Research Paper

Prevalence, profile and associations of cognitive impairment in Ugandan first-episode psychosis patients

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ABSTRACT

Introduction: The MATRICS consensus cognitive battery (MCCB) is the gold standard for neuropsychological assessment in psychotic disorders but is rarely used in low resource settings. This study used the MCCB to determine the prevalence, profile and associations of various exposures with cognitive impairment in Ugandan first-episode psychosis patients.

Methods: Patients and matched healthy controls were recruited at Butabika Hospital in Uganda. Clinical variables were first collated, and after the resolution of psychotic symptoms, a neuropsychological assessment of seven cognitive domains was performed using the MCCB. Cognitive impairment was defined as two standard deviations (SD) below the mean in one domain or 1SD below the mean in two domains. Descriptive statistics determined the prevalence and profile of impairment while regression models determined the association between various exposures with cognitive scores while controlling for age, sex and education.

Results: Neuropsychological assessment with the MCCB found the burden of cognitive impairment in first-episode psychosis patients five times that of healthy controls. The visual learning and memory domain was most impaired in first-episode psychosis patients, while it was the working memory domain for the healthy controls. 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 and previous alternative and complementary therapy use were negatively associated with impairment in the visual learning (p = 0.04) and attention/vigilance domains (p = 0.012), respectively. There were no significant associations between sex, history of childhood trauma, or illness severity with any cognitive domain.

Conclusion: A significant burden of cognitive impairment in Ugandan first-episode psychosis patients is consistent with prior data from other contexts. However, the profile of and risk factors for impairment differ from that described in such work. Therefore, interventions to reduce cognitive impairment in FEP patients specific to this setting, including dietary modifications, are required.

1. Introduction

The MATRICS consensus cognitive battery (MCCB) has been suggested as the gold standard for neuropsychological assessment in patients with psychotic disorders (Green et al., 2004; Nuechterlein et al., 2004). Developed during the Measurement and Treatment Research to Improve Cognition in Schizophrenia (MATRICS) initiative in 2002, the

MCCB assesses for impairment 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 (Kern et al., 2007; Nuechterlein et al., 2008). In psychosis populations from high-income countries (HIC) where the MCCB has been used, the prevalence of cognitive impairment has been found to range from 36%

to 78%, primarily in the domains of processing speed and verbal learning and memory (Lystad et al., 2014; Mesholam-Gately et al., 2009). Notable differences as significant as two standard deviations (2SDs) exist between the mean domain scores of first-episode psychosis (FEP) patients versus scores of healthy controls (Green et al., 2019). Cognitive impairment is also associated with various clinical, environmental, and sociodemographic variables, and these associations differ across the seven domains. For example, older age has been associated with impairment in the visual learning and speed of processing domains, while reasoning and problem solving and working memory were associated with female sex (Lee et al., 2020; Rodriguez-Jimenez et al., 2015; Atake et al., 2018; Li et al., 2019; Navarra-Ventura et al., 2018). There is also an association between childhood trauma with impairment in the verbal learning and memory domain (Ayesa-Arriola et al., 2020). Long durations of untreated psychosis have been associated with impairment in selected cognitive domains in patients from HIC but primarily among chronically medicated and not first episode psychosis patients (Stone et al., 2020; Bora et al., 2018).

There is limited research on the prevalence, profile and associations of cognitive impairment in FEP patients from low and middle-income countries (LMICs) (Green, 2016; Vinogradov, 2019; Kline et al., 2019). It is crucial to determine how FEP patients compared to their healthy controls when assessed with the MCCB in LMICs as it prevents wrongly assigning cognitive impairment (Reichenberg, 2010). There are also differing clinical, environmental, and sociodemographic exposures in low resource settings, yet how they are associated with cognitive impairment is still limited. 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, yet their association with cognitive impairment has not been well described in low resource settings (Stone et al., 2020; Stone et al., 2016). The association between cognitive impairment and clinical characteristics that are more prevalent in FEP patients from low resource settings like longer duration of untreated psychosis (DUP), higher rates of childhood trauma, and greater psychosis severity are unclear (Aas et al., 2013; Kilian et al., 2018; Lezak et al., 2004; Fawzi et al., 2013; Hecker et al., 2015). Diet is closely associated with cognitive function, yet the association of different dietary patterns like carbohydrate-rich diets with cognitive impairment have not been reviewed (Beilharz et al., 2015; Jakobsen et al., 2018). Finally, many FEP patients use alternative and complementary therapies before presenting later to care, and understanding if these therapies are associated with cognitive impairment is essential (Woolhouse, 2007).

To address these gaps in the current literature, we investigated the prevalence, profile and clinical variables associated with cognitive impairment in FEP patients from a resource-limited setting. These findings may be crucial in developing interventions for cognitive impairment that is a more significant driver of psychosis disease burden than positive, negative or affective symptoms (Vigo et al., 2016; Mihaljević-Peleš et al., 2019).

2. Methods

2.1. Study design, setting and participants

These have been previously described (Mwesiga et al., 2021). Briefly, this was a cross-sectional study design undertaken at the National Psychiatric Mental referral hospital in Uganda (Butabika hospital). The participants were in-patients aged 18–60 years with confirmed first-episode of psychosis. Additional inclusion criteria included never having been treated with antipsychotic medication or on medication for less than six weeks' duration. The six-week cut-off (as opposed to twelve weeks) was informed by prior evidence that untreated psychosis may resolve more quickly in low- and middle-income countries (LMICs) versus high-income countries (Chiliza et al., 2012; Rangaswamy et al., 2012; Kaminga et al., 2018; Emsley et al., 2006). A cut-off of 18 years

was applied to mitigate the challenges of neuropsychological assessment in adolescents versus adults. In Uganda, patients older than 60 are deemed elderly, and these individuals were excluded from participation to eliminate the potential effects of normal aging and dementia (UBOS, 2012). In addition, 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 (Nakasujja et al., 2012; Sacktor et al., 2005; Nakimuli-Mpungu et al., 2006).

Age, sex and education matched healthy controls were recruited from the outpatient dental department at Butabika Hospital and assessed on the day of recruitment to generate normative values for cognitive function in this population. Inclusion criteria for control participants were 1) no evidence of psychosis or substance use, as assessed by the Mini International Neuropsychiatric Interview (MINI), and 2) no evidence of HIV/AIDS or syphilis.

2.2. Instruments

The consent forms, sociodemographic questionnaire, Mini International Neuropsychiatric Interview (MINI) version 7.0 (Sheehan et al., 2010), Positive and Negative Signs and Symptoms of Schizophrenia (PANSS) (Kay et al., 1987) and Childhood trauma questionnaire (CTQ) (Bernstein et al., 1998) used in this study were previously described (Mwesiga et al., 2021).

The **MATRICS consensus cognitive battery** is the gold standard for assessment of cognition in patients with psychosis (Nuechterlein et al., 2008). It assesses for cognitive impairment 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 (Green et al., 2004; Nuechterlein et al., 2008). The complete battery can be completed in approximately 90 min, excluding the time needed to score. The neuropsychological assessment procedure with the MCCB was performed as previously described Nuechterlein et al. (2008). Briefly, the MCCB comprises ten different neuropsychological tests; the Trail Making Test (TMT): Part A; Brief Assessment of Cognition in Schizophrenia (BACS): symbol coding; Hopkins Verbal Learning Test-Revised (HVLT-R); Wechsler Memory Scale-Third Edition (WMS-III): Spatial Span; Letter-Number Span (LNS); Brief Visuospatial Memory Test-Revised; Category Fluency: Animal Naming; Mayer-Salovey-Caruso Emotional Intelligence Test (MSCEIT): Managing Emotions (D & H); Continuous Performance Test-Identical Pairs (CPT-IP), MATRICS International Version 2. The ten neuropsychological tests of the MATRICS are administered in the order above to ensure 1) patients start the battery with less cognitively taxing activities that are relatively straightforward to understand to facilitate optimal test-taking performance; and 2) alternate verbal with nonverbal measures, thus aiming to alleviate processing burden and minimize interference among tests (Nuechterlein et al., 2008).

The MCCB was administered by two experienced clinical psychologists currently pursuing their doctoral studies. The MCCB was not translated to any Ugandan local language. However, adjustments were needed in the administration of the MCCB tests since the study population composed of a mixed population with people from different ethnic groups and mixed age ranges. The education level of the population was also varied with majority having less than 9 years of formal education. The language of choice in most cases was one of the many local dialects even among individuals with a relatively high education. Most participants had not used a computer before, which was required for administration of the CPT-IP. The participants had never participated in psychological testing and a single reading of the MCCB instructions was often not enough for them to understand the test expectations. If we had used the age and educational criteria of the MCCB, we would have needed to exclude more than 75% of the desired population, giving us an unrepresentative sample and perpetuating the theoretical and ethical

problem of excluding the most vulnerable individuals.

We administered this cognitive battery to all consenting eligible participants with first-episode psychosis but revised the administration procedures to improve the validity of test scores. The formal scored portion of each test remained unchanged, but test administrators repeated or rephrased instructions for each test up to 5 times until respondents understood the test expectations. If respondents were not sure, the administrators asked them to describe the test expectations before beginning the formal test. We also added a training maze before administering the NAB Mazes, and we trained respondents to use a computer mouse before starting the CPT-IP.

Despite these considerations, several patients had difficulty understanding the test requirements or were otherwise unable to complete some of the tests. Standard practice when scoring the MCCB is to use the worst score (i.e., 300 s for the TMT-A and 0 points for all other tests); however, given our sample's demographic differences from participants in almost all previous studies that used the MCCB, it was important to determine whether respondents understood the assessment tasks. Therefore, we developed test-specific rules to make sure respondents understood the test expectations and the distinction was made by the objective view of the interviewer during the assessment of the individual respondents' comprehension of the required task and their ability to complete the task. For tests that required multiple trials (i.e., the HVLT-R, WMS-III Spatial Span, BVMT-R, and CPT-IP), each trial had to have an initial simplified instruction before the test administration. Scoring of all subtest was not adjusted.

2.3. Research procedure

First-episode psychosis patients were enrolled into the observational study. After obtaining informed consent, the diagnosis was confirmed using the MINI. Sociodemographic information was compiled using a standard questionnaire, and illness severity was assessed using the PANSS. Patients were then followed up weekly with the PANSS until resolution of psychotic symptoms, at which point the MCCB was administered. In addition, data on previous traumatic experiences were assessed using the CTQ. Consenting healthy controls (matched for age and level of education) were also recruited from the hospital's dental wards and assessed using the MCCB.

2.4. Data analysis

Data were analyzed using Stata version 14 (Stata, 2018). 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. These raw scores were then standardized using the means and standard deviations of the healthy controls after matching for age, sex and level of education. Next, composite scores were generated for each of the seven domain scores by summing the standardized scores of individual tests per domain.

Standardized test scores of the Trail Making Test (TMT): Part A and Brief Assessment of Cognition in Schizophrenia (BACS): symbol coding and Category Fluency: Animal Naming were combined to represent the speed of processing domain. Hopkins Verbal Learning Test-Revised (HVLT-R) sum scores represented the verbal learning and memory domain. Wechsler Memory Scale-Third Edition (WMS-III): Spatial Span and the Letter-Number Span (LNS) were combined for the working memory domain. Brief Visuospatial Memory Test-Revised sum scores represented the visual learning and memory domain. Mayer-Salovey-Caruso Emotional Intelligence Test (MSCEIT): Managing Emotions (D & H) represented social cognition and the Continuous Performance Test-Identical Pairs (CPT-IP), MATRICS International Version 2 represented attention/vigilance domain.

Cognitive impairment was classified as a categorical variable to determine the prevalence and profile of impairment. For the burden of a general cognitive impairment, participants with mean domain scores two standard deviations (SD) below the mean in one domain of the MCCB; or as 1SD below the mean in two or more domains of the MCCB were classified as impaired (Revell et al., 2015). Standardized scores of 2SD below the mean signified cognitive impairment in a specific domain. Duration of untreated psychosis was calculated by subtracting the age at which patient symptoms first presented from the patient's age at admission. 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) and depression with psychotic features were classified as affective psychoses. All other psychosis diagnoses were classified as non-affective psychoses.

Descriptive statistics were employed for the prevalence and profile for both a general cognitive impairment and impairment in particular cognitive domains. In determining the mean differences between cases and healthy controls and factors associated, cognitive impairment was classified as a continuous variable (higher scores implying better cognitive function). Student t-tests determined if mean cognitive domain scores differed across the FEP patients and healthy controls. Regression coefficients were calculated for the associations between various clinical variables and the seven different standardized domain scores in the FEP patients while controlling for sex and level of education. Due to multiple comparisons, a Bonferroni adjusted significance level was calculated to account for the increased possibility of type-1 errors. A level of significance of 0.05 was used for all analyses.

3. Results

After data cleaning, the final sample included 129 FEP patients and 52 healthy controls. 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 FEP patients, the median age for first seeking help was 26 years [IQR 21–32]. The mean time between the onset of symptoms and presenting to the hospital was 0.932 years [SD 2.798, range (0–18)]. Most participants [76/120; 63%] presented with symptoms for the first time, while 95/113 (84%) presented 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%]. Approximately 13% of FEP patients had previously received antipsychotic medication for less than six weeks' duration. Most participants ate diets rich in legumes (93.3%) and grains (90.8%) in the week before admission. 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%). 36% of participants had scores suggestive of under-reporting traumatic events (Table 1).

3.1. Comparison of the burden of cognitive impairment in patients and healthy controls

We found that 80/129 (62%) of the FEP patients and 6/52 (12%) of the healthy controls had a general cognitive impairment. There were no statistical differences in the proportions of participants with a general cognitive impairment across sex [prevalence ratio (PR) = 1.15 (p = 0.79)], age [PR = 0.46 (p = 0.19)] or diagnosis (affective versus non-affective psychosis) [PR = 1.17 (p = 0.76)].

3.2. The burden of impairment in specific cognitive domains

Most FEP patients were impaired (2 SD below the mean) in the visual learning and memory domain [38% (CI 30.0–47.5)], while most healthy controls were impaired in the working memory domain [6.1% (CI

Table 1
Sociodemographic characteristics of the study sample.[a]

Variable		Cases (129)	Healthy controls (52)	p-Value
Age	Median (IQR)	26.0 (27.3; 30.5)	31.8 (29.1; 34.5)	0.063
Sex	Male	43 (35.8%)	18 (36.7%)	0.912
	Female	77 (64.2%)	31 (63.3%)	
Handedness	Right	116 (96.7)	43 (93.5)	0.360
	Left	4 (3.3)	3 (6.5)	
Marital status	Single	63 (53.4)	12 (24.5)	0.002
	Married	36 (30.5)	28 (57.1)	
	Divorced	19 (16.1)	9 (18.4)	
Current employment status	Student	7 (5.9)	0 (0.0)	p < 0.001
	Formal	16 (13.6)	22 (44.9)	
	Non formal	47 (39.8)	17 (34.7)	
	Unemployed	48 (40.7)	10 (20.4)	
Highest level of education	No school	3 (2.6)	1 (2.0)	0.932
	Primary	44 (37.6)	15 (30.6)	
	Secondary	56 (47.9)	26 (53.1)	
	Diploma	12 (10.3)	6 (12.2)	
	University	2 (1.7)	1 (2.0)	
Ethnicity	Bantu	86 (73.5)	34 (70.8)	0.041
	Nilotic	8 (6.8)	6 (12.5)	
	NiloHamites	4 (3.4)	6 (12.5)	
	Sudanic	6 (5.1)	1 (2.1)	
	Hamites	13 (11.1)	1 (2.1)	
Current living arrangements	Renting	23 (19.5)	30 (61.2)	<0.001
	Own house	25 (21.2)	9 (18.4)	
	Living with family	69 (58.4)	10 (20.4)	
	No housing	1 (0.9)	0	
Main source of income in the household	Self	43 (36.4)	28 (58.3)	0.087
	Father	17 (14.4)	3 (6.2)	
	Mother	18 (15.2)	3 (6.2)	
	Relative/ guardian	28 (23.7)	10 (20.8)	
	Nonrelative/ organization	12 (10.2)	4 (8.3)	

[a] Bold p-values represent statistically significant differences between the cases and healthy controls.

1.9–17.80)]. Conversely, the social cognition domain was least impaired in the FEP patients [17% (CI 10.9–24.6)]. No healthy controls were assigned as impaired in visual learning and memory or verbal learning and memory (Fig. 1).
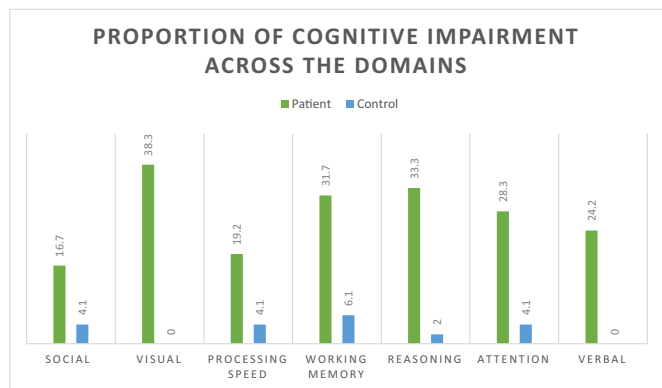

Fig. 1. Proportions of patients classified as impaired (2 standard deviations (SD) below the mean in one domain or 1SD below the mean in two domains) in the seven domains.

3.3. Profile of impairment

Statistically significant differences in mean cognitive scores between FEP patients and healthy controls were found across all domains, except social cognition. The most significant difference was in the reasoning and problem-solving domain, a statistically significant decrease of 1.834 ($p \leq 0.0001$). By contrast, the difference in mean scores between cases and controls was lowest in the social cognition domain, a statistically significant decrease of 0.189 ($p = 0.62$). Other comparisons are shown in Table 2 and Fig. 2.

3.4. Clinical variables associated with impairment in different cognitive domains

For standardized z scores on visual learning and memory domain (most impaired domain), significant associations were found with increased age ($p = 0.001$), more years of education ($p = 0.042$), being married ($p = 0.016$), Hamitic ethnicity ($p = 0.017$), living with non-family members ($p = 0.001$), cassava diet in the week before admission ($p = 0.041$) and a non-affective psychosis diagnosis ($p = 0.026$). In addition, there were significant associations in the sociodemographic variable of living with a family member ($p = 0.001$) and wage incomes for the household primary income earner ($p = 0.024$) with the reasoning and problem-solving domain. 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 ($p = 0.024$). Complete results for the visual learning and memory domain are shown in Table 3. Raw tables for associations between various clinical variables and the other cognitive domains are in the supplementary files at the end of this article.

4. Discussion

The main findings were 1) the prevalence of cognitive impairment in FEP patients was five times higher than age, sex and level of education matched healthy controls. 2) The most frequently impaired domains were visual learning and memory in FEP patients and working memory in healthy controls. 3) Strength of associations differed across the seven different cognitive domains. Increased age was associated with impairment in the speed of processing and visual learning and memory domains. Having a wage income was associated with higher cognitive scores in all domains except the social cognition domain. Cassava-rich diets and previous alternative and complementary therapy use were negatively associated with cognitive impairment in the visual learning and attention/vigilance domains. There were no significant associations

Table 2
Comparison of mean domain scores between cases and controls.

| Domain	Cases (n = 120) Mean (SD)	Controls (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
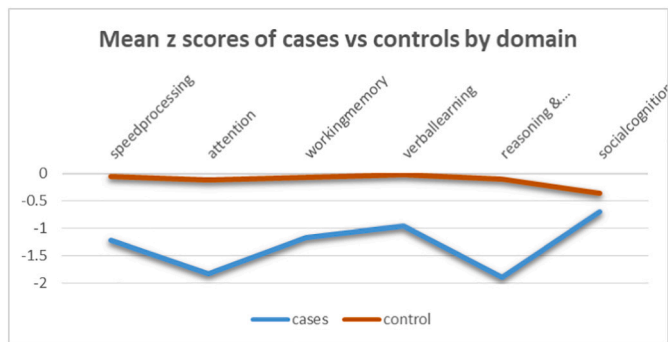
Fig. 2. Comparison of mean domain scores between the FEP patients and healthy controls.

between sex, history of childhood trauma, or illness severity with any cognitive domain.

4.1. Comparison of cognitive impairment between patients and healthy controls

In line with prior work conducted in diverse settings, the prevalence of cognitive impairment at the first episode of psychosis in our study sample was higher than in the healthy controls (Lystad et al., 2014; McCleery et al., 2014; Rodriguez-Jimenez et al., 2019; Holmén et al., 2010). However, unlike studies reporting the most significant burden in the attention/vigilance and working memory domains, most patients with first-episode psychosis in our study sample were found to have impairment in the visual learning and memory domain (Braw et al., 2008; Rhinewine et al., 2005).

We found the most significant difference in mean scores in the reasoning and problem-solving domain unlike studies from HIC which reported the most considerable mean differences in the working memory domain (Aas et al., 2014). One explanation is that – given that reasoning and problem solving is a higher-order domain – performance in this sphere is often dependent on lower-order domains such as processing speed (Kalkstein et al., 2010). Thus, the cumulative effect of impairment in lower order domains may be responsible for this finding.

In our study, the prevalence of 17% impairment in the social-cognitive domain among FEP patients was relatively low. Further, no statistically significant differences were evident between the mean scores of FEP patients and healthy controls in this domain. This finding is consistent with work from other LMICs suggesting poor psychometric properties of the MSCEIT in such settings (Kurtz et al., 2018; Mehta et al., 2011; Emsley et al., 2005; Lim et al., 2020; Stone et al., 2020).

There were no healthy controls categorized as impaired in visual learning and memory and verbal learning and memory. There are few studies on this domain in LMIC with a limited number of validated tools for assessing patients with psychotic disorders (Vingerhoets et al., 2013). Thus, further research on neuropsychological testing of the visual learning and memory domain in first-episode psychosis patients is warranted.

4.2. Sociodemographic risk factors for cognitive impairment

A 48% increase in standardized scores of the visual learning and memory domain was observed for every unit increase in age. 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 consistent with literature from high-income countries (Lee et al., 2020; Rodriguez-Jimenez et al., 2015; Rajji et al., 2009; Atake et al., 2018).

The lack of associations between sex and impairment in any cognitive domain differs from literature in HIC that often highlight considerable heterogeneity in associations of cognitive impairment in men and women (Mendrek and Mancini-Marïe, 2016). For example, in Hong Kong, the reasoning and problem solving and working memory domains were associated with the female sex, while processing speed was associated with the male sex. In addition, both sexes were associated with impairment in the attention/vigilance domain, and negative symptoms mediated the relationship (Li et al., 2019; Navarra-Ventura et al., 2018; Zhang et al., 2017). These sex differences have been linked to a disturbance in typical sexual dimorphism (males having larger ventricles and smaller frontal lobes) due to hormonal and immunological factors (Mendrek and Mancini-Marïe, 2016).

In all domains except the social cognition domain, having a wage income was associated with higher cognitive scores, keeping with elsewhere literature (Tan, 2009). However, the direction of this association needs further review as it is unclear from this study design if better cognitive function ensures employment through more excellent job opportunities and income, or rather employment and income is protective of cognitive function (Llerena et al., 2018; McGurk et al., 2009).

4.3. Diet and cognitive impairment

There was a positive association between meat and legume-rich diets with impairment in the working memory domain consistent with other published studies (Wonodi and Schwarcz, 2010; Cao et al., 2021). Among 195 Chinese patients with schizophrenia, kynurenic acid (KYNA) was associated with worse performance in the working memory domain, while 5-hydroxy indole was associated with improved performance (Huang et al., 2021). Meat and legumes are rich in tryptophan, whose metabolites include KYNA and 5-hydroxy indole 75, 76. Going forward, better quantification of these metabolites in Ugandan FEP patients may elucidate the underlying mechanisms of this association.

Fruit rich diets were not associated with impairment in any cognitive domain. High flavonoids found in citrus may be associated with improved cognitive functioning in schizophrenia patients from other settings (Bruno et al., 2017; Pontifex et al., 2021). Previous research has shown that different fruits have different quantities of flavonoids content (Stangeland et al., 2009). This flavonoid content also differs depending on the size of the portion and the part of the fruit (peelings of pomegranate, for example, have more content) (Shams Ardekani et al., 2011). The flavonoid content in the fruits could be quantified in future studies.

Cassava was associated with an increased risk for cognitive impairment in the visual learning domain. This cassava association with cognitive impairment is due to thiocyanate toxicity in poorly processed cassava (Boivin et al., 2017; Rivadeneyra-Domínguez and Rodríguez-Landa, 2020). To our knowledge, this is the first study to highlight an association between cassava diets and a specific cognitive domain in FEP patients. Given that cassava is a staple diet in Uganda, further work examining this association is required.

4.4. Trauma and its association with cognitive impairment

This study found only one association between the attention/vigilance cognitive domain and the physical abuse trauma domain. One possibility is underreporting of traumatic experiences (Church et al., 2017; Read et al., 2001; Radhakrishnan et al., 2017; Mall et al., 2020). Previous studies associated childhood trauma and cognitive impairment in the working memory and reasoning and problem-solving domains. The few studies that have highlighted an association in the attention/vigilance domain reported an association with physical neglect, not physical abuse (Mørkved et al., 2020; Olivier et al., 2015).

4.5. Clinical risk factors for cognitive impairment

There was a positive correlation between shorter DUP and increased impairment in the domains of attention vigilance which differs from other studies that correlated increased DUP with increased impairment

Table 3

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**
Participant's 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
Sex	Male	Ref		Ref	0.10
	Female	−0.458 (−1.017; 0.101)	0.107	−0.458 (−1.017; 0.100)	7
Handedness	Right	Ref		Ref	
	Left	0.202 (−1.215; 1.619)	0.779	0.311 (−1.030; 1.652)	0.648
Marital Status	Single	Ref		Ref	
	Married	0.898 (0.293; 1.503)	0.004	**0.815 (0.156; 1.475)**	**0.016**
	Divorced	0.723 (−2.019; −1.198)	0.072	0.477 (−0.493; 1.447)	0.333
Current employment history	Student	Ref		Ref	
	Formal employment	0.537 (−0.925; 2.000)	0.469	0.138 (−1.314; 1.590)	0.852
	Non formal employment	−0.354 (−1.770; 1.061)	0.622	−0.232 (−1.652; 1.187)	0.747
	Unemployed	−0.619 (−2.042; 0.804)	0.392	−0.634 (−2.059; 0.792)	0.381
Ethnicity	Bantu	Ref		Ref	
	Nilotic	0.4111 (−0.584; 1.406)	0.416	0.052 (−0.923; 1.026)	0.917
	NiloHamites	0.976 (0.183; 2.136)	0.098	0.862 (−0.300; 2.024)	0.145
	Sudanic	−0.058 (−1.428; 1.312)	0.934	−0.012 (−1.444; 1.420)	0.987
	Hamites	−1.574 (−2.569; −0.580)	0.002	**−1.197 (−2.179; −0.215)**	**0.017**
Current living arrangements	Renting	Ref		Ref	
	Owns house	−0.877 (−1.627; −0.127)	0.022	**−0.887 (−1.676; −0.097)**	**0.028**
	Living with primary family	−1.226 (−1.889; −0.562)	0.000	**−0.937 (−1.622; −0.253)**	**0.008**
	Living with other family	−2.211 (−3.163; −1.260)	0.000	**−1.728 (−2.703; −0.753)**	**0.001**
	Living with friends	−1.742 (−3.339; −0.145)	0.033	−1.257 (−2.841; 0.328)	0.119
	No housing/living on street	−0.750 (−2.520; 1.020)	0.404	−0.756 (−2.546; 1.033)	0.405
Who is main source of income in the household	Self	Ref		Ref	
	Father	−0.528 (−1.436; 0.379)	0.252	−0.315 (−1.263; 0.632)	0.512
	Mother	−0.595 (−1.486; 0.296)	0.189	−0.010 (−0.975; 0.956)	0.984
	Relative/guardian	−0.913 (−1.633; −0.192)	0.013	−0.630 (−1.376; 0.116)	0.097
	Nonrelative/organization	−0.804 (−1.797; 0.188)	0.112	−0.455 (−1.435; 0.525)	0.360
Household main source of income	Agricultural	Ref		Ref	
	Non agricultural	1.506 (−0.345; 3.357)	0.110	1.469 (−0.362; 3.299)	0.115
	Wage	1.500 (0.769; 2.231)	0.000	1.312 (0.551; 2.073)	**0.001**
	Property	0.251 (−0.933; 1.436)	0.676	0.246 (−0.894; 1.386)	0.670
	Organization	1.363 (0.311; 2.414)	0.011	1.302 (0.221; 2.384)	**0.019**
	Other	0.300 (−1.379; 1.979)	0.724	0.238 (−1.419; 1.895)	0.777
Diet within the last week					
Fruit	Never	Ref		Ref	
	Yes	0.017 (−0.028; 0.061)	0.461	0.331 (−0.380; 1.042)	0.137
Meat	Never	Ref		Ref	
	Yes	0.019 (−0.026; 0.065)	0.403	0.029 (−0.017; 0.076)	0.215
Cassava	Never	Ref		Ref	
	Yes	−0.058 (−0.107; −0.009)	0.020	−0.054 (−0.105; −0.002)	**0.041**
Beans	Never	Ref		Ref	
	Yes	−0.003 (−0.030; 0.024)	0.832	−0.001 (−0.030; −0.028)	0.952
Maize	Never	Ref		Ref	
	Yes	−0.006 (−0.361; 0.024)	0.700	−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	Ref		Ref	
	Non-Affective	−0.768 (−1.494; −0.041)	0.038	−0.801 (−1.502; −0.099)	**0.026**
Alternative and complementary therapy	No use	Ref		Ref	
	Previous use	−0.327 (−1.004; 0.349)	0.340	−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

in reasoning and problem-solving and verbal learning and memory domains (Fraguas et al., 2014; Bora et al., 2018; Lappin et al., 2007; Stone et al., 2020). This finding may support evidence that the attention/vigilance domain is impaired earliest during psychotic disorders, as shown in other settings (Hou et al., 2016). Longitudinal studies and studies in the psychosis prodrome are recommended.

To our knowledge, this is the first study to report a negative association between previous use of alternative and traditional therapies and cognitive impairment in the attention/vigilance domain. Previous work in Uganda showed that patients with psychotic disorders are treated with herbs and rituals (Abbo et al., 2012; Abbo et al., 2019). However, it is unclear if the herbs used by alternative and complementary therapies are associated with cognitive impairment. Recently a study in China highlighted an association between oxidative damage

and cognitive impairment in FEP patients treated with herbal remedies (Xie et al., 2019). The nature of the herbs used needs assessment to determine if they cause oxidative damage and cognitive impairment. It is also vital to document previous use of alternative therapies and the medication provided during neuropsychological assessment.

Significant associations were observed between non-affective psychoses with impairment in visual learning and memory and the working memory domains. However, among 64 Croatian patients, the association between non-affective psychoses and impairment in the working memory domain were not replicated (Žakić Milas and Milas, 2019). This finding might be due to a more considerable burden of affective psychoses in high-income countries than low-income countries (Rodriguez-Jimenez et al., 2015; Rodriguez-Jimenez et al., 2019; Reichenberg et al., 2009; McCleery and Nuechterlein, 2019; Mwesiga et al., 2020).

4.6. 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 determination of causality. Second, the descriptions for the duration of untreated psychosis were prone to recall bias. Future studies should use standardized instruments like the Nottingham Onset schedule for the duration of untreated psychosis (NOS-DUP) (Singh et al., 2005) and the Interview for retrospective assessment of Schizophrenia onset (IRAOS) (Mwesiga et al., 2019; Haefner and Maurer, 2006). We also used the Childhood Trauma Questionnaire, which assesses for trauma retrospectively and is prone to recall bias (Aas et al., 2011; Charak et al., 2017; Kilian et al., 2018). Third, the diet was not assessed using standardized tools like the 24-hour dietary recall or cluster analysis of dietary patterns, which may have led to misclassification bias in defining the exposure (Hu, 2002; Reedy et al., 2010; Thompson and Subar, 2001). Also, patients with psychotic disorders are at higher risk for lifestyle disorders like diabetes and hypertension, which are also risk factors for cognitive impairment (Pillinger et al., 2017). This increased risk is thought to be due to patients with psychotic disorders often preferring starch-rich diets and an underlying genetic risk (Perry et al., 2016). These need to be assessed in future studies.

These limitations notwithstanding, this is one of few studies in Africa to use the gold standard for neuropsychological assessment in FEP patients (Kilian et al., 2018). The literature on cognitive impairment has primarily focused on schizophrenia, so including both affective and non-affective psychoses highlight an important field for future study. This study also determined associated factors for cognitive impairment specific to this setting, such as dietary patterns, early childhood trauma and previous use of alternative therapies. There is an exciting basis for future studies on cognition and diet in patients with psychotic disorders from low resource settings. Future studies determining the role of various effect modifiers on the association between diet and cognitive impairment are required (Chen et al., 2016; Bioque et al., 2021). First, diet is one of the known exposures that can change genetic expression (Bottero and Potashkin, 2020). Second, the microbiome and gut-brain axis may modify the association between a diet with cognitive impairment (Luca et al., 2020).

5. Conclusion

Consistent with literature from high-income countries, there is a significant burden of cognitive impairment in Ugandan first-episode psychosis patients than their healthy controls. However, in this setting, the prevalence profile and clinical variables associated with cognitive impairment differ from the literature in HIC. Therefore, neuropsychological assessment in first-episode psychosis patients in this setting must consider the different domains impaired and exposures associated with impairment in this setting when developing interventions to reduce the burden of cognitive impairment. Interventions to improve cognitive function like atypical antipsychotics and cognitive remediation must be undertaken (Houthoofd et al., 2008; Meltzer and McGurk, 1999; Linssen et al., 2014; Koola et al., 2017; Fountoulakis, 2020; Bowie et al., 2020; Zaytseva et al., 2013; Revell et al., 2015). Dietary interventions deserve study as a cheap intervention for reducing cognitive impairment.

CRediT authorship contribution statement

Conceptualization: EKM, DA, NK, NN, DJS; **Methodology:** EKM, RR; **Validation:** EKM, RR; **Formal analysis:** EKM, RR; **Investigation:** EKM, JN; **Data curation:** EKM; **Writing original draft:** EKM, RR, DA, NK, JN, NN, DJS; **Visualization:** EKM; **Supervision:** EKM, DA, NK, NN, DJS; **Project Administration:** EKM, JN, NN; **Funding acquisition:** DA, DJS.

Declaration of competing interest

The authors declare no conflict of interest.

Ethics approval and consent to participate

The study obtained ethical approval 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 obtained from the administration of Butabika hospital. Patients were reimbursed $3 for their time, either completing the entire study assessment or withdrawing consent.

Data and material availability

All data generated or analyzed during this study are available from the corresponding author.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.scog.2021.100234.

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