cognitive impairment in the cases and the controls

Burden of impairment in specific cognitive domains

Most first-episode psychosis patients were impaired in the visual learning and memory domain [38% (CI 30.0 – 47.5)] while for the healthy peers the impairment was mostly in the working memory domain [6.1% (CI 1.9 -17.80]. Conversely, social cognition domain was found to be least impaired in the first-episode psychosis patients [17% (CI 10.9 – 24.6)]. No healthy peers were assigned as impaired in the domains of visual learning, memory, or in verbal learning, and memory, Figure 12.

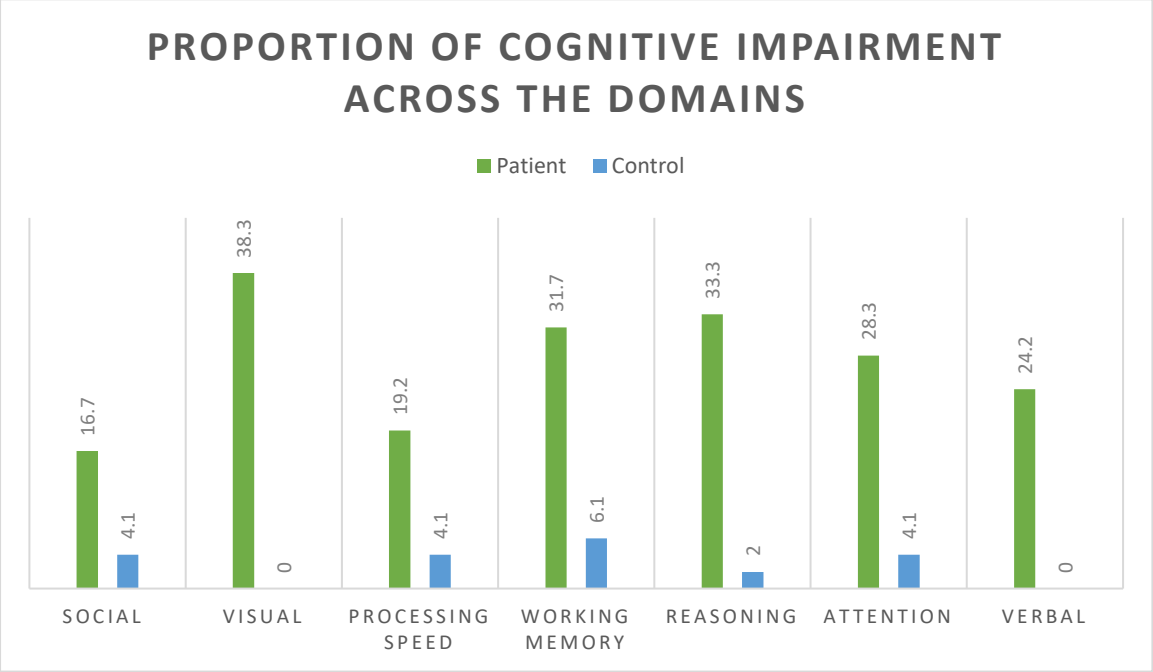

Figure 12: Proportion of patients classified as impaired across each cognitive domain.

Profile of impairment

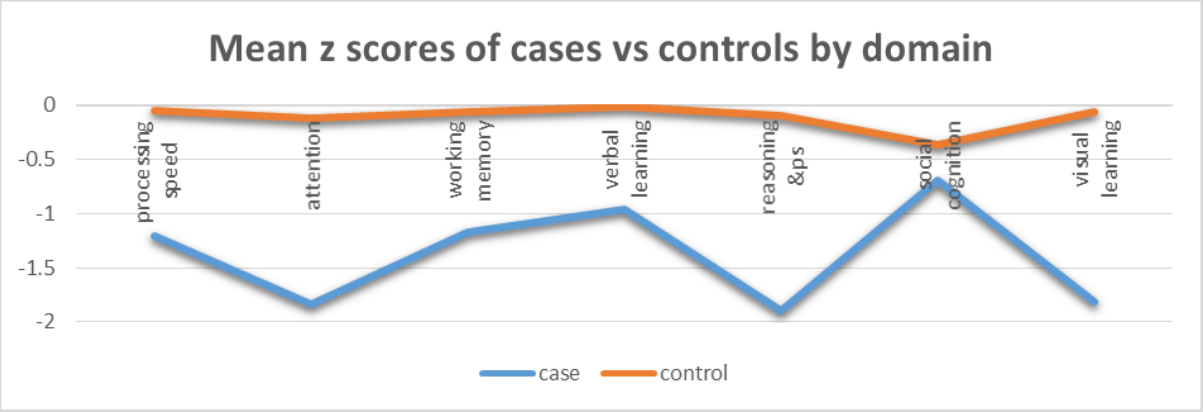

Figure 13: Comparison of the mean cognitive scores of the cases and controls across each domain

Statistically significant differences in mean cognitive scores between first-episode psychosis patients and healthy peers were found across all domains, except social cognition, Figure 12. The greatest difference between the mean scores of the cases versus controls was found in the reasoning and problem-solving domain, a statistically significant decrease of 1.83 (p= < .0001). By contrast, the difference in mean scores between first-episode psychosis patients and healthy peers was lowest in the social cognition domain, a non-statistically significant decrease of 0.19 (p= 0.63). Other comparisons are shown in Table 9 below.

Table 9: Comparison of mean domain scores between cases and controls

Domain	FEP (n=120) mean (SD)	Healthy peers (n=49) mean (SD)	Mean difference	Test statistic t	p-value
Attention/vigilance	-1.7 (2.3)	-0.1 (1.0)	1.7	4.80	<0.0001
Reasoning and problem solving	-1.9 (2.2)	-0.1 (0.9)	1.8	5.61	<0.0001
Speed of processing	-1.2 (1.1)	0.005 (0.9)	1.2	6.50	<0.0001
Verbal learning and memory	-0.9 (1.5)	0.09 (1.0)	0.9	3.89	0.0002
Visual learning and memory	-1.8 (2.1)	0.039 (0.9)	1.7	5.74	<0.0001
Working memory	-1.1 (1.7)	-0.02 (0.9)	1.1	4.22	<0.0001
Social cognition	-0.5 (1.7)	-0.4 (2.9)	0.3	0.48	0.629

FEP=first episode psychosis patient

Discussion

Key findings in this study were 1) a large burden of cognitive impairment among first-episode psychosis patients 2) the profile of impairment differed between first-episode psychosis patients and healthy peers. The visual learning and memory domain most impaired among the first-episode psychosis patients and working memory for healthy peers ; 3) large and statistically significant differences were found between the mean cognitive scores of first-episode psychosis patients versus healthy peers; 4) the largest difference in mean cognitive scores between first-episode psychosis patients and healthy peers was found in the reasoning and problem-solving domain; and 5) no healthy peers were classified as impaired in the visual learning or verbal learning and memory domains.

Burden of cognitive impairment

This is one of the few studies, and only one in Africa; to quantify the burden of cognitive impairment using the MATRICS consensus cognitive battery in first-episode psychosis patients. Most studies that have used the MATRICS consensus cognitive battery in Africa reported mean domain scores and did not go further to categorize the burden of impairment as 2SD below the mean in one domain of 1SD below the mean in 2 domains. Absolute numbers may be easier and more insightful for policy makers in making a case for neuropsychological assessment in everyday care.

In line with prior work conducted in diverse settings, the prevalence of cognitive impairment in first-episode psychosis patients was higher than their matched healthy peers (57, 251, 261, 266, 267). The prevalence of cognitive impairment in first-episode psychosis patients of 62% was lower than literature from high income countries (30). Variation in the burden may be due to the psychometric properties of the MATRICS consensus cognitive battery. For example, the MSCEIT which assessed for social cognition has been found to perform poorly in low resource settings which may affect the overall burden of impairment (268, 269). This variation may also be due to differing sociodemographic characteristics where patients were older, primarily female and less educated than high income countries. Older age (270, 271), level of education and gender (272) have been associated with differing cognitive function in first-episode psychosis patients from high income countries.

Profile of cognitive impairment between patients and healthy peers

Most first-episode psychosis patients in our study sample were found to have impairment in the visual learning and memory domain. This differs from studies of high income countries among first episode psychosis patients that reported the greatest burden of cognitive impairment in speed of processing and verbal learning and memory (28, 29). It is not clear from the results why the visual learning and memory domain is the most impaired domain in this setting. Hallucinations have been associated with worse memory functioning so it is plausible that the long duration of hallucinations before treatment may have already irreversibly impaired the visual learning and memory domain (273). This can only be confirmed in a longitudinal study as the patients described here had resolution of symptoms before assessment and the cross sectional study design implies determining causality is difficult. In some few studies, lower levels of brain derived neutrotrophic factor have been associated with poor functioning in the visual learning and memory domain (274, 275). Serum brain derived factor is a marker of brain health and may be lower in patients with poorer diets and recurrent infections that are common in this setting. Low serum BDNF levels are a plausible reason why the visual learning and memory domain was most impaired. The serum brain derived neutrotrophic factors were not measured in this study, but future studies are planned. Lastly, the hippocampus is the brain region commonly associated with control of the visual learning and memory domain (276, 277). In studies from high income countries, hippocampal atrophy has been associated with long durations of untreated psychosis that are common in low resource settings (278). It is therefore possible that long durations of untreated psychosis are associated with greater hippocampal atrophy and poorer visual learning and memory impairment in this domain. Finally, there is paucity of published work on the visual learning and memory domain in general (279). This may be in part due to the limited number of validated tools for its assessment in patients with psychotic disorders. Thus, further research on neuropsychological testing of the visual learning and memory domain in first-episode psychosis patients is warranted.

I found the largest differences in the reasoning and problem solving domain followed jointly by attention/vigilance and visual learning and memory domains. This differs from results of a systematic review of 19 studies were the largest mean differences in cognitive scores were in verbal memory followed by reasoning and problem

solving (183). Also, in literature from high income countries, there are no significant differences in mean scores of the visual learning and memory domain in the psychosis prodrome, yet the differences are present in first-episode psychosis patients (15, 280). These findings may suggest not only a different presentation but also a different trajectory of cognitive impairment in first-episode psychosis patients from low resource settings which needs further review with longitudinal studies.

In this study, the prevalence of cognitive impairment of 17% in the social cognitive domain among first-episode psychosis patients was lower than described in other settings (262, 268). Further, no statistically significant differences were evident between the mean scores of first-episode psychosis patients and healthy peers in this domain. This finding is similar to literature from other LMICs (268, 281, 282); and may be suggestive of poor psychometric properties of the MSCEIT in such settings (268, 269). We posit that the burden of impairment in the social cognition domain may have been underestimated in our study sample due to limited sensitivity of the MATRICS consensus cognitive battery to detect differences between first-episode psychosis patients and healthy peers in the social cognition domain. In future, the development of culturally specific tests to assess for impairment in the social cognition domain would be beneficial (281).

There were no healthy peers categorized as impaired in the domains of visual learning and memory and verbal learning and memory. We could not find similar literature from a low resource setting to understand this finding in healthy peers. One could hypothesize that no impairment in these domains may point to impairment in these domains being specific to patients with psychotic disorders in this setting and requires further investigation.

Strengths and Limitations

Several limitations should be borne in mind when interpreting the current study findings. First, the cross-sectional study design undertaken here does not allow a description of impairment across the psychosis lifespan, yet literature shows that the burden and profile of impairment differs across the lifespan (283-285). Second, the anticipated sample size was not achieved. However post hoc power calculations determined that the sample size of 129 patients and 52 healthy peers had 100% power to determine the mean difference between the domain scores for the cases

and controls (188). These limitations notwithstanding, this is one of few studies in Africa to use the gold standard for neuropsychological assessment to investigate cognitive impairment differences in first-episode psychosis patients and healthy peers (35).

Clinical implications

The high prevalence of impairment in the visual learning and memory domain found in our study sample is interesting. It is the cognitive domain least improved by atypical antipsychotics such as risperidone, olanzapine and clozapine, or by stimulants such as methylphenidate (168, 286-288). It is also the only domain that does not show cognitive improvement over time in patients with psychotic disorders (102). Future studies to determine the course of impairment in the visual learning and memory domain in this setting are required. Specifically, the association of impairment in the visual learning and memory domain with functional outcome and recovery are required. This may support the introduction of interventions like cognitive remediation programs to reduce the burden of impairment in this domain as has been trialled elsewhere (289, 290).

Conclusion

Based on this study's findings, first-episode psychosis patients in this setting have a higher burden of cognitive impairment than their healthy peers as described elsewhere. However, unlike in previous literature, I found that the visual learning and memory domain is the most impaired. Also mean differences between scores of the patients compared to healthy peers are higher in this low resource setting with the largest difference in the reasoning and problem solving domain. There are also no statistical differences between the scores of first-episode patients and healthy peers in the social cognition domain. Development of appropriate tools for the social cognition domain are required as has been attempted elsewhere (281). This is crucial to determining the true burden of impairment in this setting.

CHAPTER 6: CLINICAL VARIABLES ASSOCIATED WITH COGNITIVE IMPAIRMENT IN FIRST-EPISODE PSYCHOSIS PATIENTS.

Chapter 5 highlighted a large burden of cognitive impairment in first-episode psychosis patients compared to their healthy counterparts. The profile of impairment also differed across the seven different cognitive domains. This chapter will investigate the association of clinical variables with impairment in the different cognitive domains among first-episode psychosis patients from one low resource setting.

Introduction

In neuropsychological assessment, a test score is significant only when patients environmental clinical and social characteristics are considered (26, 51). For example, previous work and education history may be the best source of a patient's previous level of cognitive functioning when determining if there is a current decline. Clinical characteristics on the other hand may point to underlying illness that may affect neuropsychological test performance (26). Studies from high income countries that have used the MATRICS consensus cognitive battery to determine factors associated with cognitive impairment have shown associations with older age (270, 271), level of education, gender (272) and severity of illness at admission (291, 292). There is also an association between childhood trauma with impairment in the verbal learning and memory domain (293).

Further work is warranted in determining the associations in different cognitive domains with clinical environmental and social exposures that are more common in first-episode psychosis patients from low and middle-income countries (137, 294, 295). First, the few studies that have used complete neuropsychological tests in low and middle-income countries were not well powered to test for associations (35). Second there are clinical, environmental and socio-demographic exposures that are more prevalent in low resource settings but the associations of these exposures with impairment in different cognitive domains has not been well defined. For example, in low resource settings longer durations of untreated psychosis, and greater psychosis severity have been described in first-episode psychosis patients but the association with impairment in different cognitive domains is unclear (10, 35). Also, there are higher rates of childhood impairment in low resource settings but there is limited data on the associations between childhood trauma with impairment in different cognitive

domains (296, 297). Patients from low resource settings are also often consumers of carbohydrate rich diets (298). Diet however has been shown to be closely associated with cognitive function (299). It is unclear how such carbohydrate rich diets are associated with cognitive impairment in first-episode psychosis patients. There is also a large proportion of first-episode psychosis patients who use alternative and complimentary therapies before presenting later to care (300). The association of this previous use and whether the delay in receiving care is associated with cognitive impairment is not well described. Finally, the association between poorer welfare common in low resource settings with cognitive impairment in first-episode psychosis patients also requires review (301, 302).

I investigated the relationship between various clinical environmental and sociodemographic exposures with cognitive impairment in first-episode psychosis patients from one low resource setting. Specifically, I determined the risk associated with different sociodemographic, clinical and environmental exposures with standardized cognitive scores of the seven different cognitive domains in first-episode psychosis patients from one low resource setting.

Conceptual framework:

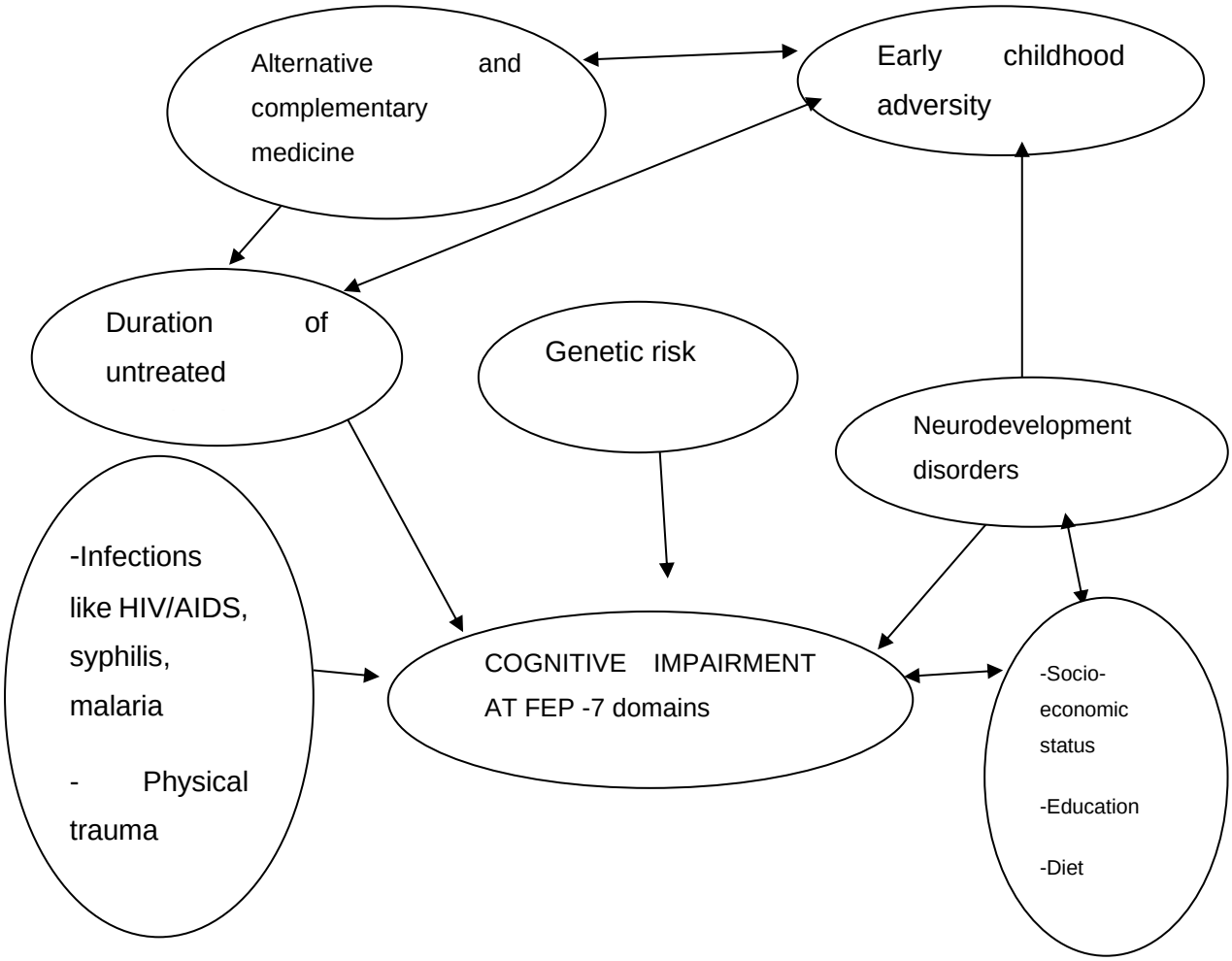

Figure 14: Conceptual framework for Chapter 6.

The conceptual framework highlighted in Figure 14 posits that there are various exposures associated with impairment in different cognitive domains in first-episode psychosis patients from low resource settings. The exposures may be directly associated with cognitive impairment, or the relationship may be mediated through other exposures. For example, previous use of alternative and complementary therapies may be directly associated with cognitive impairment in that the herbs used for therapy may worsen or improve the cognitive function (303, 304) . On the other hand, the association may be indirect by prolonging the duration of untreated psychosis so that patients present late with worse cognitive function (246). Lower socioeconomic status maybe associated with poor cognitive function through various ways including poorer quality of diets, higher risk of childhood trauma and sexually

transmitted infections like HIV/AIDS; all associated with poorer cognitive function (305, 306). It may also be the case that pre-existing lower cognitive performance leads to people 'drifting' down the socio-economic ladder due to poorer educational achievement and poorer work options (11, 17, 21, 268).

Methods

Study design and setting: This was a comparative cross sectional study in which I determined the association between various social environmental and clinical exposures with standardized cognitive domain scores in first-episode psychosis patients. The study was also performed at Butabika National Referral Mental hospital in Uganda.

Sample size: To determine the minimum sample size for linear regression analyses, a-priori sample size testing was performed. From an anticipated effect size of 0.15, desired statistical power of 95%, probability level of 0.05 and 15 predictors, a minimum sample size of 139 participants was calculated.

Study Instruments:

The MINI international neuropsychiatric inventory, positive and negative signs and symptoms scale and the MATRICS consensus cognitive battery used in this paper have been described in methods section and in aim 2 above.

i) **Sociodemographic questionnaire:** This was used to collect data on predictors like age, gender, minimum level of education attained, diet, housing, employment status, welfare and ethnicity. For the data on diets the participants were asked to report which meals they had eaten in the week prior to admission at the hospital.

ii) **Childhood trauma questionnaire:** This 28-item questionnaire provides a brief screening method for childhood abuse and neglect; which can be completed in approximately 15 minutes (192). The abuse category describes sexual abuse, emotional abuse and physical abuse. The neglect category describes emotional neglect and physical neglect. It also includes a minimization/denial scale for detecting individuals who may be underreporting traumatic events.

Research participants: Inclusion criteria were adult in-patients with a confirmed first-episode of psychosis on the MINI. They should have been antipsychotic naïve or been on medication for less than six weeks duration. Patients with HIV/AIDS, syphilis and substance use were excluded. For the healthy peers recruited for standardization of cognitive scores, inclusion criteria were adults who consented to participate in the study. Exclusion criteria were a positive psychosis diagnosis on the MINI, substance use history and illness of HIV/AIDS and syphilis

Research procedure: Recruitment procedures were also described in the methods section. Briefly, patients with a first-episode of psychosis were enrolled into the observational study. Severity of psychotic symptoms was then assessed weekly till resolution of psychotic symptoms. On resolution of psychotic symptoms data on sociodemographic characteristics, clinical characteristics, dietary history in the week prior to admission and history of childhood trauma were collected. Neuropsychological assessments were performed using the MATRICS consensus cognitive battery.

Study variables:

i) Duration of untreated psychosis was calculated by subtracting the age at which patient symptoms first presented from the patients age at admission.

ii) Diagnostic categories: Participants with diagnoses of Schizophrenia, Schizophreniform and Schizoaffective disorder on the MINI were classified as non-affective psychosis. Patients with diagnoses of bipolar (irrespective of the phase or type) as well as depression with psychotic features were classified as affective psychoses.

iii) Cognitive impairment was standardized according to age and level of education. It was classified as a continuous variable with higher scores implying better cognitive function.

iv) Previous use of alternative therapy was recoded into a categorical variable with those who had used and had not used any alternative and complementary therapy for psychotic symptoms prior to admission.

Data Analysis: All raw scores of the MCCB were first tested for normality. Those that did not have a normal distribution were log transformed. The scores of the trail making test were also reversed as higher scores on the test point to poorer performance.

Composite scores were generated for each of the seven domain scores by summing raw scores of individual tests specific to each domain. Means and standard deviations of the domains were then calculated for the control group which was used to standardise the participant scores according to different age and gender categories of the health controls. After, regression coefficients for the various exposures with the seven different cognitive domains in first-episode psychosis patients were calculated while controlling again for gender and level of education.

Results

Our final sample included 129 first-episode psychosis patients which was 92.8% of our anticipated sample size. Sociodemographic characteristics of the participants are presented in Table 1 below. Most participants were female (64.2%), single (53.4%), with median age of 28 years (IQR=22-34) and 6 years of education (IQR=3-9). Other sociodemographic characteristics are highlighted in Table 10.

Table 10: Sociodemographic characteristics among the first-episode psychosis patients

Factor	Level	N (%)
Age	Median (IQR)	28 (22-34)
Gender	Male Female	43 (35.8) 77 (64.2)
Participants years of education	Median (IQR)	6 (3-9)
Father years of education	Median (IQR)	3 (2-6)
Mother years of education	Median (IQR)	2.5 (2-4)
Current Living Arrangements	Renting Owns house Living with family No housing, Living on street	23 (19.5) 25 (21.2) 65 (55.1) 5 (4.2)
Ethnicity	Bantu Nilotic NiloHamites Sudanic Hamites	86 (73.5) 8 (6.8) 4 (3.4) 6 (5.1) 13 (11.1)
Who is main source of income in the household	Self Father Mother Relative/ Guardian Organization	43 (36.4) 17 (14.4) 18 (15.3) 28 (23.7) 12 (10.2)
Marital status	Single Married Divorced	63 (53.4) 36 (30.5) 19 (16.1)
Current employment history	Student Formal employment Non formal Unemployed	7 (5.9) 16 (13.6) 47 (39.8) 48 (40.7)
Handedness	Right Left	116 (96.7) 4 (3.3)

Most participants ate diets rich in legumes (93.3%) and grains (90.8%) in the week prior to admission. The proportions of the different diets for the cases are highlighted in Table 11.

Table 11: Baseline characteristics of diets in the week prior to admission in the first-episode psychosis patients.

Factor	Level	N (%)
Fruits and vegetables	None Yes	30 (25.2) 89 (74.8)
Meat, Eggs, Fish	None Yes	31 (26.1) 88 (73.9)
Cassava	None Yes	45 (37.8) 74 (62.2)
Beans, Groundnuts, Peas	None Yes	8 (6.7) 111 (93.3)
Maize, Millet, Sorghum	None Yes	11 (9.2) 108 (90.8)

Most participants reported no history of previous trauma in all the domains. The proportions of participants that reported no prior history of childhood trauma in the different domains were physical neglect [36.0%), emotional neglect (42.7%), sexual abuse (72.0%), physical abuse (58.7%), emotional abuse (46.7%). About 36% of participants however had scores suggestive of minimization/denial of traumatic events. Mean trauma domain scores are highlighted in Table 12.

Table 12: Baseline characteristics of trauma exposures among the patients with first-episode psychosis

Factor	Mean (SD)	Range
Physical neglect	9.26 (4.3)	5-19
Emotional neglect	10.16 (4.2)	5-19
Sexual abuse	6.63 (3.5)	5-23
Physical abuse	8.21 (4.1)	5-20
Emotional abuse	9.57 (4.2)	5-24
Minimization/Denial	0.73 (1.12)	0-3

The baseline clinical characteristics for the cases are highlighted in the Table below. 73/128 (61.9%) of participants had used alternative and complementary therapy prior to admission. The duration of untreated psychosis (DUP) had a range of 0-34 years with median of 0 (less than one year). Other clinical characteristics are highlighted in Table 13.

Table 13: Baseline clinical characteristics of the patients with first-episode psychosis.

Factor	Level	N (%)
Duration of untreated psychosis (years)	Mean (SD)	0.88(3.32)
PANSS scores (9 items)	Mean (SD)	22.1(5.68)
Diagnosis	Affective Nonaffective	43 (37.7) 71 (62.3)
Previous use of alternative therapy	None Used	45 (38.1) 73 (61.9)

Sociodemographic, environmental and clinical exposures were then tested for strength of associations with the standardized z-scores of the seven different cognitive domains in the patients with a first-episode of psychosis. For standardized z scores on visual learning and memory domain, significant associations were found with increased age, more years of education and different living arrangements. Other significant associations are highlighted in Table 14.

Table 14: Association of different exposures with z scores of the visual learning and memory domain.

Factor	level	Unadjusted Coeff (95% CI)	p-value	Adjusted Coeff (95% CI)	p-value
Sociodemographic characteristics					
Age	Median (IQR)	0.049(0.019; 0.079)	0.002	**0.052(0.022; 0.081)**	**0.001**
Participants years of education	Median (IQR)	0.115(0.054; 0.177)	0.000	**0.070(0.002; 0.137)**	**0.042**
Father years of education	Median (IQR)	0.025(-0.009; 0.059)	0.153	0.025(-0.009; 0.059)	0.146
Mother years of education	Median (IQR)	0.103(0.006; 0.200)	0.037	0.097(-0.011; 0.205)	0.077
gender	Male Female	Ref -0.458(-1.017; 0.101)	 0.107	Ref -0.458(-1.017; 0.100)	0.107
Handedness	Right Left	Ref 0.202(-1.215; 1.619)	 0.779	Ref 0.311(-1.030; 1.652)	 0.648
Marital Status	Single Married Divorced	Ref 0.898(0.293; 1.503) 0.723(-2.019; -1.198)	 0.004 0.072	Ref **0.815(0.156; 1.475)** 0.477(-0.493; 1.447)	 **0.016** 0.333
Current Employment History	Student Formal Employment Non formal employment Unemployed	Ref 0.537(-0.925; 2.000) -0.354(-1.770; 1.061) -0.619(-2.042; 0.804)	 0.469 0.622 0.392	Ref 0.138(-1.314; 1.590) -0.232(-1.652; 1.187) -0.634(-2.059; 0.792)	 0.852 0.747 0.381
Ethnicity	Bantu Nilotic NiloHamites Sudanic Hamites	Ref 0.4111(-0.584; 1.406) 0.976(0.183; 2.136) -0.058(-1.428; 1.312) -1.574(-2.569; -0.580)	 0.416 0.098 0.934 0.002	Ref 0.052(-0.923; 1.026) 0.862(-0.300; 2.024) -0.012(-1.444; 1.420) **-1.197(-2.179; -0.215)**	 0.917 0.145 0.987 **0.017**
Current Living arrangements	Renting Owns house Living with primary family Living with other family Living with friends No housing/living on street	Ref -0.877(-1.627; -0.127) -1.226(-1.889; -0.562) -2.211(-3.163; -1.260) -1.742(-3.339; -0.145) -0.750(-2.520; 1.020)	 0.022 0.000 0.000 0.033 0.404	Ref **-0.887(-1.676; -0.097)** **-0.937(-1.622; -0.253)** **-1.728(-2.703; -0.753)** -1.257(-2.841; 0.328) -0.756(-2.546; 1.033)	 **0.028** **0.008** **0.001** 0.119 0.405
Who is main source of income in the household	Self Father Mother Relative/ guardian Nonrelative/ organization	Ref -0.528(-1.436; 0.379) -0.595(-1.486; 0.296) -0.913(-1.633; -0.192) -0.804(-1.797; 0.188)	 0.252 0.189 0.013 0.112	Ref -0.315(-1.263; 0.632) -0.010(-0.975; 0.956) -0.630(-1.376; 0.116) -0.455(-1.435; 0.525)	 0.512 0.984 0.097 0.360
Household main source of income	Agricultural Non agricultural Wage Property Organization Other	Ref 1.506(-0.345; 3.357) 1.500(0.769; 2.231) 0.251(-0.933; 1.436) 1.363(0.311; 2.414) 0.300(-1.379; 1.979)	 0.110 0.000 0.676 0.011 0.724	Ref 1.469(-0.362; 3.299) 1.312(0.551; 2.073) 0.246(-0.894; 1.386) 1.302(0.221; 2.384) 0.238(-1.419; 1.895)	 0.115 **0.001** 0.670 **0.019** 0.777
Diet within the last week					

Fruit	Never Yes	Ref 0.017(-0.028;0.061)	0.461	Ref 0.331(-0.380; 1.042)	0.137
Meat	Never Yes	Ref 0.019(-0.026; 0.065)	0.403	Ref 0.029(-0.017; 0.076)	0.215
Cassava	Never Yes	Ref -0.058(-0.107; -0.009)	0.020	Ref -0.054(-0.105; -0.002)	**0.041**
Beans	Never Yes	Ref -0.003(-0.030; 0.024)	0.832	Ref -0.001(-0.030; -0.028)	0.952
Maize	Never Yes	Ref -0.006(-0.361; 0.024)	0.700	Ref -0.005(-0.038; 0.027)	0.749
Trauma scores on the CTQ					
Emotional Abuse	Mean (SD)	0.484(-0.329; 1.298)	0.240	0.320(-0.445; 1.085)	0.408
Physical Abuse	Mean (SD)	0.885(0.082; 1.688)	0.031	0.721(-0.40; 1.482)	0.063
Sexual abuse	Mean (SD)	0.193(-0.691; 1.077)	0.665	0.218(-0.668; 1.104)	0.626
Emotional neglect	Mean (SD)	-0.528(-1.344; 0.287)	0.201	-0.325(-1.093; 0.443)	0.403
Physical neglect	Mean (SD)	-0.227(-1.087; 0.633)	0.602	0.038(-0.769; 0.846)	0.925
Minimization/Denial	Mean (SD)	0.051(-0.811; 0.912)	0.907	-0.103(-0.897; 0.692)	0.798
Clinical features					
DUP	Median (IQR)	-0.074(-0.207; 0.060)	0.278	-0.064(-0.193; 0.064)	0.324
Diagnosis	Affective Non-Affective	Ref -0.768(-1.494; -0.041)	0.038	Ref -0.801(-1.502; -0.099)	**0.026**
Alternative and complementary therapy	No use Previous use	Ref -0.327(-1.004; 0.349)	0.340	Ref -0.291(-0.952; 0.370)	0.385
PANSS	Median (IQR)	-0.055(-0.134; 0.023)	0.163	-0.047(-0.121; 0.027)	0.210

For the reasoning and problem solving domain, there were significant associations in the sociodemographic variable of current living arrangements (p-value 0.001) and who the main source of income in the household is (p- value 0.030). Table 15 shows the strength of associations with other exposures.

Table 15: Association of selected exposures with the reasoning and problem-solving domain

Factor	level	Unadjusted Coeff (95% CI)	p-value	Adjusted Coeff (95% CI)	p-value
Sociodemographic characteristics					
Age or age category	Median (IQR)	-0.017(-0.053; 0.194)	0.364	-0.013(-0.051; 0.024)	0.487
Participants years of education	Median (IQR)	0.099(0.025; 0.172)	0.009	0.082(-0.003; 0.167)	0.058
Father years of education	Median (IQR)	0.013(-0.025; 0.050)	0.504	0.015(-0.024; 0.054)	0.453
Mother years of education	Median (IQR)	0.052(-0.059; 0.163)	0.355	0.051(-0.076; 0.177)	0.426
gender	Male	Ref		Ref	
	Female	-0.397(-1.078; 0.284)	0.251	-0.308(-1.008; 0.393)	0.387
Handedness	Right	Ref		Ref	
	Left	-0.402(-2.053; 1.249)	0.631	-0.418(-2.092; 1.257)	0.623
Marital Status	Single	Ref		Ref	
	Married	0.142(-0.589; 0.873)	0.701	0.444(-0.396; 1.284)	0.298
	Divorced	-0.213(-1.164; 0.739)	0.660	0.344(-0.891; 1.580)	0.583
Current Employment History	Student	Ref		Ref	
	Formal Employment	-0.586(-2.310; 1.137)	0.503	-0.441(-2.248; 1.367)	0.631
	Non formal employment	-1.391(-3.059; 0.278)	0.102	-1.102(-2.868; 0.665)	0.220
	Unemployed	-1.773(-3.450; -0.096)	0.038	-1.521(-3.295; 0.253)	0.092
Ethnicity	Bantu	Ref		Ref	
	Nilotic	-0.652(-1.840; 0.537)	0.281	-0.833(-2.054; 0.389)	0.180
	NiloHamites	1.041(-0.345; 2.426)	0.140	0.946(-0.511; 2.403)	0.202
	Sudanic	0.717(-0.920; 2.353)	0.388	0.582(-1.214; 2.378)	0.523
	Hamites	-1.351(-2.539; -0.162)	0.026	-1.176(-2.408; 0.055)	0.061
Current Living arrangements	Renting	Ref		Ref	
	Owns house	-1.407(-2.324; -0.490)	0.003	-1.138(-2.143; -0.133)	**0.027**
	Living with primary family	-1.050(-1.861; -0.240)	0.011	-1.122(-1.994; -0.251)	**0.012**
	Living with other family	-1.384(-2.547; -0.221)	0.020	-1.136(-2.377; 0.105)	0.073
	Living with friends	-0.691(-2.643; 1.260)	0.485	-0.636(-2.652; 1.381)	0.534
	None	-2.372(-4.535; -0.209)	0.032	-2.522(-4.800; -0.244)	**0.030**
Who is main source of income in the household	Self	Ref		Ref	
	Father	0.275(-0.820; 1.370)	0.621	-0.013(-1.216; 1.189)	0.982
	Mother	-0.028(-1.103; 1.047)	0.959	-0.025(-1.250; 1.200)	0.968
	Relative/ guardian	-0.001(-0.870; 0.869)	0.999	0.045(-0.902; 0.992)	0.925
	Nonrelative/ organization	-0.043(-1.240; 1.154)	0.944	0.063(-1.181; 1.307)	0.920
Household main source of income	Agricultural	Ref		Ref	
	Nonagricult	0.105(-2.138; 2.349)	0.926	-0.214(-2.541; 2.112)	0.856
	Wage	1.127(0.241; 2.014)	0.013	1.118(0.150; 2.085)	**0.024**
	Property	0.935(-0.501; 2.371)	0.200	1.016(-0.433; 2.465)	0.168
	Organization	0.611(-0.663; 1.886)	0.345	0.814(-0.561; 2.189)	0.244
	Other	-0.873(-2.908; 1.162)	0.398	-0.676(-2.782; 1.430)	0.527

Diet in the last one week					
Fruit	Never Yes	Ref -0.026(-0.067; 0.016)	0.221	Ref -0.016(-0.056; 0.025)	0.450
Meat	Never Yes	Ref -0.001(-0.044; 0.414)	0.403	Ref 0.004(-0.389; 0.047)	0.848
Cassava	Never Yes	Ref -0.040(-0.86; 0.006)	0.084	Ref -0.037(-0.083; 0.012)	0.137
Beans	Never Yes	Ref 0.009(-0.016;0.034)	0.489	Ref 0.010(-0.016; -0.036)	0.457
Maize	Never Yes	Ref 0.006(-0.022; 0.034)	0.680	Ref -0.005(-0.024; 0.035)	0.726
Trauma scores on CTO					
Emotional Abuse		0.473(-0.507; 1.453)	0.340	0.505(-0.503; 1.512)	0.322
Physical Abuse		0.823(-0.152; 1.799)	0.097	0.828(-0.181; 1.837)	0.107
Sexual abuse		0.367(-0.693; 1.427)	0.493	0.214(-0.956; 1.384)	0.717
Emotional neglect		-0.194(-1.182; 0.794)	0.697	-0.171(-1.188; 0.846)	0.738
Physical neglect		0.037(-0.997; 1.072)	0.943	0.023(-1.042; 1.088)	0.965
Minimization/Denial		0.160(-0.874; 1.194)	0.759	0.052(-0.996; 1.101)	0.921
Clinical features					
DUP		-0.153(-0.320; 0.015)	0.074	-0.121(-0.297; 0.056)	0.177
Diagnosis	Affective Non-Affective	-0.734(-1.618; 0.150)	0.103	-0.714(-1.631; 0.202)	0.125
Alternative and complementary therapy	No use Previous use	-0.738(-1.543; 0.066)	0.072	-0.665(-1.518; 0.189)	0.126
PANSS		-0.070(-0.165; 0.025)	0.146	-0.062(-0.163; 0.039)	0.225

Only results for two domains are represented above (visual learning and memory and reasoning and problem solving) as they were the domains with the largest burden and greatest mean difference in objective 1. The Tables for the other five domains can be found in the appendices. Table 16 summarizes the significant associations found across the seven different domains. There were no significant associations between trauma exposures and standardized z scores across the seven domains except for a positive association between the attention/vigilance domain and the physical abuse domain [β=1.027(CI 0.136; 1.918; p=0.024)].

Table 16: Association of selected exposures with the seven cognitive domains.

	SC	RP	VSM	VLM	WM	AV	SP
Age or age category							
Participants years of education							
Father years of education							
Mother years of education							
Gender							
Handedness							
Marital Status							
Current Employment History							
Ethnicity							
Current Living arrangements							
Who is main source of income in the household							
Household main source of income							
Fruit							
Meat							
Cassava							
Beans							
Maize							
Emotional Abuse							
Physical Abuse							
Sexual abuse							
Emotional neglect							
Physical neglect							
Minimization/Denial							
DUP							
Diagnosis							
Alternative and complementary therapy use							
PANSS							

A positive association between the exposure and cognitive scores was determined.

A negative association between the exposure and cognitive scores was determined.

SC=Social Cognition; RP=Reasoning and problem solving; VSM=Visual learning and memory; VLM= Verbal Learning and Memory; WM=Working Memory; AV= Attention/Vigilance; SP=Speed of Processing.

Discussion

The main findings of this study were that there are significant associations between various clinical, environmental and sociodemographic exposures with impairment in different cognitive domains in first-episode psychosis patients from Uganda. Also, the strength and direction of these associations varied across the seven cognitive domains. Novel associations were described between previous use of alternative and traditional therapies and impairment in the attention/vigilance domain; meat rich diets that were protective against cognitive impairment in the working memory domain and cassava rich diets associated with cognitive impairment in the visual learning and

memory domain. There were no significant associations between sex, history of childhood trauma or illness severity with any of the seven cognitive domains.

Sociodemographic risk factors for cognitive impairment

For every unit increase in age, there was a 48% increase in standardized scores of the visual learning and memory domain. For the speed of processing domain, a unit increase in age was associated with a 57% increase in cognitive scores. This age associated difference is like literature from high income countries (307-310). For neuropsychological assessment procedures, this finding points to a need to emphasize neuropsychological assessments for younger patients where scores are worse.

The lack of associations between sex and impairment in any cognitive domain differs from literature in high income countries that often highlight considerable heterogeneity in associations of cognitive impairment in men and women (311). For example, in studies from Hong Kong and China, reasoning and problem solving and working memory was associated with female gender while processing speed was associated with the male gender in women. Both genders were associated with impairment in the attention/vigilance domain and negative symptoms mediated the relationship (312-314). In another study among Chinese patients assessed using the MATRICS consensus cognitive battery, male patients had more cognitive impairment than females in the seven cognitive domains (272). These gender differences have been linked to a disturbance in normal sexual dimorphism (males are expected to have larger ventricles and smaller frontal lobes) due to hormonal and immunological factors (311).

The Hamite ethnic group were 26% and 4% more likely to be cognitively impaired in the domains of attention/vigilance and working memory respectively compared to the Bantu ethnic group. Recent genome wide association studies of Schizophrenia have implicated various risk genes each with a small effect for various cognitive domains (315). Ethnicity may be viewed as a phenotypic marker for genetic variance. As such the association of ethnicity with cognitive impairment may support the genetic underpinnings for cognitive impairment in patients with psychotic disorders (316). Large scale genetic studies are required to replicate this finding. Already studies on polygenic risk scores for cognitive impairment have shown significant correlations with

all cognitive domains (317). As Uganda is the most ethnically diverse country on earth it is plausible that the associations may be more robust (230).

There was a significant positive association between patient years of education and impairment in the domains of visual learning and memory [β=0.07(p=0.04)] and speed of processing domains [β=0.05 p=0.02)]. This differs from high income countries that described an association between patient years of education with the working memory domain (316). While it is known that the educational attainment of parents is a strong predictor of the cognitive development of children in general this was not replicated in this study. The literature on the association between parents level of education and cognitive impairment in their children is limited for first-episode of psychosis (316, 318) but has been documented in other disorders like sickle cell disease (319). In the Recovery After an Initial Schizophrenia Episode Early Treatment Program (RAISE-ETP) study, the association between patient education and cognitive impairment was found in black and not Caucasian families. Beyond genetic differences this association may be due to racial disparities in wealth education and general opportunities. To further understand this association in low resource settings, longitudinal studies are required.

In all domains except the social cognition domain, having a wage income was associated with higher cognitive scores. The finding on wage employment being associated with better cognitive function is in keeping with literature from elsewhere (320). The direction of this association needs further review as it is unclear from this study design to determine if better cognitive function ensures employment through greater job opportunities and income or employment and income is protective of cognitive function. This however is an important patient variable as it is a possible target for intervention programs like cognitive remediation (321, 322).

Diet and cognitive impairment

There was a positive association between meat and legume rich diets with impairment in the working memory domain. Although literature from high income countries has highlighted an association between obesity and cognitive impairment (323), no study to our knowledge has shown an association between a specific domain and a specific diet in psychotic populations. Fruit rich diets were not associated with impairment in any cognitive domain. In elderly nonwestern societies, fruit rich diets have been

associated with better cognitive function (324). This may support the notion that the impairment in psychotic disorders is different to that found in normal ageing. Cassava was associated with increased risk for cognitive impairment in the visual learning domain. This association of cassava with worse cognitive functioning has been described before where it is speculated that the thiocyanate toxicity due to poorly processed cassava is responsible for the impairment (325, 326). This however is the first study, to our knowledge, to highlight an association with cassava diets and a specific cognitive domain in first-episode psychosis patients.

A positive association between dietary choices and cognitive impairment, though an interesting finding; must be interpreted with caution as there are many limitations. First, diet was not assessed using standardized tools like the 24-hour dietary recall or cluster analysis of dietary patterns leading to misclassification bias in defining the exposure (327-329). Second, since diet is a one of the known exposures that can change genetic expression the underlying genetic variations may confound the association (330). Therefore, it is important to perform longitudinal studies to better understand if this association with cognitive impairment is mediated through genetic modification. Second, patients with psychotic disorders are known to be at higher risk for lifestyle disorders like diabetes and hypertension (331). This risk is thought to be due to patients with psychotic disorders often preferring starch rich diets but also having an underlying genetic risk (332). Understanding if the association of diet with cognitive impairment is not confounded by the greater risk for lifestyle diseases (which are also risk factors for cognitive impairment on their own) are required (333). Finally, the association between diet with cognitive impairment in psychosis may be moderated through the microbiome and gut-brain axis (334). Diet is an important modulator of the microbiome and gut-brain axis and as such this association found in this study could be confounded by multiple factors (335). Despite these limitations this finding highlights an interesting basis for future studies on cognition and diet in patients with psychotic disorders from low resource settings.

Trauma and cognitive impairment.

This study found only one association between attention/vigilance cognitive domain and the physical abuse trauma domain. I hypothesize that the associations between trauma and cognitive domains were not be as robust as literature from high income

countries due to the minimization (underreporting) of traumatic experiences. Minimization of trauma experiences was common in this population in keeping with literature from high income countries (336). Development of more sensitive markers for trauma exposure may help better investigate the association between childhood trauma and impairment in specific cognitive domains in first-episode psychosis. As trauma exposure is known to have long standing neurobiological changes, future studies utilizing known biomarkers of trauma exposure are suggested (337-339).

Previous studies on the association between childhood trauma and cognitive impairment have shown an association with the working memory and reasoning and problem solving domains. Not many studies have observed an association between childhood traumatic events and cognitive impairment in patients with psychotic disorders. The few studies that have highlighted an association reported an association between the attention vigilance domain and physical neglect not physical abuse (204, 340, 341). For example, one Australian study among 444 patients with Schizophrenia and 292 healthy controls replicated this finding that was mediated thorough the common variants of the FK506 binding protein 5 (FKBP5) gene (342). However, physical abuse was not defined as a single trauma domain and was combined with emotional, or sexual abuse or physical or emotional neglect. Various studies have shown that traumatic experiences are associated with changes in genetic structure and functioning (343, 344). Structural change due to traumatic stress may be the underlying mechanism responsible for impairment in cognitive function but in this population, it is unclear why it is only due to physical abuse and in the attention/vigilance domain in this setting and needs further review.

Clinical risk factors for cognitive impairment

There was a correlation between shorter DUP and increased impairment in the domains of attention vigilance [β=-0.23(p=0.009)]. This differs from other studies that found a correlation between increased DUP and increased impairment the domains of reasoning and problem solving domain (105, 345) as well as verbal learning and memory (346). This finding may support evidence of the attention/vigilance domain to be impaired earliest during psychotic disorders as has been shown in other settings (181). Longitudinal studies as well as studies in the psychosis prodrome are recommended.

To our knowledge this is the first study to report an association between previous use of alternative and traditional therapies and cognitive impairment in the attention/vigilance domain [β=-1.073(CI -1.903; -0.242, p=0.012)]. Previous work by Abbo et al showed that patients with psychotic disorders in Uganda are treated with herbs and rituals (347). Recently a study in China highlighted an association between oxidative damage and cognitive impairment at the first-episode of psychosis (348). It is unclear if the herbs used by alternative and complementary therapies are responsible for the impairment in cognition but given that some of these herbs are toxic and can cause oxidative damage; this requires further review. However, this finding highlights the importance of documenting previous use of alternative therapies and the medication provided during neuropsychological assessment.

Significant associations were observed between non-affective psychoses and the domains of visual learning and memory [β= -0.80(p=0.02)] and working memory domains [β= -0.63p=0.04)]. Among 64 Croatian patients, the association between non affective psychoses and impairment in the working memory domain were not replicated (101).This is finding also differs from high income countries in that the impairment in this setting is worse in affective psychoses compared to non-affective psychoses unlike literature in high income countries (266, 308, 349, 350). This could be due to the higher burden of non-affective psychoses in this setting (66).

Strengths and limitations

This study determined risk factors for cognitive impairment that are specific to this setting such as inadequate diet, early childhood trauma and previous use of alternative therapies. The dietary history taken was not comprehensive (only in the week prior to admission) and deeper dietary histories are required (329, 351). The descriptions for duration of untreated psychosis were prone to recall bias and standardized instruments like the Nottingham Onset schedule for duration of untreated psychosis (NOS-DUP) (352) and the Interview for retrospective assessment of Schizophrenia onset (IRAOS) need to be utilized (353). As these tools need to be administered with family members in attendance this was not possible in this study but follow up studies are being implemented (247). I also used the Childhood trauma questionnaire which assesses for trauma retrospectively and therefore prone to recall bias (35, 238, 354).

Clinical implication

Understanding the modifiable risk factors for cognitive impairment in psychotic disorders may aid in the development of screening algorithms for neuropsychological assessment in psychotic disorders (137, 294). These algorithms based on various risk factors for impairment are already in use among patients with Alzheimer's dementia (355-357) and HIV/AIDS (265, 358, 359). The algorithms are based on everyday clinical characteristics like age, sex, educational level, the amount of daily sleeping hours, reading habits and subjective complaints of memory loss (265, 360). A recent study in 98 patients with psychotic disorders showed that a clinical criterion for cognitive impairment may be more valid for neuropsychological assessment than the criteria suggested in the DSM-5 (361). The criterion studied may not be generalizable to low resource settings where I have shown the risk factors for cognitive impairment in patients with psychotic disorders differ. This study may therefore form the basis for future studies on clinical criterion for cognitive impairment in low resource settings.

Conclusion

Neuropsychological assessment in first-episode psychosis patients must consider the various exposures associated with impairment in different cognitive domains. Given the large patient numbers and limited human resource in low resource settings, there might be more benefit in prioritizing neuropsychological assessment in first-episode psychosis patients of younger age, fewer years of education, those on specific diets and those who previously used alternative and complementary therapies. Future studies using these exposures to develop screening algorithms may also have promise.

CHAPTER 7: VALIDATION OF THE NEUROSCREEN.

Chapter 4 highlighted how most measures for neuropsychological assessment in low and middle-income countries are inappropriate. Chapter 5 and 6 highlighted how in one low resource setting cognitive impairment varies in presentation and risk factors when assessed with a comprehensive neuropsychological battery. Chapter 7 will determine if a mobile health application is valid for use in this low resource setting to overcome the limitations of neuropsychological assessment with comprehensive batteries.

Introduction

There is need for valid, easy to administer, self-scoring neuropsychological instruments in clinical settings of low and middle-income countries to assess cognition in first-episode psychosis patients (37, 38, 67). The gold standard instruments from high-income countries, like the MATRICS consensus cognitive battery (MCCB), are lengthy and require specialized personnel to administer and score (4, 60). Furthermore, few gold-standard batteries have been validated for use in low and middle income countries or have established population-specific validated test performance thresholds and normative data. Mobile health (mHealth) applications may be useful in improving cognitive screening in patients with a first-episode of psychosis (38, 45, 362). Mobile health applications can be designed to be used by non-specialized staff to deliver assessments in a shorter time frame and many do not require hand scoring (177). They are extremely useful for low resource settings characterized by high numbers of patients and few highly skilled health worker settings (173, 363). Brief screening tests like Brief Assessment of Cognition in Schizophrenia have been validated as mobile health applications in high income countries (179).

NeuroScreen may be useful in the screening for cognitive impairment in patients with psychotic disorders (39, 42). It is a mhealth application that consist of brief neuropsychological tests that are delivered using a tablet (39). In an HIV population, NeuroScreen demonstrated clinically useful psychometric indicators for a screening measure (59, 364, 365). It was found to have high sensitivity in detecting cognitive impairment; with moderate correlation with paper and pencil tests assessing the same cognitive domains (39, 40). It was also brief and narrow in scope assessing for impairment in six cognitive domains in less than an hour (225). In HIV/AIDS

populations, NeuroScreen was used on an outpatient setting and found to have a high level of acceptability both by patients and clinicians (39). It could also score the assessment implying that nonspecialised staff could deliver the assessments (365).

NeuroScreen has never been validated for use in patients with psychotic disorders. It is also unclear if the tests administered by NeuroScreen in assessment for impairment in various cognitive domains have the prerequisite sensitivity and specificity when compared to the corresponding domain scores of the MATRICS consensus cognitive battery. It would also be important to know if NeuroScreen measures the same constructs as the MCCB across similar domains as well as whether it can discriminate between cases and controls with impairment. Finally, patients with psychotic disorders in low and middle-income countries present with greater prevalence of affective psychoses (43), longer duration of untreated psychosis (44-47), greater illness severity (48) higher antipsychotic dosages (49, 50) and greater burden of previous childhood trauma (51, 52). The impact of these clinical, environmental and social characteristics factors on NeuroScreen test scores is not known.

We aimed to examine validity of NeuroScreen for neuropsychological assessment in patients with a first-episode of psychosis. Specifically, we determined the sensitivity, specificity, concurrent validity and discriminant validity of NeuroScreen as compared to the MATRICS consensus cognitive battery across the different cognitive domains. We also determined the impact of clinical, environmental and social characteristics common among patients in this setting on neuropsychological test performance of NeuroScreen.

Methods

Study design: This was a cross sectional study in which we compared NeuroScreen to the MATRICS consensus cognitive battery.

Sample size: Using Buderer's formula for estimating sample sizes in validation of medical tests (229) we anticipated that the prevalence of CI among patients with psychosis would be 62% based on our study findings in objective 1. Precision was set at 10%, and at 95% confidence intervals. The desired sensitivity was set at 80% and desired specificity of 90% because cognitive impairment is common at the first-episode of psychosis (20, 366, 367). The sample size calculated was 95 participants for sensitivity analyses and 99 for specificity analyses.

Study Instruments: The sociodemographic questionnaire, PANSS, NeuroScreen and the MCCB.

NeuroScreen: This is a collection of brief neuropsychological tests administered using a smart phone application (225). It assesses six cognitive domains - learning and memory, working memory, processing speed, motor speed and executive function. In this study administration of NeuroScreen was performed by research assistants who had received training on its use. NeuroScreen was available in English and Luganda. Participants decided preference of language administration.

NeuroScreen does not require extensive support from the research assistant or clinician. The research assistant is primarily an observer to ensure that the participant is doing the assessment rather than administering the tests. In some instances, however the research assistant/ clinician handles the tablet to ask the test questions while other sections require the participant to answer the tests as shown on NeuroScreen.

Current limitations of this version of the NeuroScreen include the lack of tests assessing for impairment in the social cognition and visual learning and memory domains. Tests can be performed offline, but an internet connection is needed to upload results for scoring. Scoring is instant, but currently getting an indication is not possible although an updated version will include assignment if impairment once validation and cut offs have been determined. Tests of the NeuroScreen were described in the methods section.

Study Procedure: The NeuroScreen was translated, pretested and piloted for use in our study population prior to commencing the study. On resolution of psychotic symptoms participants were assessed for cognitive impairment using the MCCB and the NeuroScreen. Half the participants had the MCCB administered first while the other half had the NeuroScreen administered first. The participant was introduced to the NeuroScreen by the research assistant. This involved giving a brief overview of how the assessment is performed and the role of the research assistant. The research assistant then registered the participant in the app by taking the participants biodata. The research assistant selected the tests to administer and the language before handing the tablet over to the participant to begin the assessment.

Data Analysis: Chi square and student t tests were used to compare cases and controls across various sociodemographic characteristics. Standardized scores for the MCCB and NeuroScreen were calculated using the means and standard deviations of the healthy peers. Two composite scores for NeuroScreen and the MCCB were then computed. The composite score comprised of standardized scores for the domains of verbal learning and memory, attention/vigilance, speed of processing, working memory and reasoning and problem solving.

To examine sensitivity and specificity of NeuroScreen, Receiver Operating Curve (ROC) scores at various cut-offs were computed using the standardized and categorized MCCB scores as the gold standard. The MCCB was our dependent variable. Scores less than 2sd below the mean (SD <-2) in a particular domain of the MCCB were categorized as impaired and categorized as 1 while those not impaired (SD>-2) were categorized as 0. Thereafter, positive predictive and negative predictive values, as well as sensitivity and specificity for the optimized NeuroScreen cut-off score were calculated.

Multiple regression analyses were conducted to determine the impact of greater prevalence of affective psychoses (66), longer duration of untreated psychosis (129, 232-234), greater illness severity (235), higher antipsychotic dosages (236, 237), and more childhood trauma (148, 238) on the test scores of the NeuroScreen.

To determine the discriminant validity Wilcoxon sign ranked tests were calculated for the difference of NeuroScreen test scores between cases and controls. Concurrent validity was determined by calculating the Spearman's correlation coefficients between NeuroScreen and MCCB.

Results

In total 102 participants had both the MCCB and NeuroScreen administered. This included 40 patients with first-episode of psychosis and 62 healthy peers. The mean (SD) age of the FEP participants was 26.9 (1.3) while that of the healthy peers was 27.3 (0.9) years. Cases and controls did not differ in age, gender and years of education. This is highlighted in the Table below.

Table 17: Baseline characteristics of the cases and controls.

Item	level	FEP	Healthy peer	p-value
Age	Mean (SD)	26.9(1.3)	27.3(0.9)	0.828
Gender	Male	19(50)	20(34.5)	0.184
	female	19(50)	38(65.5)	
Respondents years of school	Mean (SD)	9.5(4.3)	9.5(5.2)	0.978

The mean time to assess six domains on the NeuroScreen was 27.8mins (SD4.6; Range 20-43minutes). The mean time to administer the MCCB was 100minutes and another 30minutes to score the results. The mean time for the patients with the NeuroScreen was 29.4minutes (SD 5.04) while the mean time for the controls was 26.9 minutes (SD 4.02); [Mean difference -2.5, p-value 0.007].

For validity of the NeuroScreen, the area under the curve (AUC) for comparisons of the NeuroScreen composite score to the MCCB was 0.7899 as shown in the graph below. For the specific cognitive domains, the AUC were 0.554, 0.683, 0.546, 0.595 and 0.580 for verbal learning, working memory, reasoning and problem solving, attention/vigilance and speed of processing, respectively.

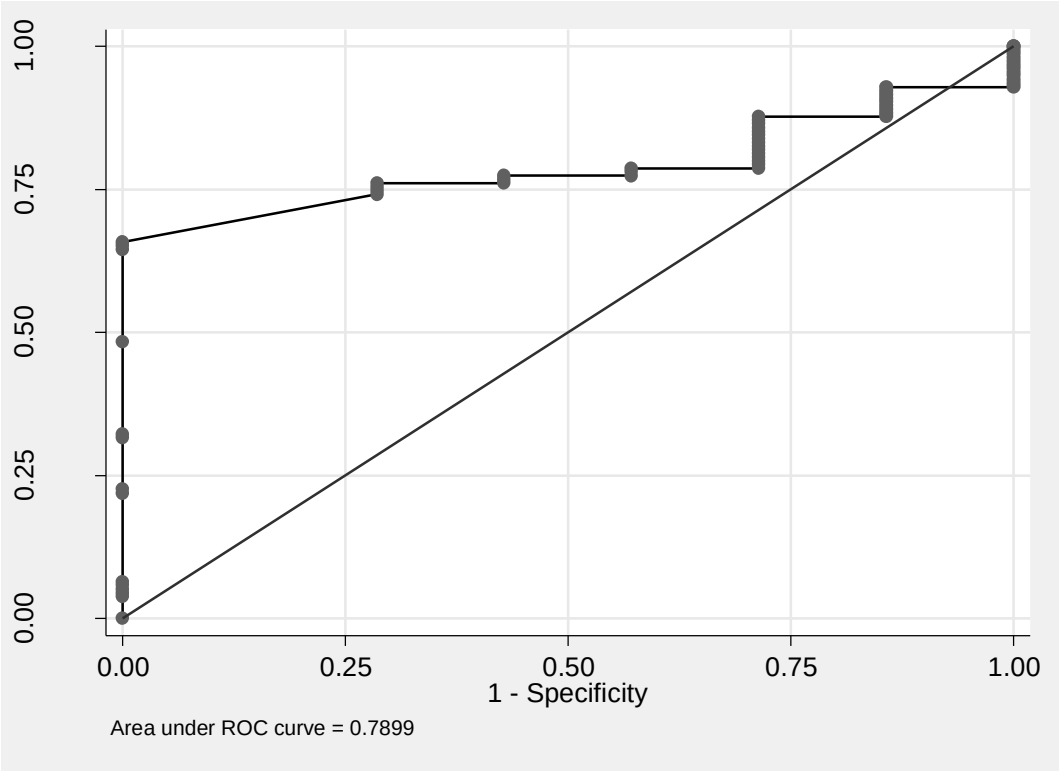

Figure 15: Receiver operating characteristics for the composites scores from the five domains of the NeuroScreen and MCCB composite scores.

The sensitivity, specificity, positive predictive value, negative predictive value, likelihood ratios for cut off points that optimized the balance between sensitivity and specificity, test false positive, test false negative are shown in Table below. Discriminative analysis for the NeuroScreen composite score indicates that a score of 1SD obtains the best balance between sensitivity (64.4%) and specificity (20.0%). This is shown in the Table below.

Table 18: Possible cut offs for the NeuroScreen composite score

DOMAIN	CUT POINT	SENS	SPEC	CORRECT CLASSIFIED	PPV	NPV	FALSE+ RATE	FALSE- RATE
NEUROSCREEN COMPOSITE SCORE	≥-3	0.0	100.0	9.43	-	9.43	0.0	100
	≥-2	0.0	100	9.43	-	9.43	0.0	100
	≥-1	13.3	100	22.0	100	11.4	0.0	86.7
	≥0	24.4	80.0	30.0	91.7	10.5	20.0	75.6
	≥1	64.4	20.0	60.0	87.8	5.9	80.0	35.6
	≥2	93.3	0	84.0	89.4	0	100.0	6.7
	≥3	97.8	0	88.0	89.8	0	100.0	2.2

SENS= Sensitivity; SPEC=Specificity; PPV=Positive predictive value; NPV=Negative predictive value.

In the cases, the effect of illness severity, duration of untreated psychosis, diagnosis, mean drug doses, age and gender on domain scores was calculated. This is shown in the Table below.

Table 19: Association of various common assessment problems on NeuroScreen test scores

Domain	Illness severity	DUP	age	Chlorpromazine equivalents	Diagnosis (non-affective)	Gender (female)
	B (95% CI) p-value	B (95% CI) p-value	B (95% CI) p-value	B (95% CI) p-value	B (95% CI) p-value	B (95% CI) p-value
NeuroScreen composite score	-0.554 (-4.22; 3.12) P=0.714	0.028 (-3.011; 3.067) P=0.984	0.067 (-0.127; 0.261) P=0.489	-0.003 (-0.009; 0.002) P=0.081	-3.761 (-14.694; 7.172) P=0.456	0.142 (-3.379; 3.664)
Verbal Learning and Memory	-0.16 (-0.26;-0.05) P=0.004	-0.05 (-0.21; 0.09) P=0.492	-0.09 (-0.16; -0.04) P=0.002	-0.01 (-0.01; 0.003) P=0.798	-0.9 (-1.90; 0.10) P=0.079	-0.29 (-1.45; 0.86) P=0.613
Working memory	-0.06 (-0.19; 0.06) P=0.304	0.25 (-0.11; 0.62) P=0.178	-0.02 (-0.06; 0.02) P=0.319	0.002 (-0.003; 0.009) P=0.362	-0.825 (-1.88; 0.23) P=0.123	-0.01 (-0.64; 0.62) P=0.971
Reasoning and problem solving	8.64 (-38.4; 55.72) P=0.709	-18.14 (-148; 112.30) P=0.779	-2.66 (-12.21; 6.89) P=0.581	-0.002 (-0.10; 0.09) P=0.957	-169 (-542; 203) P=0.361	-57 .86 (-81.01; 196.74) P=0.410
Attention	-0.47 (-2.21 ; 1.26) P=0.583	-0.08 (-5.39 ; 5.23) P=0.977	0.30 (-0.37; 0.98) P=0.374	-0.03 (-0.13; 0.06) P=0.442	-8.96 (-23.41; 5.49) P=0.216	-7.85 (-17.62; 1.92) P=0.114
Processing speed	0.53 (-0.89; 1.94) P=0.213	0.92 (-3.44; 5.29) P=0.324	-0.24 (-0.65; 0.18) P=0.263	-0.07 (-0.15; 0.01) P=0.075	7.66 (-4.71; 20.04) P=0.217	4.82 (-1.38; 11.01) P=0.126

For the discriminant validity, composite scores of NeuroScreen differed between patients and controls (z=4.787, p-value <0.0001). Other comparisons between cases and controls are shown in the Table 20 .

Table 20: Discriminant validity of the NeuroScreen.

Domain	Median (IQR)		Wilcoxon Rank sum	Pvalue
	FEP(n=40)	Healthy peers(n=62)		
Verbal Learning and Memory	0(0, 0)	10(0, 13)	4.912	<0.001
Working memory	5(3.7 , 6.5)	5.5(4.5, 6.5)	0.607	0.544
Reasoning and problem solving	33.7(19.5 , 48.8)	35.7(20.6, 56.7)	0.040	0.968
Attention	33.6(25.3 , 41.3)	26.4(21.6, 37.3)	0.160	0.873
Processing speed	82.6(71.2 , 92.6)	77.9(71.5, 86.4)	0.207	0.836
Composite z-score	-1.01(-1.34; 0.65)	0.09(-1.01; 0.71)	4.787	<0.0001

For convergent validity, Spearman's rank correlation coefficients were calculated between the composite scores of the NeuroScreen and the generated composite score of the five domains of MCCB that measure the same domain. This is shown in figure 16.

Pearson Correlation Coefficients, N = 54
Prob > |r| under H0: Rho=0

	verball1	workmem1	reasons1	att1	spdproc1	social1	visuall1
vll_1	0.29567	0.27095	0.11939	0.21144	0.26571	0.08376	0.28501
vll_1	0.0300	0.0475	0.3899	0.1248	0.0521	0.5471	0.0367
nsp	0.37152	0.44535	0.37954	0.32750	0.40545	0.17285	0.31384
nsp	0.0057	0.0007	0.0046	0.0156	0.0024	0.2113	0.0208
tmt22	-0.11327	-0.13171	-0.15886	-0.13625	-0.16443	-0.21247	-0.09453
tmt2.2	0.4148	0.3424	0.2512	0.3259	0.2348	0.1230	0.4966
tmt	-0.27648	-0.34999	-0.25730	-0.13670	-0.20562	0.00158	-0.23073
tmt	0.0430	0.0095	0.0603	0.3243	0.1358	0.9909	0.0932
vd	0.31402	-0.14953	-0.01334	-0.00551	-0.03503	0.20533	0.03983
vd	0.0208	0.2805	0.9238	0.9684	0.8014	0.1364	0.7749

Figure 16: Correlation between test scores of the NeuroScreen and MATRICS consensus cognitive battery.

Domains of Neuroscreen; Vll_1=verbal learning and memory; nsp=working memory; tmt22=reasoning and problem solving; tmt=attention/vigilance; vd=speed of processing

Discussion

The main findings of this study were 1) a five domain composite score of the NeuroScreen is moderately accurate for brief neuropsychological assessment in patients with psychotic disorders. 2)"*Common assessment problems*" like illness severity, duration of untreated psychosis and antipsychotic dosages were not associated with test performance of the NeuroScreen. The NeuroScreen may therefore be appropriate for use in this setting as it is also attractive in terms of the duration, scope of assessments and its ability to be used by non-specialized mental health cadres.

Validity of the NeuroScreen

The sensitivity and specificity of the individual domains of the NeuroScreen was poor. However, the accuracy (area under the curve) of 78.9% of the composite score is noteworthy as not many tests have been validated against a gold standard (43, 281, 368). The composite score of the NeuroScreen was able to discriminate between cases and healthy peers. This is like other brief tests like the Brief Assessment for Cognition in Schizophrenia (260).For example, the NeuroScreen composite score had better accuracy than tests like the COBRA and SOCRATIS which assess for cognitive impairment in only one domain of social cognition (281, 368). There was poor correlation between the composite score from five domains of the NeuroScreen and the MCCB. This may be because no factor analysis was performed yet there might be other relatively dissociable domains of performance measured by the NeuroScreen (260).

Selecting cut offs for the various domains.

The common rule of thumb in determining the best cutoff for a diagnostic test is where the sensitivity and specificity are almost equal. In some scenarios greater sensitivity may be preferred (for example if disease is highly contagious) and in others higher specificity may be preferred (if the diagnostic test is expensive or difficult to perform). As the MCCB requires specialized staff that are not easily available, greater specificity of the NeuroScreen may be preferred for this setting. At a cut off of -1SD below the mean one would confidently refer patients who require further assessment with the MATRICS consensus cognitive battery. As the NeuroScreen is a screening instrument the MATRICS consensus cognitive battery would then be administered to confirm the

diagnosis. Also, the MATRICS consensus cognitive battery has multiple tests per domain that would give a better description of the impairment.

Effect of common assessment problems on the NeuroScreen

There was no association between "*common assessment problems*" of age, gender, antipsychotic dosages, illness severity, duration of untreated psychosis and diagnosis with the composite score of the NeuroScreen. This finding is important as these means the NeuroScreen can be utilized in low resource populations like Uganda where these patient characteristics are common. For individual domain scores, test scores of the verbal learning and memory domain were associated with illness severity and increasing age. These factors therefore need to be controlled for when performing assessments in the verbal learning and memory domain. In patients presenting with early onset Schizophrenia (illness before 18 years of age) verbal learning and memory was the most affected cognitive domain while attention/vigilance was the least impaired domain (369). This might imply that verbal learning and memory is impaired earliest in the course of the psychotic illness and the NeuroScreen is better suited to use in early onset Schizophrenia and not first-episode or chronic psychosis patients. Further studies of the NeuroScreen across the psychosis spectrum are required.

Limitations of the scope of the NeuroScreen

The Neuroscreen does not include the visual learning and memory as well as the social cognition domain yet these domains have been shown to be important for neuropsychological assessment in this low resource setting. Also, the mean time for assessment of five domains was short, the assessments did not include the visual learning and memory and social cognition domains. The NeuroScreen might therefore take longer to perform assessment for all seven domains. The NeuroScreen has limited involvement by the health workers in the assessments which may have affected test performance. Studies have shown that rapport improves neuropsychological test performance in tests like the grooved peg board and the controlled oral word test (370). This will need to be assessed in further studies. The study was underpowered to determine the accuracy and cut offs for the individual five different cognitive domains. Using the sample sizes of impairment calculated in objective 1 the required sample sizes were 155, 129, 110, 122 and 203 for verbal learning, attention/vigilance,

reasoning and problem solving, working memory and speed of processing respectively. This could have led to less than acceptable accuracy as found above.

Clinical implications

According to the 2014 Working Group on Screening and Assessment (WGSA) guidelines, the Neuroscreen may an appropriate screening measure (59). The composite score from five domains of the NeuroScreen a) can be used to identify early on individuals at high risk for impairment, b) is sensitive enough to determine those who need further review, c) is brief and narrow in scope, d) can be administered as part of a routine clinic visit, e) can be administered by support staff with the help of an electronic devices. It is important to determine if it can be used to monitor progress and outcomes in longitudinal study designs.

Strengths and Limitations of the study design

The study was carried out according to best practices for critical appraisal diagnostic test studies (371). First there was an independent blind comparison with the gold standard. Specialized staff performed the gold standard assessment while research assistants supervised the NeuroScreen. Neither assessor was aware of the status of the patient at the time of the test. Second, the diagnostic test was evaluated in patients that one is likely to see in this setting i.e. severe illness severity, more affective psychoses and on high antipsychotic dosages (66).

One limitation however of the study is that the study was not replicated in an independent sample. Future studies are planned to do so as well as including neuropsychological tests for visual learning and memory and social cognitive domains. The test-retest ability of the Neuroscreen was not assessed in this study. This is a major limitation as the consistency of test scores over time is a key component of validating a screening instrument . The high rates of disengagement from care among patients with first episode psychosis made this component of analysis difficult. In yet to be published data I will show that 65% of patients disengaged immediately discharge from in-patient care .

Conclusion

The NeuroScreen is an appropriate measure for brief neuropsychological assessment in patients with psychotic disorders in low resource settings. Future studies in which

the validity of the tests for assessment of specific domains are required. Further studies are required to determine if this tool can used to monitor progress and outcomes in a longitudinal study design.

SUMMARY OF THE AIMS METHODS AND RESULTS OF THE THESIS

A recap of the aims, methods and key results are highlighted in Table 21.

Table 21: Summary of the results in the thesis

Aim	Brief methodology	Key results
Aim 1: To determine if the measures researched for brief neuropsychological assessment in patients with psychotic disorders from low and middle-income countries are appropriate.	**Systematic review** **Population:** Patients with psychosis **Intervention:** Use of a brief neuropsychological test for assessment **Comparator:** Healthy peers **Outcomes:** Tests used, domains assessed, cadre assessing, duration of assessments, validation **Study designs:** All quantitative study designs **Settings:** Low and middle-income countries as defined by the World Bank	Tests researched for brief neuropsychological assessment in patients with psychotic disorders in low and middle-income countries are not appropriate for use. The tests are 1) not used early at the first-episode of psychosis 2) not validated against comprehensive batteries 3) take long to perform 4) not used in the clinical setting 5) performed by specialized staff and 6) not used for follow up.
Aim 2: To compare the prevalence and profile of cognitive impairment between first-episode psychosis patients and healthy peers in a low and middle-income country.	**Study design:** Comparative cross sectional study design **Sample size:** 129 first-episode psychosis patient and 52age and education matched healthy peers **Tools used:** MATRICS consensus cognitive battery, MINI International Neuropsychiatric Inventory, sociodemographic questionnaire. **Main study outcomes:** -Prevalence of cognitive impairment -Profile of impairment -Differences of impairment across the seven domains	1) Large burden of cognitive impairment especially in the visual learning and memory domain. 2) Large and significant differences between the mean cognitive scores of first-episode psychosis patients and healthy peers. 3) The reasoning and problems solving domain is most impaired in patients with first-episode psychosis

Aim 3: To determine the association between patient variables and impairment in specific cognitive domains in first-episode psychosis patients from a low and middle-income country.	**Study design:** Cross sectional study design **Sample size:** 129 first-episode psychosis patient **Tools used:** MATRICS consensus cognitive battery, MINI International Neuropsychiatric Inventory, sociodemographic questionnaire. **Main study outcome:** Risk factors for cognitive impairment	1) These associations between patient variables and impairment in specific cognitive domains vary across the seven cognitive domains. 2. Novel associations were described between previous use of alternative and traditional therapies and impairment in the attention/vigilance domain; meat rich diets that were protective against cognitive impairment in the working memory domain and cassava rich diets associated with cognitive impairment in the visual learning and memory domain. 3.There were no significant associations between sex, history of childhood trauma or illness severity with any of the seven cognitive domains.
Aim 4: To determine the validity of the NeuroScreen (a collection of brief neuropsychological test delivered via smart phone) for brief neuropsychological assessment in patients with psychotic disorders.	**Study design:** Cross sectional study design **Sample size:** 102 patients who received the NeuroScreen and MCCB **Tools used:** NeuroScreen and MCCB **Main study outcome:** Sensitivity, specificity, concurrent and discriminant validity, effect of common assessment problems on test scores	1) Area under the curve for NeuroScreen composite score was 0.789. 2) NeuroScreen composite score could discriminate between cases and controls. 3) There was poor correlation between NeuroScreen composite scores with MCCB composite score

CHAPTER EIGHT: DISCUSSION OF THESIS FINDINGS

In Chapters 4-7, I presented the results and brief discussions for the four main research questions of the thesis. In this section I will tie the results together and discuss the clinical implications and future recommendations from my findings.

Main findings

This thesis proposed 4 null hypotheses, namely 1) brief neuropsychological assessment measures researched in low resource settings are appropriate; 2) a large burden and differing profile of cognitive impairment would not be evident in the study sample; 3) no associations would exist between patient variables and impairment in different cognitive domains., and 4) the NeuroScreen would not have the prerequisite sensitivity and specificity to identify cognitive impairment in this study sample.

In the study addressing aim 1, most brief neuropsychological assessment measures researched in low resource settings were inappropriate according to the WGSA criteria. Most measures required specialized personnel to administer and score the assessments, took long to administer and did not use technological support. Also, no measure had been validated for use in this setting. The heterogeneity of tests made meta-analysis impossible and as such the burden and profile of impairment were not summarized. There were no measures that had been designed for use specifically in patients with psychotic disorders from low resource settings where patient volumes are high with limited human and financial resources. To ensure greater uptake of neuropsychological assessment in patients with psychotic disorders in this setting, there is need for development of appropriate tools. More measures need to be validated for use in this setting than is currently the case. Also these measures need to be able to overcome the human resource challenges in this setting. The use of technological support as has been utilized in neuropsychological assessment for other disorders like Alzheimer's disease must be promoted.

In the study addressing aim 2, I highlighted the differences in cognitive impairment between first-episode psychosis patients and their healthy peers. Unlike literature from high income countries, most patients were impaired in the visual learning and memory domain while the largest difference between cognitive performance of patients and healthy peers was in the reasoning and problem solving domain. There were also no differences in scores of the social cognition domain between first-episode psychosis

patients and healthy peers. The results for aim 2 highlighted how the domains commonly impaired in first-episode psychosis patients in this setting differ from those described in high income countries (57, 263, 350). As such there is need for promotion of neuropsychological assessment in domains more impaired in this setting. It is also important that the measures for assessment of social cognition in this setting need to be developed and validated as the MATRICS consensus cognitive battery failed to differentiate scores of first-episode psychosis patients and healthy peers.

In the study addressing aim 3, I found that the association between clinical variables and cognitive impairment differed across the seven cognitive domains in first-episode psychosis patients. As described at the beginning of chapter 6, knowledge of these clinical variables is an important part of neuropsychological assessment as it determines what factors to control for during assessment procedures. It also guides policy on what clinical variables may point to a high risk of cognitive impairment in first-episode psychosis patients. Furthermore, these clinical variables may provide the basis for development of interventions to reduce cognitive impairment in this setting. Again, the findings highlighted that the clinical variables associated with cognitive impairment across the different cognitive domains in this setting differ from literature described in high income countries (100, 145, 273, 372). I did not find, for example, an association between any domain of childhood trauma with impairment in any cognitive domain. This is in keeping with similar literature in low resource settings but differs from literature from high income countries (35). The associations of clinical variables with impairment in specific domains highlights how various patient variables in this setting need to be considered in developing appropriate measures. For example, further research is needed on the neuropsychological assessment in young versus older psychotic patients since increasing age was associated with cognitive impairment in different domains. Lack of gender differences across the cognitive domains needs further review. Neuropsychological assessment must be cognizant of employment having a strong association with cognitive impairment with all domains except the social cognition domain. The results on the association between ethnicity and diet need to be replicated. Diet may be a feasible intervention to improve cognitive impairment in patients with psychotic disorders in low resource settings (305, 373). Better designed studies on trauma and cognitive impairment in first-episode psychosis patients from this low resource setting are required.

In the study addressing Aim 4, I determined that the NeuroScreen may be valid for neuropsychological assessment in first-episode psychosis patients from low resource settings. The NeuroScreen was able to differentiate the cognitive performance between the first-episode psychosis patients and their healthy peers. A composite score of the NeuroScreen was also sensitive when compared to the gold standard MCCB battery. Importantly, the patient variables associated with different cognitive domains did not impact the NeuroScreen composite score test performance. This adds credence to its use in low resource settings. The results however have some caveats. First the composite score of the NeuroScreen met the prerequisite sensitivity and specificity yet the individual domain scores did not. Individual domain scores and not composite scores are preferred in describing cognitive impairment (26). Different medication and remediation strategies have varied impact on different domains and as such it is important to track individual cognitive domain performance (289, 374, 375). Second, the NeuroScreen does not assess for impairment in the visual learning and memory domain which is most impaired in this setting. Further work on adding that domain and the social cognition domain to the NeuroScreen are required.

Clinical Implications

Neuropsychological assessment needs to become routine in the care of first-episode psychosis patients from low resource settings. The thesis highlights how there is little assessment in routine care with most literature coming from research studies using inappropriate tools. Inappropriate measures cannot provide a clear picture of the true burden of cognitive impairment in first-episode psychosis patients. This is important since this impairment has been described as major predictor of poor patient outcomes (18, 376). As such there is limited literature on the burden of cognitive impairment to drive policy promoting routine impairment.

The various clinical variables associated with impairment in the seven cognitive domains point to the potential of developing interventions to reduce cognitive impairment in this setting. Some clinical variables found in this thesis like increasing age have been highlighted before in the literature from high income countries. This thesis however highlighted how these clinical variables may impact neuropsychological assessments for particular domains. Also, the thesis described clinical variables associated with cognitive impairment that are more common in low resource settings like previous use of alternative therapies and long durations of

untreated psychosis. Interventions targeting these clinical variables may improve outcomes for cognitive impairment in low resource settings. Different diets being associated with cognitive impairment is specifically important as these are possible easy to develop interventions for cognitive impairment in this setting was a novel finding. Interventions targeting dietary choices for cognitive impairment are an interesting prospect (157). Longitudinal studies to elucidate the mechanisms underlying this association are beneficial.

Greater use of mobile health technologies may revolutionize the care for first-episode psychosis patients in this setting. The NeuroScreen highlighted how mobile health technologies could overcome the human resource limitations common in low resource settings. The reduced time for assessment and scoring of the tests is noteworthy highlighting how they NeuroScreen has potential to be used in the clinical setting and not just a research setting. Although the study was specific to improvement of neuropsychological assessment, these mobile health applications also have immense potential in tracking various aspects of care like engagement, drug adherence and symptom progression.

There is renewed interest in the remediation of cognitive impairment in first-episode psychosis patients (294, 377). The remediation, however, is often for specific cognitive domains and not for a unitary cognitive construct (289, 374, 375, 378, 379). For example, many of the cognitive remediation programs target the reasoning and problem solving, verbal learning and memory and working memory domains yet these are not the most impaired domain in this setting (374, 378, 379). Also, many of these cognitive remediation programs were designed in high income and not low income countries (380, 381). Response to these remediation programs may also be dependent on underlying genetic factors (382). The thesis has highlighted how cognitive impairment in this low resource setting is different from that described in high income countries. There is a serious risk that cognitive remediation programs currently being developed in high income countries may not be effective in low resource settings. Given the large burden, different presentation and risk factors for cognitive impairment in this population it is important to determine whether these remediation programs are effective in this setting.

Future directions

Neuropsychological assessments for first-episode psychosis patients like the NeuroScreen need to be validated for use across the psychosis spectrum. Although the study designs included in this thesis were all cross sectional in nature the ability of a test to be used repeatedly over time is essential (27). There is need to determine the ability of NeuroScreen to be used in longitudinal assessments across the whole spectrum of the psychosis illness. This is important as literature from high income countries has highlighted the changing profile of cognitive impairment across the psychosis spectrum (15, 120, 383).

It is also imperative that future studies correlate neuropsychological assessment to functioning in the real world (384). Cognitive impairment is a key domain of psychotic disorders given its association with worse long term social and functional outcomes. It is therefore imperative that the assessment measures like the NeuroScreen can be used to track the association of cognitive impairment with real world long term functional outcomes like quality of life and school/work functioning. In this setting where there are no social services for supported employment, the assessment measures must be correlated to non-formal employment like taking part in agricultural activities which is the main economic activity in Uganda.

Future work in identifying the genetic risk factors for impairment may have benefit in the long term in developing rapid tests for cognitive impairment (315). In this study we found significant association between ethnicity and cognitive impairment in the domains of working memory and attention/vigilance. Cognitive impairment is known to be moderately heritable with strong evidence from genome wide association studies of multiple gene loci associated with different cognitive domains (385). There is still limited diversity in genetic studies of psychotic disorders with most studies from Caucasian populations (386, 387). This has led to a small proportion of the heritability for cognitive impairment in psychotic disorders to be identified. Large scale genome wide association studies among African populations are required. African ethnicity has greater genetic diversity and genetic adaptations in response to environmental factors such as climate, diet, childhood adversity and infectious disease (388). Currently there is a large scale neuropsychiatric genetics study in patients with psychotic disorders in Uganda (191). Addition of cognitive measures to the study may be of benefit to help understand the genetic underpinnings of cognitive impairment in psychotic disorders.

Dietary changes may be a feasible intervention that can easily be scaled up to improve cognitive function for first-episode psychosis patients. Studies on dietary supplementation in other disorders like Alzheimer's dementia have shown some benefit (305, 324, 373). It is unclear however if the same benefit would be seen in this population and therefore requires further review. Few studies have shown the benefit of diets rich in folic acid while others have noted that vitamin D supplementation would worsen cognitive function in patients with Schizophrenia (389, 390). Most studies were small preliminary studies hence better designed follow up studies are required to confirm the association found here between different dietary choices and cognitive impairment in different cognitive domains. This would also help better understand the confounders in this association.

The validity of interview based measures of cognition in this setting needs to be determined as these measures may be more practical for clinicians already accustomed to interview formats (391). Interview based measures like the Cognitive Assessment Interview and the Schizophrenia Cognition Rating Scale are already in use although they have not been validated in low resource settings (392, 393). Interview based measures that take into consideration the different burden, profile and risk factors for cognitive impairment in this setting are required. If these measures can then be utilized together with smart phone technology, it would revolutionize neuropsychological assessment in clinical settings of low income countries.

Further studies are required to elucidate the causal mechanisms through which early childhood trauma predicts cognitive impairment in psychotic disorders. As this was an observational study, I was unable to provide strong evidence of causation and yet experimental studies of childhood trauma are unethical. I also used the Childhood trauma questionnaire which assesses for trauma retrospectively and therefore prone to recall bias (35, 238, 354). There was also minimization of the traumatic experiences through reduced ability of patients to appropriately contextualize past experiences (336, 394). Also, neither early childhood trauma nor cognitive impairment are unitary constructs (35, 152, 153, 338, 354, 395, 396); the course of cognitive impairment in psychotic disorders differs throughout the illness (13, 350) and the timing of early childhood trauma in patients is not consistent. All these factors may confound our estimation of the strength of associations between early childhood trauma and cognitive impairment in first-episode psychosis patients. Since there is literature to

support the genetic differences in trauma response, use of study designs that can overcome these confounding factors like Mendelian randomization studies are recommended. Mendelian randomization is an emerging study design that may allow one to determine causality and control for various confounders that are common in childhood trauma research (397)

Strengths of the thesis

The observational studies were performed among patients with a first-episode of psychosis. This is an important patient demographic in psychosis research as most interventions during this period have the largest effect on patient outcomes. In this thesis the first episode psychosis patients were also antipsychotic naïve and as such the descriptions of impairment highlighted here are not changed by antipsychotic medication.

This is one of few studies in Africa that have used the MATRICS consensus cognitive battery for neuropsychological assessment in Africa. Previous studies were primarily performed in South Africa and among Caucasians (35, 36, 204). This is one of the few studies to perform neuropsychological assessment among first-episode psychosis patients of African descent. This gives a marker of cognitive impairment in first-episode psychosis patients of African descent when assessed with the MATRICS consensus cognitive battery.

The thesis studied factors that are more common in low resource settings. For example, my findings on the association of cognitive impairment with alternative and complementary therapies as well as diets specific to this setting were novel in that they describe factors more common in this setting.

Limitations of the thesis

Unfortunately, we only excluded participants requiring urgent medical attention at enrollment and the rest were deemed able to consent. On resolution of psychotic symptoms, participants were asked for permission to have neuropsychological assessments performed. In hindsight we should have used the University of California, San Diego Brief Assessment of Capacity to Consent (UBACC) test at enrollment. This is a 10-item scale used to determine one's comprehension of the research purpose and ability to make an informed decision (398). It is being used at

the hospital in the Neuropsychiatric genetics of African populations-psychosis study, with a cut off score of 10 and above deemed able to consent to the study (399).

Assessing for intellectual ability in this population may have added another dimension of our understanding of cognitive function. Although the cognitive profiles and intellectual ability both provide a measure of cognitive function, intellectual ability assesses whether these abilities are fully developed in an individual (120). In patients with Schizophrenia, intellectual ability may be more impaired than most domains (6).However the MATRICS initiative did not include intellectual ability as it is a unitary construct covering various domains. .

The psychometric properties of the MATRICS consensus cognitive battery have not been determined in this population (43, 58). The MATRICS consensus battery was chosen since it is suggested as the gold standard for neuropsychological assessment in psychotic disorders. Inability to determine the psychometric properties was due to time and financial limitations rather than not knowing the importance of the process. Also, some of the tests used in the MATRICS consensus cognitive battery have been used and validated individually in this setting implying that the results may be representative of cognitive impairment in this setting.

The study did not assess for metabolic syndrome and associated risk factors like weight, height, abdominal circumference, blood pressure, random blood glucose and non- fasting lipid profile (400). Recent literature in similar settings to this one have highlighted an association between psychotic disorders and greater risk for metabolic syndrome (401). Metabolic syndrome is a key risk factor for cognitive impairment in patients with psychotic disorders (402). In comparative studies, metabolic syndrome has been found to be associated with worse cognitive function in primarily in the domains of working memory, attention/vigilance, verbal learning and reasoning and problem solving (403, 404). This relationship is mediated thorough various immunological, genetic and sociodemographic factors which might present differently in low resource settings (405, 406). Metabolic syndrome may also negatively impact cognitive remediation studies thus an important variable to study (407). Future studies on the association between metabolic syndrome and cognition in patients with psychotic disorders are required.

Conclusion

This thesis aimed to identify gaps that may limit the extrapolation of neuropsychological assessment in first-episode psychosis patients to routine care of low resource settings. Overall, the findings highlight the need for more research on neuropsychological assessment in first-episode psychosis patients from low resource settings like Uganda. In the first aim, I determined that many of the measures researched in studies of brief neuropsychological assessment in patients with psychotic disorders from low and middle-income countries are are 1) not used early at the first-episode of psychosis 2) not validated against comprehensive batteries 3) take long to perform 4) are not used in the clinical setting 5) not performed by non-specialised staff and 6), not used for follow-up of patients. Several candidate assessments were, however, attractive in terms of their scope and duration, and at least one of these, the Brief Assessment of Cognition in Schizophrenia; has been validated in high-income settings. It is important that future research on brief neuropsychological assessment in patients with psychotic disorders from low resource settings utilize appropriate measures.

In the second aim, I determined first-episode psychosis patients have a higher burden and different profile of cognitive impairment than their healthy peers. The visual learning and memory domain was most impaired domain while the largest mean difference between scores of the patients compared to healthy peers was in the reasoning and problem solving domain. These findings are important to highlight 1) the importance of neuropsychological assessment in this setting and 2) be cognizant of the fact that impairment in this setting may present differently from high income countries. It is also important that the assessment for impairment in the social cognition domain is improved in this setting.

In the third aim, I determined that the clinical variables associated with impairment in different cognitive domains in first-episode psychosis patients in this setting are different from literature described in high income countries. Younger age, fewer years of education previous use of alternative and complementary therapies and diet were all associated with impairment in different cognitive domains. These factors need to be taken into consideration when performing neuropsychological assessment in patients with psychotic disorders in this setting. Development of a clinical criterion for

cognitive impairment in patients with psychotic disorders from low resource settings may have benefit.

In the fourth and final aim, I determined that mobile health applications like the NeuroScreen may be useful for brief neuropsychological assessment in first-episode psychosis patients from low resource settings. Further studies are required to improve the validity of tests of the NeuroScreen for the assessment in specific domains. It is also important to validate the NeuroScreen use in monitoring progress and outcomes through a longitudinal study design.

In a nutshell, this thesis has shown that neuropsychological assessment procedures developed in high income countries cannot necessarily be generalized to routine care in low resource settings. Most of the measures researched in studies of brief neuropsychological assessment in patients with psychotic disorders from low and middle-income countries are inappropriate. Also, the neuropsychological assessment measures developed in high income countries may not be extrapolated to low resource setting as first-episode psychosis patients here have differing clinical variables associated with cognitive impairment. The NeuroScreen may offer great promise for use in this setting, although further research on improving its validity for different domains would be beneficial. It should also be modified to assess for impairment in the visual learning and memory domain which is most impaired in this low resource setting.

AFTERWORD

I was skeptical when Prof. Stein suggested “neuropsychological assessment in first-episode psychosis patients from low resource settings” as a doctoral thesis topic. A medical doctor and psychiatrist by training, I always viewed neuropsychological assessment as a purview of clinical psychologists. Psychiatrists in my warped worldview were meant to worry more about positive and negative symptoms, antipsychotic medications and drug side effects. This thesis has shown the folly of my thinking and I am now a firm believer that neuropsychological assessment in patients with psychotic disorders may be as important or more important than assessing for other psychotic domains. As a lecturer in the department of Psychiatry at Makerere University, I hope this thesis will lead to a change in training outputs for residents in Psychiatry. Given, a lot more needs to be done in terms of improving neuropsychological assessment in our setting, but I hope we can promote neuropsychological assessment for patients with psychotic disorders as one of the routine practices in care.

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APPENDICES

Systematic Review Search Strategy

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#12	Add	Search	**((((((("psychotic disorders"[MeSH Terms] OR Psychosis [TW] OR Psychoses OR Bipolar Disorder OR Affective Disorders OR Neurotic disorders OR Schizophrenia spectrum OR Schizophrenia OR Schizophreniform Dis* OR brief psychosis OR Brief Reactive Psycho* OR catatonic OR paranoid OR undifferentiated OR Disorganized OR Shared or "simple" OR psychotic disorders OR trauma and stressor disorder OR hallucinations OR delusions OR negative symptoms OR thought disturbance OR behavioral disturbance OR psychopathy OR Schizoaffective Dis* OR delusional disorder OR delusions OR hallucinations OR negative symptoms))) AND (("Cognition"[MeSH Term] OR Cognition [tw] OR Overinclusion OR "cognitive impairment" OR Deficit OR "cognition disorders" OR "Cognition disorders" OR Memory OR Memory Disorders OR Brain OR working memory OR attention OR vigilance OR "verbal learning and memory" OR "visual learning and memory" OR "reasoning and problem solving" OR "information processing speed" OR social cognition OR domains OR "cognitive dysfunction"))) AND ((diagnos*[tw] OR screen*[tiab] OR Mass Screening[mh] OR Screening intervention* [tw]OR test*[tiab]))))) AND ((((((Developing Countries[Mesh:noexp] OR Africa[Mesh:noexp] OR Africa, Northern[Mesh:noexp] OR Africa South of the Sahara[Mesh:noexp] OR Africa, Central[Mesh:noexp] OR Africa, Eastern[Mesh:noexp] OR Africa, Southern[Mesh:noexp] OR Africa, Western[Mesh:noexp] OR Angola[Mesh:noexp] OR Benin[Mesh:noexp] OR Botswana[Mesh:noexp] OR Burkina Faso[Mesh:noexp] OR Burundi[Mesh:noexp] OR Cameroon[Mesh:noexp] OR Cape Verde[Mesh:noexp] OR Central African Republic[Mesh:noexp] OR Chad[Mesh:noexp] OR Comoros[Mesh:noexp] OR Congo[Mesh:noexp] OR Cote d'Ivoire[Mesh:noexp] OR Djibouti[Mesh:noexp] OR "Democratic Republic of the Congo"[Mesh:noexp] OR Eritrea[Mesh:noexp] OR Ethiopia[Mesh:noexp] OR Gabon[Mesh:noexp] OR Gambia[Mesh:noexp] OR Ghana[Mesh:noexp] OR Guinea[Mesh:noexp] OR Guinea-Bissau[Mesh:noexp] OR Kenya[Mesh:noexp] OR Lesotho[Mesh:noexp] OR**	927	10:57:34

Liberia[Mesh:noexp] OR Madagascar[Mesh:noexp] OR Malawi[Mesh:noexp] OR Mali[Mesh:noexp] OR Mauritania[Mesh:noexp] OR Mauritius[Mesh:noexp] OR Mozambique[Mesh:noexp] OR Namibia[Mesh:noexp] OR Niger[Mesh:noexp] OR Nigeria[Mesh:noexp] OR Rwanda[Mesh:noexp] OR Senegal[Mesh:noexp] OR Seychelles[Mesh:noexp] OR Sierra Leone[Mesh:noexp] OR Somalia[Mesh:noexp] OR South Africa[Mesh:noexp] OR Sudan[Mesh:noexp] OR Suriname[Mesh:noexp] OR Swaziland[Mesh:noexp] OR Tanzania[Mesh:noexp] OR Togo[Mesh:noexp] OR Uganda[Mesh:noexp] OR Zambia[Mesh:noexp] OR Zimbabwe[Mesh:noexp]))) **OR ((Madagascar[tw] OR Malagasy Republic[tw] OR Malawi[tw] OR Nyasaland[tw] OR Mali[tw] OR Mauritania[tw] OR Mauritius[tw] OR Agalega Islands[tw] OR Mozambique[tw] OR Namibia[tw] OR Niger[tw] OR Nigeria[tw] OR Rwanda[tw] OR Ruanda[tw] OR Sao Tome[tw] OR Senegal[tw] OR Seychelles[tw] OR Sierra Leone[tw] OR Somalia[tw] OR South Africa[tw] OR South Sudan[tw] OR Sudan[tw] OR Surinam[tw] OR Swaziland[tw] OR Tanzania[tw] OR Togo[tw] OR Togolese Republic[tw] OR Uganda[tw] OR Zambia[tw] OR Zimbabwe[tw] OR Rhodesia[tw]))) OR ((Africa[tw] OR Angola[tw] OR Benin[tw] OR Botswana[tw] OR Burkina Faso[tw] OR Burkina Fasso[tw] OR Upper Volta[tw] OR Burundi[tw] OR Urundi[tw] OR Cameroon[tw] OR Cameroons[tw] OR Cameron[tw] OR Camerons[tw] OR Cape Verde[tw] OR Central African Republic[tw] OR Chad[tw] OR Comoros[tw] OR Comoro Islands[tw] OR Comores[tw] OR Mayotte[tw] OR Congo[tw] OR Zaire[tw] OR Congo Democratic Republic[tw] OR Cote d'Ivoire[tw] OR Ivory Coast[tw] OR Djibouti[tw] OR French Somaliland[tw] OR Equatorial Guinea[tw] OR Eritrea[tw] OR Ethiopia[tw] OR Gabon[tw] OR Gabonese Republic[tw] OR Gambia[tw] OR Ghana[tw] OR Gold Coast[tw] OR Guinea[tw] OR Guinea-Bissau[tw] OR Kenya[tw] OR Lesotho[tw] OR Basutoland[tw] OR Liberia[tw]))) OR (("developing country"[tw] OR "developing countries"[tw] OR "developing nation"[tw] OR "developing nations"[tw] OR "developing population"[tw] OR "developing populations"[tw] OR "developing world"[tw] OR "less developed country"[tw] OR "less developed countries"[tw] OR "less developed nation"[tw] OR "less developed nations"[tw] OR "less developed population"[tw] OR "less developed populations"[tw] OR "less developed world"[tw] OR "lesser developed country"[tw] OR "lesser developed countries"[tw] OR "lesser developed nation"[tw] OR "lesser developed nations"[tw] OR "lesser developed population"[tw] OR "lesser developed populations"[tw] OR "lesser developed world"[tw] OR "under developed**

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"lower gross domestic"[tw] OR "lower gross national"[tw] OR lmic[tw] OR lmics[tw] OR "third world"[tw] OR "lami country"[tw] OR "lami countries"[tw] OR "transitional country"[tw] OR "transitional countries"[tw])))

#11 Add Search **(((((Developing Countries[Mesh:noexp] OR Africa[Mesh:noexp] OR Africa, Northern[Mesh:noexp] OR Africa South of the Sahara[Mesh:noexp] OR Africa, Central[Mesh:noexp] OR Africa, Eastern[Mesh:noexp] OR Africa, Southern[Mesh:noexp] OR Africa, Western[Mesh:noexp] OR Angola[Mesh:noexp] OR Benin[Mesh:noexp] OR Botswana[Mesh:noexp] OR Burkina Faso[Mesh:noexp] OR Burundi[Mesh:noexp] OR Cameroon[Mesh:noexp] OR Cape Verde[Mesh:noexp] OR Central African Republic[Mesh:noexp] OR Chad[Mesh:noexp] OR Comoros[Mesh:noexp] OR Congo[Mesh:noexp] OR Cote d'Ivoire[Mesh:noexp] OR Djibouti[Mesh:noexp] OR "Democratic Republic of the Congo"[Mesh:noexp] OR Eritrea[Mesh:noexp] OR Ethiopia[Mesh:noexp] OR Gabon[Mesh:noexp] OR Gambia[Mesh:noexp] OR Ghana[Mesh:noexp] OR Guinea[Mesh:noexp] OR Guinea-Bissau[Mesh:noexp] OR Kenya[Mesh:noexp] OR Lesotho[Mesh:noexp] OR Liberia[Mesh:noexp] OR Madagascar[Mesh:noexp] OR Malawi[Mesh:noexp] OR Mali[Mesh:noexp] OR Mauritania[Mesh:noexp] OR Mauritius[Mesh:noexp] OR Mozambique[Mesh:noexp] OR Namibia[Mesh:noexp] OR Niger[Mesh:noexp] OR Nigeria[Mesh:noexp] OR Rwanda[Mesh:noexp] OR Senegal[Mesh:noexp] OR Seychelles[Mesh:noexp] OR Sierra Leone[Mesh:noexp] OR Somalia[Mesh:noexp] OR South Africa[Mesh:noexp] OR Sudan[Mesh:noexp] OR Suriname[Mesh:noexp] OR Swaziland[Mesh:noexp] OR Tanzania[Mesh:noexp] OR Togo[Mesh:noexp] OR Uganda[Mesh:noexp] OR Zambia[Mesh:noexp] OR Zimbabwe[Mesh:noexp])) OR ((Madagascar[tw] OR Malagasy Republic[tw] OR Malawi[tw] OR Nyasaland[tw] OR Mali[tw] OR Mauritania[tw] OR Mauritius[tw] OR Agalega Islands[tw] OR Mozambique[tw] OR Namibia[tw] OR Niger[tw] OR Nigeria[tw] OR Rwanda[tw] OR Ruanda[tw] OR Sao Tome[tw] OR Senegal[tw] OR Seychelles[tw] OR Sierra Leone[tw] OR Somalia[tw] OR South Africa[tw] OR South Sudan[tw] OR Sudan[tw] OR Surinam[tw] OR Swaziland[tw] OR Tanzania[tw] OR Togo[tw] OR Togolese Republic[tw] OR Uganda[tw] OR Zambia[tw] OR Zimbabwe[tw] OR Rhodesia[tw])) OR ((Africa[tw] OR Angola[tw] OR Benin[tw] OR Botswana[tw] OR Burkina Faso[tw] OR Burkina Fasso[tw] OR Upper Volta[tw] OR Burundi[tw] OR Urundi[tw] OR Cameroon[tw] OR Cameroons[tw] OR Cameron[tw] OR Camerons[tw] OR Cape Verde[tw] OR Central African Republic[tw] OR** 530216 07:48:43

Chad[tw] OR Comoros[tw] OR Comoro Islands[tw] OR Comores[tw] OR Mayotte[tw] OR Congo[tw] OR Zaire[tw] OR Congo Democratic Republic[tw] OR Cote d'Ivoire[tw] OR Ivory Coast[tw] OR Djibouti[tw] OR French Somaliland[tw] OR Equatorial Guinea[tw] OR Eritrea[tw] OR Ethiopia[tw] OR Gabon[tw] OR Gabonese Republic[tw] OR Gambia[tw] OR Ghana[tw] OR Gold Coast[tw] OR Guinea[tw] OR Guinea-Bissau[tw] OR Kenya[tw] OR Lesotho[tw] OR Basutoland[tw] OR Liberia[tw]))) **OR (("developing country"[tw] OR "developing countries"[tw] OR "developing nation"[tw] OR "developing nations"[tw] OR "developing population"[tw] OR "developing populations"[tw] OR "developing world"[tw] OR "less developed country"[tw] OR "less developed countries"[tw] OR "less developed nation"[tw] OR "less developed nations"[tw] OR "less developed population"[tw] OR "less developed populations"[tw] OR "less developed world"[tw] OR "lesser developed country"[tw] OR "lesser developed countries"[tw] OR "lesser developed nation"[tw] OR "lesser developed nations"[tw] OR "lesser developed population"[tw] OR "lesser developed populations"[tw] OR "lesser developed world"[tw] OR "under developed country"[tw] OR "under developed countries"[tw] OR "under developed nation"[tw] OR "under developed nations"[tw] OR "under developed population"[tw] OR "under developed populations"[tw] OR "under developed world"[tw] OR "underdeveloped country"[tw] OR "underdeveloped countries"[tw] OR "underdeveloped nation"[tw] OR "underdeveloped nations"[tw] OR "underdeveloped population"[tw] OR "underdeveloped populations"[tw] OR "underdeveloped world"[tw] OR "middle-income country"[tw] OR "middle-income countries"[tw] OR "middle-income nation"[tw] OR "middle-income nations"[tw] OR "middle-income population"[tw] OR "middle-income populations"[tw] OR "low income country"[tw] OR "low income countries"[tw] OR "low income nation"[tw] OR "low income nations"[tw] OR "low income population"[tw] OR "low income populations"[tw] OR "lower income country"[tw] OR "lower income countries"[tw] OR "lower income nation"[tw] OR "lower income nations"[tw] OR "lower income population"[tw] OR "lower income populations"[tw] OR "underserved country"[tw] OR "underserved countries"[tw] OR "underserved nation"[tw] OR "underserved nations"[tw] OR "underserved population"[tw] OR "underserved populations"[tw] OR "underserved world"[tw] OR "under served country"[tw] OR "under served countries"[tw] OR "under served nation"[tw] OR "under served nations"[tw] OR "under served population"[tw] OR "under served populations"[tw] OR "under served world"[tw] OR**

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#10 Add Search **("developing country"[tw] OR "developing countries"[tw] OR "developing nation"[tw] OR "developing nations"[tw] OR "developing population"[tw] OR "developing populations"[tw] OR "developing world"[tw] OR "less developed country"[tw] OR "less developed countries"[tw] OR "less developed nation"[tw] OR "less developed nations"[tw] OR "less developed population"[tw] OR "less developed populations"[tw] OR "less developed world"[tw] OR "lesser developed country"[tw] OR "lesser developed countries"[tw] OR "lesser developed nation"[tw] OR "lesser developed nations"[tw] OR "lesser developed population"[tw] OR "lesser developed populations"[tw] OR "lesser developed world"[tw] OR "under developed country"[tw] OR "under developed countries"[tw] OR "under developed nation"[tw] OR "under developed nations"[tw] OR "under developed population"[tw] OR "under developed populations"[tw] OR "under developed world"[tw] OR "underdeveloped country"[tw] OR "underdeveloped countries"[tw] OR "underdeveloped nation"[tw] OR "underdeveloped nations"[tw] OR "underdeveloped population"[tw] OR "underdeveloped populations"[tw] OR "underdeveloped world"[tw] OR "middle-income country"[tw] OR "middle-income countries"[tw] OR "middle-income nation"[tw] OR "middle-** 132318 07:48:04

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#9	Add	Search	**(Africa[tw] OR Angola[tw] OR Benin[tw] OR Botswana[tw] OR Burkina Faso[tw] OR Burkina Fasso[tw] OR Upper Volta[tw] OR Burundi[tw] OR Urundi[tw] OR Cameroon[tw] OR Cameroons[tw] OR Cameron[tw] OR Camerons[tw] OR Cape Verde[tw] OR Central African Republic[tw] OR Chad[tw] OR Comoros[tw] OR Comoro Islands[tw] OR Comores[tw] OR Mayotte[tw] OR Congo[tw]**	343819	07:47:26

OR Zaire[tw] OR Congo Democratic Republic[tw] OR Cote d'Ivoire[tw] OR Ivory Coast[tw] OR Djibouti[tw] OR French Somaliland[tw] OR Equatorial Guinea[tw] OR Eritrea[tw] OR Ethiopia[tw] OR Gabon[tw] OR Gabonese Republic[tw] OR Gambia[tw] OR Ghana[tw] OR Gold Coast[tw] OR Guinea[tw] OR Guinea-Bissau[tw] OR Kenya[tw] OR Lesotho[tw] OR Basutoland[tw] OR Liberia[tw])

#8	Add	Search	**(Madagascar[tw] OR Malagasy Republic[tw] OR Malawi[tw] OR Nyasaland[tw] OR Mali[tw] OR Mauritania[tw] OR Mauritius[tw] OR Agalega Islands[tw] OR Mozambique[tw] OR Namibia[tw] OR Niger[tw] OR Nigeria[tw] OR Rwanda[tw] OR Ruanda[tw] OR Sao Tome[tw] OR Senegal[tw] OR Seychelles[tw] OR Sierra Leone[tw] OR Somalia[tw] OR South Africa[tw] OR South Sudan[tw] OR Sudan[tw] OR Surinam[tw] OR Swaziland[tw] OR Tanzania[tw] OR Togo[tw] OR Togolese Republic[tw] OR Uganda[tw] OR Zambia[tw] OR Zimbabwe[tw] OR Rhodesia[tw])**	154711	07:47:00
#7	Add	Search	**(Developing Countries[Mesh:noexp] OR Africa[Mesh:noexp] OR Africa, Northern[Mesh:noexp] OR Africa South of the Sahara[Mesh:noexp] OR Africa, Central[Mesh:noexp] OR Africa, Eastern[Mesh:noexp] OR Africa, Southern[Mesh:noexp] OR Africa, Western[Mesh:noexp] OR Angola[Mesh:noexp] OR Benin[Mesh:noexp] OR Botswana[Mesh:noexp] OR Burkina Faso[Mesh:noexp] OR Burundi[Mesh:noexp] OR Cameroon[Mesh:noexp] OR Cape Verde[Mesh:noexp] OR Central African Republic[Mesh:noexp] OR Chad[Mesh:noexp] OR Comoros[Mesh:noexp] OR Congo[Mesh:noexp] OR Cote d'Ivoire[Mesh:noexp] OR Djibouti[Mesh:noexp] OR "Democratic Republic of the Congo"[Mesh:noexp] OR Eritrea[Mesh:noexp] OR Ethiopia[Mesh:noexp] OR Gabon[Mesh:noexp] OR Gambia[Mesh:noexp] OR Ghana[Mesh:noexp] OR Guinea[Mesh:noexp] OR Guinea-Bissau[Mesh:noexp] OR Kenya[Mesh:noexp] OR Lesotho[Mesh:noexp] OR Liberia[Mesh:noexp] OR Madagascar[Mesh:noexp] OR Malawi[Mesh:noexp] OR Mali[Mesh:noexp] OR Mauritania[Mesh:noexp] OR Mauritius[Mesh:noexp] OR Mozambique[Mesh:noexp] OR Namibia[Mesh:noexp] OR Niger[Mesh:noexp] OR Nigeria[Mesh:noexp] OR Rwanda[Mesh:noexp] OR Senegal[Mesh:noexp] OR Seychelles[Mesh:noexp] OR Sierra Leone[Mesh:noexp] OR Somalia[Mesh:noexp] OR South Africa[Mesh:noexp] OR Sudan[Mesh:noexp] OR Suriname[Mesh:noexp] OR Swaziland[Mesh:noexp] OR Tanzania[Mesh:noexp] OR Togo[Mesh:noexp] OR Uganda[Mesh:noexp] OR Zambia[Mesh:noexp] OR Zimbabwe[Mesh:noexp])**	250017	07:46:25

#6	Add	Search	**((((("psychotic disorders"[MeSH Terms] OR Psychosis [TW] OR Psychoses OR Bipolar Disorder OR Affective Disorders OR Neurotic disorders OR Schizophrenia spectrum OR Schizophrenia OR Schizophreniform Dis* OR brief psychosis OR Brief Reactive Psycho* OR catatonic OR paranoid OR undifferentiated OR Disorganized OR Shared or "simple" OR psychotic disorders OR trauma and stressor disorder OR hallucinations OR delusions OR negative symptoms OR thought disturbance OR behavioral disturbance OR psychopathy OR Schizoaffective Dis* OR delusional disorder OR delusions OR hallucinations OR negative symptoms))) AND (("Cognition"[MeSH Term] OR Cognition [tw] OR Overinclusion OR "cognitive impairment" OR Deficit OR "cognition disorders" OR "Cognition disorders" OR Memory OR Memory Disorders OR Brain OR working memory OR attention OR vigilance OR "verbal learning and memory" OR "visual learning and memory" OR "reasoning and problem solving" OR "information processing speed" OR social cognition OR domains OR "cognitive dysfunction"))) AND ((diagnos*[tw] OR screen*[tiab] OR Mass Screening[mh] OR Screening intervention* [tw]OR test*[tiab]))**	94946	07:46:01
#5	Add	Search	**(diagnos*[tw] OR screen*[tiab] OR Mass Screening[mh] OR Screening intervention* [tw]OR test*[tiab])**	6296168	07:45:19
#4	Add	Search	**("Cognition"[MeSH Term] OR Cognition [tw] OR Overinclusion OR "cognitive impairment" OR Deficit OR "cognition disorders" OR "Cognition disorders" OR Memory OR Memory Disorders OR Brain OR working memory OR attention OR vigilance OR "verbal learning and memory" OR "visual learning and memory" OR "reasoning and problem solving" OR "information processing speed" OR social cognition OR domains OR "cognitive dysfunction")**	2525658	07:44:36
#3	Add	Search	**("psychotic disorders"[MeSH Terms] OR Psychosis [TW] OR Psychoses OR Bipolar Disorder OR Affective Disorders OR Neurotic disorders OR Schizophrenia spectrum OR Schizophrenia OR Schizophreniform Dis* OR brief psychosis OR Brief Reactive Psycho* OR catatonic OR paranoid OR undifferentiated OR Disorganized OR Shared or "simple" OR psychotic disorders OR trauma and stressor disorder OR hallucinations OR delusions OR negative symptoms OR thought disturbance OR behavioral disturbance OR psychopathy OR Schizoaffective Dis* OR delusional disorder OR delusions OR hallucinations OR negative symptoms)**	1400846	07:43:25

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"psychotic disorders OR Psychosis OR Psychoses OR Bipolar Disorder OR Affective Disorders OR Neurotic disorders OR Schizophrenia spectrum OR Schizophrenia OR Schizophreniform Dis* OR brief psychosis OR Brief Reactive Psycho* OR catatonic OR paranoid OR undifferentiated OR Disorganized OR Shared or "simple" OR psychotic disorders OR trauma and stressor disorder OR hallucinations OR delusions OR negative symptoms OR thought disturbance OR behavioral disturbance OR psychopathy OR Schizoaffective Dis* OR delusional disorder OR delusions OR hallucinations OR negative symptoms

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AND

diagnos*OR screen*OR Mass Screening OR Screening intervention* OR test*

AND

(Developing Countries OR AfricaOR Africa, Northern OR Africa South of the Sahara OR Africa, Central OR Africa, Eastern OR Africa, Southern OR Africa, Western OR Angola OR Benin OR Botswana OR Burkina Faso OR Burundi OR Cameroon OR Cape Verde OR Central African Republic OR Chad OR Comoros OR Congo OR Cote

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Pysch info

"psychotic disorders" OR Psychosis OR Psychoses OR Bipolar Disorder OR Affective Disorders OR Neurotic disorders OR Schizophrenia spectrum OR Schizophrenia OR Schizophreniform Dis* OR brief psychosis OR Brief Reactive Psycho* OR catatonic OR paranoid OR undifferentiated OR Disorganized OR Shared or "simple" OR psychotic disorders OR trauma and stressor disorder OR hallucinations OR delusions OR negative symptoms OR thought disturbance OR behavioural disturbance OR psychopathy OR Schizoaffective Dis* OR delusional disorder OR delusions OR hallucinations OR negative symptoms

AND

"Cognition" OR Cognition OR Overinclusion OR "cognitive impairment" OR Deficit OR "cognition disorders" OR "Cognition disorders" OR Memory OR Memory Disorders OR Brain OR working memory OR attention OR vigilance OR "verbal learning and memory" OR "visual learning and memory" OR "reasoning and problem solving" OR "information processing speed" OR social cognition OR domains OR “cognitive dysfunction”

AND

diagnos*OR screen*OR Mass Screening OR Screening intervention* OR test*

Developing Country OR (Africa or Asia or Caribbean or West Indies or South America or Latin America or Central America) OR (Afghanistan or Albania or Algeria or Angola or Antigua or Barbuda or Argentina or Armenia or Armenian or Aruba or Azerbaijan or Bahrain or Bangladesh or Barbados or Benin or Byelarus or Byelorussian or Belarus or Belorussian or Belorussia or Belize or Bhutan or Bolivia or Bosnia or Herzegovina or Hercegovina or Botswana or Brazil or Brasil or Bulgaria or Burkina Faso or Burkina Fasso or Upper Volta or Burundi or Urundi or Cambodia or Khmer Republic or Kampuchea or Cameroon or Cameroons or Cameron or Camerons or Cape Verde or Central African Republic or Chad or Chile or China or Colombia or Comoros or Comoro Islands or Comores or Mayotte or Congo or Zaire or Costa Rica or Cote d’Ivoire or Ivory Coast or Croatia or Cuba or Cyprus or Czechoslovakia or Czech Republic or Slovakia or Slovak Republic or Djibouti or French Somaliland or Dominica or Dominican Republic or East Timor or East Timur or Timor Leste or Ecuador or Egypt

or United Arab Republic or El Salvador or Eritrea or Estonia or Ethiopia or Fiji or Gabon or Gabonese Republic or Gambia or Gaza or Georgia Republic or Georgian Republic or Ghana or Gold Coast or Greece or Grenada or Guatemala or Guinea or Guam or Guiana or Guyana or Haiti or Honduras or Hungary or India or Maldives or Indonesia or Iran or Iraq or Isle of Man or Jamaica or Jordan or Kazakhstan or Kazakh or Kenya or Kiribati or Korea or Kosovo or Kyrgyzs tan or Kirghizia or Kyrgyz Republic or Kirghiz or Kirgizstan or Lao PDR or Laos or Latvia or Lebanon or Lesotho or Basutoland or Liberia or Libya or Lithuania or Macedonia or Madagascar or Malagasy Republic or Malaysia or Malaya or Malay or Sabah or Sarawak or Malawi or Nyasaland or Mali or Malta or Marshall Islands or Mauritania or Mauritius or Agalega Islands or Mexico or Micronesia or Middle East or Moldova or Moldovia or Moldovian or Mongolia or Montenegro or Morocco or Ifni or Mozambique or Myanmar or Myanma or Burma or Namibia or Nepal or Netherlands Antilles or New Caledonia or Nicaragua or Niger or Nigeria or Northern Mariana Islands or Oman or Muscat or Pakistan or Palau or Palestine or Panama or Paraguay or Peru or Philippines or Philipines or Phillipines or Phillippines or Poland or Portugal or Puerto Rico or Romania or Rumania or Roumania or Russia or Russian or Rwanda or Ruanda or Saint Kitts or St Kitts or Nevis or Saint Lucia or St Lucia or Saint Vincent or St Vincent or Grenadines or Samoa or Samoan Islands or Navigator Island or Navigator Islands or Sao Tome or Saudi Arabia or Senegal or Serbia or Montenegro or Seychelles or Sierra Leone or Slovenia or Sri Lanka or Ceylon or Solomon Islands or Somalia or Sudan or Suriname or Surinam or Swaziland or Syria or Tajikistan or Tadzhikistan or Tadjikistan or Tadzhik or Tanzania or Thailand or Togo or Togolese Republic or Tonga or Trinidad or Tobago or Tunisia or Turkey or Turkmenistan or Turkmen or Uganda or Ukraine or Uruguay or USSR or Soviet Union or Union of Soviet Socialist Republics or Uzbekistan or Uzbek or Vanuatu or New Hebrides or Venezuela or Vietnam or Viet Nam or West Bank or Yemen or Yugoslavia or Zambia or Zimbabwe or Rhodesia) OR (developing or less* developed or under developed or underdeveloped or middle-income or low* income or underserved or under served or deprived or poor*) adj (countr* or nation? or population? or world) OR (developing or less* developed or under developed or underdeveloped or middle-income or low* income) adj (economy or economies)) OR (low* adj (gdp or gnp or gross domestic or gross national)) OR low adj3 middle adj3 countr* OR (lmic or lmics or third world or lami countr*) OR transitional countr*

Developing Country

Africa or Asia or Caribbean or West Indies or South America or Latin America or Central America

Afghanistan or Albania or Algeria or Angola or Antigua or Barbuda or Argentina or Armenia or Armenian or Aruba or Azerbaijan or Bahrain or Bangladesh or Barbados or Benin or Byelarus or Byelorussian or Belarus or Belorussian or Belorussia or Belize or Bhutan or Bolivia or Bosnia or Herzegovina or Hercegovina or Botswana or Brazil or Brasil or Bulgaria or Burkina Faso or Burkina Fasso or Upper Volta or Burundi or Urundi or Cambodia or Khmer Republic or Kampuchea or Cameroon or Cameroons or Cameron or Camerons or Cape Verde or Central African Republic or Chad or Chile or China or Colombia or Comoros or Comoro Islands or Comores or Mayotte or Congo or Zaire or Costa Rica or Cote d'Ivoire or Ivory Coast or Croatia or Cuba or Cyprus or Czechoslovakia or Czech Republic or Slovakia or Slovak Republic or Djibouti or French Somaliland or Dominica or Dominican Republic or East Timor or East Timur or Timor Leste or Ecuador or Egypt or United Arab Republic or El Salvador or Eritrea or Estonia or Ethiopia or Fiji or Gabon or Gabonese Republic or Gambia or Gaza or Georgia Republic or Georgian Republic or Ghana or Gold Coast or Greece or Grenada or Guatemala or Guinea or Guam or Guiana or Guyana or Haiti or Honduras or Hungary or India or Maldives or Indonesia or Iran or Iraq or Isle of Man or Jamaica or Jordan or Kazakhstan or Kazakh or Kenya or Kiribati or Korea or Kosovo or Kyrgyzs tan or Kirghizia or Kyrgyz Republic or Kirghiz or Kirgizstan or Lao PDR or Laos or Latvia or Lebanon or Lesotho or Basutoland or Liberia or Libya or Lithuania or Macedonia or Madagascar or Malagasy Republic or Malaysia or Malaya or Malay or Sabah or Sarawak or Malawi or Nyasaland or Mali or Malta or Marshall Islands or Mauritania or Mauritius or Agalega Islands or Mexico or Micronesia or Middle East or Moldova or Moldovia or Moldovian or Mongolia or Montenegro or Morocco or Ifni or Mozambique or Myanmar or Myanma or Burma or Namibia or Nepal or Netherlands Antilles or New Caledonia or Nicaragua or Niger or Nigeria or Northern Mariana Islands or Oman or Muscat or Pakistan or Palau or Palestine or Panama or Paraguay or Peru or Philippines or Philipines or Phillipines or Phillippines or Poland or Portugal or Puerto Rico or Romania or Rumania or Roumania or Russia or Russian or Rwanda or Ruanda or Saint Kitts or St Kitts or Nevis or Saint Lucia or St Lucia or Saint Vincent or St Vincent or Grenadines or Samoa or Samoan Islands or Navigator Island or

Navigator Islands or Sao Tome or Saudi Arabia or Senegal or Serbia or Montenegro or Seychelles or Sierra Leone or Slovenia or Sri Lanka or Ceylon or Solomon Islands or Somalia or Sudan or Suriname or Surinam or Swaziland or Syria or Tajikistan or Tadzhikistan or Tadjikistan or Tadzhik or Tanzania or Thailand or Togo or Togolese Republic or Tonga or Trinidad or Tobago or Tunisia or Turkey or Turkmenistan or Turkmen or Uganda or Ukraine or Uruguay or USSR or Soviet Union or Union of Soviet Socialist Republics or Uzbekistan or Uzbek or Vanuatu or New Hebrides or Venezuela or Vietnam or Viet Nam or West Bank or Yemen or Yugoslavia or Zambia or Zimbabwe or Rhodesia

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developing or less* developed or under developed or underdeveloped or middle-income or low* income) adj (economy or economies)

low* adj (gdp or gnp or gross domestic or gross national)

low adj3 middle adj3 countr*

lmic or lmics or third world or lami countr*

transitional countr*

(Developing Countries OR Africa OR Africa, Northern OR Africa South of the Sahara OR Africa, Central OR Africa, Eastern OR Africa, Southern OR Africa, Western OR Angola OR Benin OR Botswana OR Burkina Faso OR Burundi OR Cameroon OR Cape Verde OR Central African Republic OR Chad OR Comoros OR Congo OR Cote d'Ivoire OR Djibouti OR "Democratic Republic of the Congo" OR Eritrea OR Ethiopia OR Gabon OR Gambia OR Ghana OR Guinea OR Guinea-Bissau OR Kenya OR Lesotho OR Liberia OR Madagascar OR Malawi OR Mali OR Mauritania OR Mauritius OR Mozambique OR Namibia OR Niger OR Nigeria OR Rwanda OR Senegal OR Seychelles OR Sierra Leone OR Somalia OR South Africa OR Sudan OR Suriname OR Swaziland OR Tanzania OR Togo OR Uganda OR Zambia OR Zimbabwe OR ((Madagascar[tw] OR Malagasy Republic[tw] OR Malawi[tw] OR Nyasaland[tw] OR Mali[tw] OR Mauritania[tw] OR Mauritius[tw] OR Agalega Islands[tw] OR

Mozambique[tw] OR Namibia[tw] OR Niger[tw] OR Nigeria[tw] OR Rwanda[tw] OR Ruanda[tw] OR Sao Tome[tw] OR Senegal[tw] OR Seychelles[tw] OR Sierra Leone[tw] OR Somalia[tw] OR South Africa[tw] OR South Sudan[tw] OR Sudan[tw] OR Surinam[tw] OR Swaziland[tw] OR Tanzania[tw] OR Togo[tw] OR Togolese Republic[tw] OR Uganda[tw] OR Zambia[tw] OR Zimbabwe[tw] OR Rhodesia[tw]))) OR ((Africa[tw] OR Angola[tw] OR Benin[tw] OR Botswana[tw] OR Burkina Faso[tw] OR Burkina Fasso[tw] OR Upper Volta[tw] OR Burundi[tw] OR Urundi[tw] OR Cameroon[tw] OR Cameroons[tw] OR Cameron[tw] OR Camerons[tw] OR Cape Verde[tw] OR Central African Republic[tw] OR Chad[tw] OR Comoros[tw] OR Comoro Islands[tw] OR Comores[tw] OR Mayotte[tw] OR Congo[tw] OR Zaire[tw] OR Congo Democratic Republic[tw] OR Cote d'Ivoire[tw] OR Ivory Coast[tw] OR Djibouti[tw] OR French Somaliland[tw] OR Equatorial Guinea[tw] OR Eritrea[tw] OR Ethiopia[tw] OR Gabon[tw] OR Gabonese Republic[tw] OR Gambia[tw] OR Ghana[tw] OR Gold Coast[tw] OR Guinea[tw] OR Guinea-Bissau[tw] OR Kenya[tw] OR Lesotho[tw] OR Basutoland[tw] OR Liberia[tw]))) OR (("developing country"[tw] OR "developing countries"[tw] OR "developing nation"[tw] OR "developing nations"[tw] OR "developing population"[tw] OR "developing populations"[tw] OR "developing world"[tw] OR "less developed country"[tw] OR "less developed countries"[tw] OR "less developed nation"[tw] OR "less developed nations"[tw] OR "less developed population"[tw] OR "less developed populations"[tw] OR "less developed world"[tw] OR "lesser developed country"[tw] OR "lesser developed countries"[tw] OR "lesser developed nation"[tw] OR "lesser developed nations"[tw] OR "lesser developed population"[tw] OR "lesser developed populations"[tw] OR "lesser developed world"[tw] OR "under developed country"[tw] OR "under developed countries"[tw] OR "under developed nation"[tw] OR "under developed nations"[tw] OR "under developed population"[tw] OR "under developed populations"[tw] OR "under developed world"[tw] OR "underdeveloped country"[tw] OR "underdeveloped countries"[tw] OR "underdeveloped nation"[tw] OR "underdeveloped nations"[tw] OR "underdeveloped population"[tw] OR "underdeveloped populations"[tw] OR "underdeveloped world"[tw] OR "middle-income country"[tw] OR "middle-income countries"[tw] OR "middle-income nation"[tw] OR "middle-income nations"[tw] OR "middle-income population"[tw] OR "middle-income populations"[tw] OR "low income country"[tw] OR "low income countries"[tw] OR "low income nation"[tw] OR "low income nations"[tw] OR "low income population"[tw] OR "low income populations"[tw] OR "lower income country"[tw] OR "lower income

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Additional results Tables for objective 2.

Table 22: Association of selected exposures with the verbal learning and memory domain.

Factor	level	Unadjusted Coeff (95% CI)	p-value	Adjusted Coeff (95% CI)	p-value
Sociodemographic characteristics					
Age or age category	Median (IQR)	0.021(-0.002; 0.044)	0.078	0.021(-0.001; 0.043)	0.056
Participants years of education	Median (IQR)	0.063(0.015;0.111)	0.010	0.010(-0.039; 0.060)	0.686
Father years of education	Median (IQR)	-0.016(-0.040; 0.009)	0.200	-0.014(-0.038; 0.011)	0.264
Mother years of education	Median (IQR)	0.026(-0.048; 0.100)	0.486	0.001(-0.077; 0.078)	0.991
gender	Male	Ref		Ref	
	Female	0.237(-0.210; 0.684)	0.297	0.280(-0.127; 0.688)	0.177
Handedness	Right	Ref		Ref	
	Left	-0.569(-1.643; 0.505)	0.297	-0.473(-1.442; 0.495)	0.336
Marital Status	Single	Ref		Ref	
	Married	0.098(-0.382; 0.577)	0.688	-0.081(-0.570; 0.409)	0.745
	Divorced	0.133(-0.491; 0.757)	0.674	-0.320(-1.040; 0.400)	0.381
Current Employment History	Student	Ref		Ref	
	Formal Employment	0.409(-0.723; 1.541)	0.476	0.228(-0.844; 1.299)	0.675
	Non formal employment	-0.423(-1.518; 0.672)	0.447	-0.031(-1.078; 1.016)	0.953
	Unemployed	0.102(-0.999; 1.202)	0.856	0.140(-0.912; 1.192)	0.793
Ethnicity	Bantu	Ref		Ref	
	Nilotic	0.626(-0.151; 1.404)	0.114	0.270(-0.448; 0.989)	0.459
	NiloHamites	0.632(-0.275; 1.538)	0.171	0.230(-0.627; 1.087)	0.597
	Sudanic	-0.247(-1.317; 0.824)	0.649	-0.378(-1.434; 0.678)	0.481
	Hamites	-0.812(-1.589; -0.034)	0.041	-0.522(-1.246; 0.202)	0.156
Current Living arrangements	Renting	Ref		Ref	
	Owns house	-0.957(-1.545; -0.370)	0.002	-0.671(-1.255; -0.087)	**0.025**
	Living with primary family	-0.860(-1.380; -0.341)	0.001	-0.626(-1.132; -0.120)	**0.016**
	Living with other family	-1.227(-1.972; -0.481)	0.001	-0.655(-1.376; 0.066)	0.075
	Living with friends	-0.514(-1.765; 0.737)	0.418	0.072(-1.100; 1.243)	0.904
	No housing/living on street	0.173(-1.214; 1.559)	0.806	0.250(-1.074; 1.243)	0.710
Who is main source of income in the household	Self	Ref		Ref	
	Father	-0.676(-1.378; 0.027)	0.059	-0.683(-1.364; -0.002)	**0.049**
	Mother	0.150(-0.539; 0.839)	0.668	0.402(-0.292; 1.096)	0.254
	Relative/ guardian	-0.132(-0.689; 0.426)	0.641	-0.041(-0.578; 0.495)	0.879
	Nonrelative/ organization	-0.853(-1.620; -0.085)	0.030	-0.495(-1.200; 0.209)	0.167
Household main source of income	Agricultural	Ref		Ref	
	Non agricultural	1.982(0.587; 3.377)	0.006	1.347(0.003; 2.691)	**0.049**
	Wage	1.329(0.778; 1.880)	0.000	0.784(0.225; 1.343)	**0.006**
	Property	0.355(-0.538; 1.248)	0.433	0.282(-0.555; 1.119)	0.507
	Organization	0.847(0.055; 1.640)	0.036	0.424(-0.370; 1.218)	0.293
	Other	0.469(-0.797; 1.734)	0.466	0.016(-1.200; 1.233)	0.979
Diet					
Fruit	Never	Ref		Ref	
	Sometimes	-0.007(-0.561; 0.547)	0.981	0.235(-0.282; 0.752)	0.370
	Often	-0.176(-0.815; 0.462)	0.586	0.042(-0.544; 0.628)	0.888
	Always	0.609(-0.315; 1.532)	0.195	0.595(-0.250; 1.439)	0.166

Meat	Never	Ref		Ref	
	Sometimes	0.026(-0.495; 0.547)	0.923	0.059(-0.420; 0.538)	0.809
	Often	0.384(-0.307; 1.075)	0.274	0.100(-0.533; 0.734)	0.755
	Always	0.514(-0.947; 1.975)	0.488	0.337(-0.989; 1.664)	0.616
Cassava	Never	Ref		Ref	
	Sometimes	-0.560(-1.056; -0.064)	0.027	-0.307(-0.775; 0.161)	0.197
	Often	-0.621(-1.227; -0.015)	0.045	-0.468(-1.026; 0.089)	0.099
	Always	-0.627(-1.436; 0.182)	0.128	-0.636(-1.406; 0.134)	0.105
Beans	Never	Ref		Ref	
	Sometimes	-0.056(-1.088; 0.977)	0.916	0.253(-0.684; 1.189)	0.595
	Often	0.233(-0.756; 1.222)	0.643	0.418(-0.473; 1.310)	0.356
	Always	0.372(-0.632; 1.376)	0.466	0.521(-0.394; 1.435)	0.262
Maize	Never	Ref		Ref	
	Sometimes	-0.062(-0.981; 0.858)	0.895	0.355(-0.479; 1.189)	0.402
	Often	0.170(-0.685; 1.025)	0.695	0.308(-0.459; 1.075)	0.429
	Always	-0.069(-0.922; 0.784)	0.873	0.278(-0.498; 1.055)	0.480
Trauma					
Emotional Abuse		0.227(-0.431; 0.886)	0.494	0.192(-0.407; 0.790)	0.526
Physical Abuse		0.267(-0.395; 0.929)	0.426	0.204(-0.401; 0.810)	0.504
Sexual abuse		0.395(-0.313; 1.102)	0.271	0.126(-0.566; 0.819)	0.718
Emotional neglect		-0.399(-1.056; 0.258)	0.231	-0.347(-0.944; 0.251)	0.251
Physical neglect		-0.471(-1.157; 0.215)	0.176	-0.295(-0.922; 0.332)	0.352
Minimization/Denial		0.223(-0.468; 0.915)	0.523	0.80(-0.541; 0.700)	0.799
Clinical features					
DUP		-0.061(-0.168; 0.045)	0.257	-0.036(-0.134; 0.061)	0.462
Diagnosis		-0.173(-0.733; 0.386)	0.540	-0.108(-0.616; 0.400)	0.674
Therapy		-0.129(-0.649; 0.390)	0.623	-0.104(-0.593; 0.385)	0.674
PANSS		-0.023(-0.087; 0.042)	0.488	-0.016(-0.075; 0.044)	0.600

Table 23: Association of selected exposures with the working memory domain.

Factor	level	Unadjusted Coeff (95% CI)	p-value	Adjusted Coeff (95% CI)	p-value
Sociodemographic characteristics					
Age or age category	Median (IQR)	0.007(-0.020; 0.034)	0.615	0.005(-0.019; 0.030)	0.660
Participants years of education	Median (IQR)	0.110(0.058; 0.163)	0.000	0.051(-0.005; 0.106)	0.073
Father years of education	Median (IQR)	0.009(-0.020; 0.039)	0.532	0.013(-0.016; 0.042)	0.385
Mother years of education	Median (IQR)	0.052(-0.036; 0.140)	0.243	0.017(-0.075; 0.109)	0.716
gender	Male	Ref		Ref	
	Female	-0.132(-0.640; 0.376)	0.608	-0.021(-0.480; 0.439)	0.929
Handedness	Right	Ref		Ref	
	Left	-0.732(-1.956; 0.491)	0.239	-0.647(-1.744; 0.450)	0.246
Marital Status	Single	Ref		Ref	
	Married	0.338(-0.200; 0.876)	0.217	0.423(-0.124; 0.970)	0.129
	Divorced	-0.098(-0.798; 0.602)	0.782	-0.052(-0.857; 0.752)	0.898
Current Employment History	Student	Ref		Ref	
	Formal Employment	-0.401(-1.647; 0.845)	0.526	-0.453(-1.637; 0.731)	0.451
	Non formal employment	-1.543(-2.749; -0.337)	0.012	-1.009(-2.167; 0148)	0.087
	Unemployed	-1.323(-2.535; -0.111)	0.033	-1.110(-2.272; 0.052)	0.061
Ethnicity	Bantu	Ref		Ref	
	Nilotic	0.312(-0.536; 1.160)	0.468	-0.105(-0.895; 0.685)	0.794
	NiloHamites	1.086(0.098; 2.074)	0.031	0.746(-0.196; 1.688)	0.120
	Sudanic	0.437(-0.731; 1.604)	0.461	0.405(-0.756; 1.567)	0.491
	Hamites	-1.423(-2.271; -0.575)	0.001	-1.048(-1.844; -0.252)	**0.010**
Current Living arrangements	Renting	Ref		Ref	
	Owns house	-1.028(-1.701; -0.354)	0.003	-0.513(-1.183; 0.158)	0.133
	Living with primary family	-0.789(-1.385; 0.194)	0.010	-0.606(-1.187; -0.024)	**0.041**
	Living with other family	-1.445(-2.299; -0.590)	0.001	-0.725(-1.554; 0.103)	0.086
	Living with friends	-0.851(-2.285; 0.583)	0.243	-0.283(-1.629; 1.063)	0.678
	No housing/living on street	-0.771(-2.361; 0.819)	0.340	-0.711(-2.232; 0.809)	0.357
Who is main source of income in the household	Self	Ref		Ref	
	Father	0.383(-0.421; 1.187)	0.348	0.298(-0.486; 1.083)	0.454
	Mother	-0.008(-0.797; 0.781)	0.984	0.214(-0.585; 1.013)	0.597
	Relative/ guardian	-0.326(-0.964; 0.313)	0.315	-0.189(-0.897; 0.429)	0.547
	Nonrelative/ organization	-0.297(-1.176; 0.582)	0.505	0.040(-0.772; 0.851)	0.923
Household main source of income	Agricultural	Ref		Ref	
	Non agricultural	2.189(0.618; 3.759)	0.007	1.512(0.017; 3.016)	**0.048**
	Wage	1.635(1.014; 2.255)	0.000	1.122(0.498; 1.746)	**0.001**
	Property	0.948(-0.057; 1.953)	0.064	0.958(0.024; 1.892)	**0.044**
	Organization	1.160(0.268; 2.053)	0.011	0.998(0.112; 1.884)	**0.028**
	Other	0.383(-1.041; 1.808)	0.596	0.179(-1.179; 1.536)	0.795
Diet					
Fruit	Never	Ref		Ref	
	Sometimes	-0.472(-1.090; 0.147)	0.134	-0.200(-0.780; 0.381)	0.498
	Often	-0.203(-0.916; 0.509)	0.574	0.088(-0.569; 0.746)	0.791
	Always	0.837(-0.194; 1.868)	0.111	0.848(-0.100; 1.796)	0.079

Meat	Never	Ref		Ref	
	Sometimes	0.230(-0.348; 0.808)	0.434	0.268(-0.267; 0.802)	0.324
	Often	1.095(0.328; 1.861)	0.005	0.822(0.115; 1.529)	**0.023**
	Always	0.977(-0.643; 2.597)	0.236	0.696(-0.784; 2.175)	0.354
Cassava	Never	Ref		Ref	
	Sometimes	-0.630(-1.192; -0.068)	0.028	-0.356(-0.887; 0.176)	0.188
	Often	-0.730(-1.417; -0.043)	0.037	-0.528(-1.161; 0.105)	0.101
	Always	-0.678(-1.595; 0.239)	0.146	-0.681(-1.555; 0.193)	0.126
Beans	Never	Ref		Ref	
	Sometimes	0.381(-0.790; 1.552)	0.521	0.854(-0.201; 1.910)	0.112
	Often	0.587(-0.534; 1.708)	0.303	0.877(-0.128; 1.882)	0.087
	Always	0.739(-0.400; 1.877)	0.202	1.039(0.009; 2.070)	0.048
Maize	Never	Ref		Ref	
	Sometimes	-0.457(-1.500; 0.587)	0.389	-0.002(-0.950; 0.946)	0.997
	Often	-0.249(-1.220; 0.721)	0.613	-0.041(-0.913; 0.831)	0.926
	Always	-0.333(-1.301; 0.635)	0.498	0.083(-0.799; 0.966)	0.852
Trauma					
Emotional Abuse		0.365(-0.385; 1.115)	0.336	0.307(-0.334; 0.949)	0.343
Physical Abuse		0.161(-0.597; 0.919)	0.674	0.018(-0.635; 0.671)	0.956
Sexual abuse		0.041(-0.772; 0.854)	0.920	-0.280(-1.023; 0.462)	0.455
Emotional neglect		-0.483(-1.232; 0.267)	0.204	-0.356(-0.999; 0.287)	0.274
Physical neglect		0.091(-0.700; 0.883)	0.819	0.203(-0.474; 0.879)	0.553
Minimization/Denial		0.388(-0.400;1.175)	0.330	0.181(-0.485; 0.847)	0.590
Clinical features					
DUP		-0.093(-0.213; 0.027)	0.129	-0.046(-0.154; 0.061)	0.392
Diagnosis		-0.786(-1.431; -0.141)	0.017	-0.636(-1.225; -0.047)	**0.035**
Therapy		-0.302(-0.898; 0.294)	0.318	-0.262(-0814;0.291)	0.351
PANSS		-0.049(-0.123; 0.024)	0.185	-0.018(-0.083; 0.046)	0.572

Table 24: Association of selected exposures with the attention/vigilance domain.

Factor	level	Unadjusted Coeff (95% CI)	p-value	Adjusted Coeff (95% CI)	p-value
Sociodemographic characteristics					
Age or age category	Median (IQR)	-0.009(-0.046; 0.027)	0.609	-0.009(-0.046; 0.028)	0.632
Participants years of education	Median (IQR)	0.060(-0.015; 0.134)	0.118	0.041(-0.044; 0.127)	0.340
Father years of education	Median (IQR)	0.004(-0.039; 0.046)	0.864	0.010(-0.035; 0.055)	0.652
Mother years of education	Median (IQR)	0.014(-0.112; 0.139)	0.828	0.025(-0.117; 0.168)	0.725
gender	Male	Ref		Ref	
	Female	0.146(-0.541; 0.833)	0.676	0.324(-0.373; 1.020)	0.360
Handedness	Right	Ref		Ref	
	Left	-1.223(-2.876; 0.430)	0.146	-1.259(-2.912; 0.393)	0.134
Marital Status	Single	Ref		Ref	
	Married	0.309(-0.424; 1.042)	0.406	0.515(-0.318; 1.348)	0.224
	Divorced	-0.164(-1.118; 0.789)	0.734	0.108(-1.118; 1.333)	0.862
Current Employment History	Student	Ref		Ref	
	Formal Employment	0.039(-1.714; 1.791)	0.965	-0.109(-1.916; 1.699)	0.905
	Non formal employment	-0.770(-2.466; 0.927)	0.372	-0.649(-2.415; 1.118)	0.469
	Unemployed	-0.924(-2.629; 0.781)	0.286	-1.088(-2.863; 0.686)	0.228
Ethnicity	Bantu	Ref		Ref	
	Nilotic	-0.763(-1.958; 0.432)	0.209	-0.999(-2.209; 0.211)	0.105
	NiloHamites	1.204(-0.189; 2.597)	0.090	1.056(-0.387; 2.498)	0.150
	Sudanic	-0.112(-1.757; 1.533)	0.893	0.235(-1.544; 2.014)	0.794
	Hamites	-1.337(-2.532; -0.142)	0.029	-1.260(-2.480; -0.041)	**0.043**
Current Living arrangements	Renting	Ref		Ref	
	Owns house	-0.571(-1.502; 0.359)	0.227	-0.237(-1.240; 0.766)	0.641
	Living with primary family	-0.660(-1.483; 0.163)	0.115	-0.750(-1.621; 0.120)	0.091
	Living with other family	-1.017(-2.197; 0.164)	0.091	-0.748(-1.987; 0.491)	0.235
	Living with friends	-0.540(-2.522; 1.442)	0.591	-0.373(-2.387; 1.640)	0.715
	No housing/living on street	-3.398(-5.595; -1.202)	0.003	-3.316(-5.590; -1.042)	**0.005**
Who is main source of income in the household	Self	Ref		Ref	
	Father	0.001(-1.085; 1.088)	0.998	-0.294(-1.474; 0.886)	0.623
	Mother	0.073(-0.993; 1.139)	0.893	-0.022(-1.225; 1.180)	0.971
	Relative/ guardian	0.219(-0.643; 1.082)	0.616	0.105(-0.825; 1.034)	0.825
	Nonrelative/ organization	-0.482(-1.670; 0.706)	0.424	-0.337(-1.558; 0.884)	0.587
Household main source of income	Agricultural	Ref		Ref	
	Non agricultural	1.246(-0.900; 3.392)	0.253	0.642(-1.575; 2.860)	0.568
	Wage	1.232(0.385; 2.080)	0.005	0.936(0.014; 1.859)	**0.047**
	Property	1.309(-064; 2.683)	0.062	1.267(-0.114; 2.648)	0.072
	Organization	0.990(-0.229; 2.209)	0.111	0.829(-0.481; 2.139)	0.213
	Other	-2.461(-4.408; -0.515)	0.014	-2.731(-4.738; -0.723)	**0.008**
Diet					
Fruit	Never	Ref		Ref	
	Sometimes	-0.851(-1.685; -0.016)	0.046	-0.865(-1.731; 0.001)	0.050
	Often	-0.099(-1.061; 0.862)	0.839	-0.001(-0.982; 0.980)	0.999
	Always	1.155(-0.237; 2.547)	0.103	1.040(-0.375; 2.454)	0.148
Meat	Never	Ref		Ref	

	Sometimes	0.109(-0.693; 0.910)	0.789	0.009(-0.810; 0.829)	0.983
	Often	0.822(-0.242; 1.885)	0.129	0.647(-0.437; 1.731)	0.240
	Always	1.363(-0.885; 3.611)	0.233	0.986(-1.283; 3.255)	0.392
Cassava	Never	Ref		Ref	
	Sometimes	-0.290(-1.065; 0.485)	0.461	-0.163(-0.974; 0.648)	0.692
	Often	-0.726(-1.673; 0.221)	0.132	-0.602(-1.568; 0.363)	0.219
	Always	-1.031(-2.295; 0.233)	0.109	-0.944(-2.276; 0.389)	0.164
Beans	Never	Ref		Ref	
	Sometimes	-0.040(-1.638; 1.558)	0.960	0.289(-1.317; 1.895)	0.723
	Often	0.182(-1.348; 1.713)	0.814	0.452(-1.076; 1.981)	0.560
	Always	0.617(-0.937; 2.171)	0.434	1.001(-0.567; 2.569)	0.209
Maize	Never	Ref		Ref	
	Sometimes	-0.694(-2.111; 0.722)	0.335	-0.427(-1.852; 0.998)	0.555
	Often	-0.553(-1.871; 0.765)	0.409	-0.399(-1.710; 0.912)	0.548
	Always	-0.085(-1.399; 1.229)	0.899	0.258(-1.068; 1.585)	0.701
Trauma					
Emotional Abuse		0.597(-0.275; 1.470)	0.177	0.657(-0.240; 1.554)	0.149
Physical Abuse		0.986(0.125; 1.848)	0.025	1.027(0.136; 1.918)	**0.024**
Sexual abuse		0.630(-0.312; 1.572)	0.187	0.457(-0.587; 1.502)	0.386
Emotional neglect		0.455(-0.425; 1.335)	0.307	0.435(-0.472; 1.343)	0.343
Physical neglect		0.552(-0.366; 1.471)	0.235	0.597(-0.348; 1.543)	0.212
Minimization/Denial		-0.169(-1.094; 0.757)	0.718	-0.268(-1.207; 0.670)	0.571
Clinical features					
DUP		-0.243(-0.407; -0.078)	0.004	-0.231(-0.403; -0.060)	**0.009**
Diagnosis		-0.733(-1.628; 0.163)	0.108	-0.571(-1.494; 0.351)	0.222
Therapy		-0.942(-1.734; -0.149)	0.020	-1.073(-1.903; -0.242)	**0.012**
PANSS		-0.004(-0.091; 0.083)	0.933	-0.002(-0.094; 0.091)	0.970

Table 25: Association of selected exposures with the speed of processing domain.

Factor	level	Unadjusted Coeff (95% CI)	p-value	Adjusted Coeff (95% CI)	p-value
Sociodemographic characteristics					
Age or age category	Median (IQR)	0.047(0.028; 0.066)	0.000	0.043(0.026; 0.060)	**0.000**
Participants years of education	Median (IQR)	0.095(0.056; 0.134)	0.000	0.045(0.007; 0.083)	**0.020**
Father years of education	Median (IQR)	0.002(-0.023; 0.026)	0.888	0.001(-0.021; 0.022)	0.962
Mother years of education	Median (IQR)	0.084(0.011; 0.156)	0.024	0.050(-0.021; 0.121)	0.163
gender	Male	Ref		Ref	
	Female	0.003(-0.380; 0.385)	0.990	0.006(-0.313; 0.324)	0.972
Handedness	Right	Ref		Ref	
	Left	-1.061(-1.971; -0.151)	0.023	-0.915(-1.665; -0.165)	**0.017**
Marital Status	Single	Ref		Ref	
	Married	0.699(0.312; 1.086)	0.000	0.448(0.075; 0.822)	**0.019**
	Divorced	0.569(0.065; 1.073)	0.027	-0.024(-0.573; 0.526)	0.933
Current Employment History	Student	Ref		Ref	
	Formal Employment	1.058(0.126; 1.991)	0.026	0.757(-0.070; 1.584)	0.073
	Non formal employment	0.153(-0.749; 1.055)	0.738	0.429(-0.379; 1.237)	0.296
	Unemployed	0.432(-0.475; 1.339)	0.348	0.420(-0.392; 1.232)	0.308
Ethnicity	Bantu	Ref		Ref	
	Nilotic	0.455(-0.195; 1.104)	0.169	0.101(-0.461; 0.663)	0.723
	NiloHamites	0.416(-0.342; 1.173)	0.280	0.207(-0.463; 0.877)	0.542
	Sudanic	-0.326(-1.220; 0.568)	0.472	-0.182(-1.007; 0.644)	0.664
	Hamites	-0.816(-1.466; -0.166)	0.014	-0.465(-1.032; 0.101)	0.106
Current Living arrangements	Renting	Ref		Ref	
	Owns house	-0.358(-0.848; 0.133)	0.152	-0.207(-0.664; 0.251)	0.374
	Living with primary family	-0.931(-1.365; -0.498)	0.000	-0.598(-0.995; -0.201)	**0.003**
	Living with other family	-1.102(-1.724; -0.480)	0.001	-0.544(-1.110; 0.021)	0.059
	Living with friends	-0.769(-1.813; 0.275)	0.148	-0.145(-1.064; 0.774)	0.756
	No housing/living on street	-0.372(-1.529; 0.785)	0.526	-0.404(-1.442; 0.633)	0.443
Who is main source of income in the household	Self	Ref		Ref	
	Father	-0.530(-1.116; 0.056)	0.076	-0.262(-0.806; 0.281)	0.342
	Mother	-0.658(-1.233; -0.083)	0.025	-0.203(-0.756; 0.351)	0.470
	Relative/ guardian	-0.554(-1.019; -0.088)	0.020	-0.335(-0.763; 0.093)	0.124
	Nonrelative/ organization	-0.507(-1.148; 0.134)	0.120	-0.187(-0.749; 0.375)	0.512
Household main source of income	Agricultural	Ref		Ref	
	Non agricultural	1.202(0.007; 2.397)	0.049	0.935(-0.125; 1.995)	0.083
	Wage	1.058(0.586; 1.530)	0.000	0.534(0.093; 0.975)	**0.018**
	Property	0.656(-0.108; 1.421)	0.092	0.581(-0.079; 1.242)	0.084
	Organization	0.819(0.140; 1.498)	0.018	0.486(-0.140; 1.113)	0.127
	Other	0.113(-0.971; 1.197)	0.837	-0.285(-1.244; 0.675)	0.559
Diet					
Fruit	Never	Ref		Ref	
	Sometimes	-0.121(-0.586; 0.345)	0.609	0.007(-0.398; 0.412)	0.973
	Often	0.228(-0.308; 0.765)	0.402	0.289(-0.170; 0.748)	0.215
	Always	0.571(-0.205; 1.348)	0.148	0.381(-0.281; 1.043)	0.258
Meat	Never	Ref		Ref	

	Sometimes	-0.003(-0.434; 0.428)	0.988	-0.018(-0.389; 0.353)	0.923
	Often	0.664(0.093; 1.236)	0.023	0.291(-0.199; 0.782)	0.242
	Always	0.954(-0.255; 2.162)	0.121	0.899(-0.127; 1.926)	0.086
Cassava	Never	Ref		Ref	
	Sometimes	-0.218(-0.645; 0.209)	0.314	-0.110(-0.482; 0.262)	0.559
	Often	-0.201(-0.722; 0.321)	0.449	-0.170(-0.612; 0.273)	0.450
	Always	-0.048(-0.744; 0.649)	0.892	-0.303(-0.914; 0.308)	0.329
Beans	Never			Ref	
	Sometimes	0.259(-0.618; 1.135)	0.561	0.472(-0.264; 1.208)	0.207
	Often	0.252(-0.587; 1.092)	0.554	0.306(-0.394; 1.007)	0.389
	Always	0.396(-0.456; 1.249)	0.360	0.420(-0.299; 1.138)	0.250
Maize	Never	Ref		Ref	
	Sometimes	-0.256(-1.031; 0.519)	0.515	0.184(-0.472; 0.840)	0.580
	Often	0.072(-0.649; 0.793)	0.843	0.158(-0.446; 0.762)	0.606
	Always	-0.179(-0.898; 0.540)	0.623	0.202(-0.409; 0.813)	0.515
Trauma					
Emotional Abuse		0.055(-0.481; 0.591)	0.840	-0.053(-0.502; 0.395)	0.813
Physical Abuse		0.192(-0.346; 0.730)	0.481	0.061(-0.393; 0.515)	0.791
Sexual abuse		0.179(-0.398; 0.756)	0.539	0.088(-0.430; 0.606)	0.737
Emotional neglect		-0.553(-1.078; -0.028)	0.039	-0.430(-0.870; 0.011)	0.056
Physical neglect		-0.475(-1.029; 0.079)	0.092	-0.259(-0.727; 0.209)	0.275
Minimization/Denial		0.302(-0.257; 0.861)	0.286	0.183(-0.280; 0.645)	0.434
Clinical features					
DUP		-0.032(-0.113; 0.049)	0.433	-0.031(-0.099; 0.036)	0.358
Diagnosis		-0.251(-0.678; 0.176)	0.247	-0.237(-0.598; 0.124)	0.196
Therapy		-0.108(-0.524; 0.308)	0.608	-0.134(-0.490; 0.222)	0.457
PANSS		-0.043(-0.091; 0.006)	0.084	-0.039(-0.080; 0.001)	0.057

Table 26: Association of selected exposures with the social cognition domain.

Factor	level	Unadjusted Coeff (95% CI)	p-value	Adjusted Coeff (95% CI)	p-value
Sociodemographic characteristics					
Age or age category	Median (IQR)	0.006(-0.033; 0.044)	0.776	0.009(-0.030; 0.048)	0.660
Participants years of education	Median (IQR)	0.062(-0.017; 0.141)	0.125	0.014(-0.076; 0.103)	0.763
Father years of education	Median (IQR)	0.000(-0.049; 0.050)	0.993	0.007(-0.044; 0.059)	0.776
Mother years of education	Median (IQR)	-0.005(-0.095; 0.085)	0.911	-0.030(-0.133; 0.073)	0.558
gender	Male Female	Ref 0.061(-0.667; 0.789)	0.869	Ref 0.165(-0.563; 0.893)	0.655
Handedness	Right Left	Ref -2.019(-3.760; -0.278)	0.023	Ref -2.044(-3.764; -0.325)	**0.020**
Marital Status	Single Married Divorced	Ref -0.247(-1.026; 0.532) -0.143(-1.157; 0.870)	0.532	Ref -0.444(-1.317; 0.429) -0.526(-1.810; 0.758)	0.317 0.419
Current Employment History	Student Formal Employment Non formal employment Unemployed	Ref 0.154(-1.676; 1.984) -1.321(-3.092; 0.450) -0.586(-2.366; 1.194)	0.868 0.143 0.517	Ref 0.084(-1.796; 1.964) -1.102(-2.939; 0.736) -0.433(-2.279; 1.413)	0.930 0.238 0.644
Ethnicity	Bantu Nilotic NiloHamites Sudanic Hamites	Ref 0.019(-1.254; 1.293) 0.354(-1.130; 1.839) 0.770(-2.523; 0.984) -1.171(-2.444; 0.103)	0.976 0.638 0.387 0.071	Ref -0.274(-1.550; 1.002) -0.141(-1.662; 1.381) -0.913(-2.789; 0.962) -1.040(-2.326; 0.246)	0.672 0.855 0.338 0.112
Current Living arrangements	Renting Owns house Living with primary family Living with other family Living with friends No housing/living on street	 -0.791(-1.803; 0.221) -0.355(-1.249; 0.540) -0.247(-1.530; 1.037) -0.682(-2.836; 1.473) -0.104(-2.491; 2.284)	 0.125 0.435 0.705 0.533 0.932	Ref -0.527(-1.605; 0.550) -0.114(-1.048; 0.820) 0.293(-1.037; 1.623) -0.205(-2.367; 1.957) 0.099(-2.541; 2.343)	0.335 0.810 0.664 0.851 0.936
Who is main source of income in the household	Self Father Mother Relative/ guardian Nonrelative/ organization	Ref 0.282(-0.880; 1.444) 0.655(-0.485; 1.796) 0.328(-0.595; 1.251) 0.328(-0.595; 1.251)	 0.632 0.258 0.483 0.767	Ref 0.289(-0.949; 1.527) 1.187(-0.075; 2.448) 0.447(-0.528; 1.422) 0.120(-1.160; 1.401)	 0.645 0.065 0.367 0.853
Household main source of income	Agricultural Non agricultural Wage Property Organization Other	Ref 2.380(-0.017; 4.777) 1.236(0.289; 2.182) 0.876(0.658; 2.410) 0.727(0.635; 2.089) 0.611(-1.563; 2.786)	 0.052 0.011 0.261 0.293 0.580	Ref 1.846(-0.609; 4.301) 0.922(-0.100; 1.943) 0.861(-0.668; 2.391) 0.761(-0.690; 2.212) 0.379(-1.843; 2.602)	 0.139 0.077 0.267 0.302 0.737
Diet					
Fruit	Never Sometimes Often	Ref -0.676(-1.582; 0.229) -0.192(-1.235; 0.851)	 0.142 0.717	Ref -0.458(-1.390; 0.475) -0.030(-1.087; 1.027)	 0.334 0.955

	Always	0.291(-1.017; 0.478)	0.704	0.304(-1.220; 1.827)	0.694
Meat	Never	Ref	0.236	Ref	
	Sometimes	0.513(-0.338; 1.363)	0.198	0.604(-0.252; 1.460)	0.165
	Often	0.738(-0.390; 1.866)	0.174	0.558(-0.574; 1.690)	0.331
	Always	1.648(-0.736; 4.033)	0.004	1.534(-0.836; 3.903)	0.203
					0.629
Cassava	Never	Ref		Ref	
	Sometimes	-0.309(-1.138; 0.519)	0.462	-0.145(-0.999; 0.710)	0.738
	Often	-0.078(-1.090; 0.934)	0.879	0.016(-1.001; 1.034)	0.974
	Always	-0.365(-1.717; 0.986)	0.594	-0.415(-1.820; 0.989)	0.560
Beans	Never	Ref		Ref	
	Sometimes	0.333(-1.369; 2.035)	0.699	0.601(-1.093; 2.295)	0.484
	Often	0.444(-1.186; 2.074)	0.591	0.624(-0.988; 2.236)	0.445
	Always	0.414(-1.242; 2.069)	0.622	0.664(-0.990; 2.318)	0.429
Maize	Never	Ref		Ref	
	Sometimes	-0.004(-1.505; 1.497)	0.996	0.285(-1.210; 1.781)	0.707
	Often	0.692(-0.704; 2.088)	0.329	0.820(-0.557; 2.196)	0.241
	Always	0.352(-1.040; 1.744)	0.618	0.667(-0.725; 2.060)	0.345
Trauma					
Emotional Abuse		1.197(0.003; 2.390)	0.049	1.177(-0.030; 2.384)	0.056
Physical Abuse		0.208(-1.020; 1.436)	0.738	0.078(-1.172; 1.328)	0.901
Sexual abuse		-0.409(-1.724; 0.905)	0.538	-0.866(-2.280; 0.547)	0.226
Emotional neglect		-0.900(-2.110; 0.311)	0.143	-0.896(-2.120; 0.328)	0.149
Physical neglect		-0.661(-1.935; 0.614)	0.306	-0.535(-1.828; 0.757)	0.412
Minimization/Denial		1.098(-0.162; 2.358)	0.087	0.915(-0.347; 2.176)	0.153
Clinical features					
DUP		-0.096(-0.239; 0.047)	0.188	-0.085(-0.228; 0.058)	0.242
Diagnosis		0.212(-0.575; 1.000)	0.594	0.385(-0.389; 1.159)	0.326
Therapy		0.175(-0.526; 0.875)	0.623	0.140(-0.566; 0.847)	0.695
PANSS		-0.054(-0.144; 0.036)	0.232	-0.046(-0.137; 0.045)	0.318