An Examination of the Validity of the Bengali Addenbrooke's Cognitive Examination-III for Detecting Mild Cognitive Impairment and Dementia

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Abstract:

The Addenbrooke's Cognitive Examination-III (ACE-III) is a cognitive screening tool that is useful for the detection of cognitive impairment. Recently, the ACE-III has been adapted for the Bengali speaking population in India. The aim of this study was to examine the validity of the newly adapted Bengali ACE-III for detecting cognitive impairment, evaluate the influence of demographic variables on test performance, and produce appropriate normative data.

305 cognitively healthy controls and 159 patients with cognitive impairment were administered the Bengali ACE-III at the research site in Kolkata, India. Statistical analyses were performed on this data. This involved the construction of receiver operating characteristic (ROC) curves to obtain an overall measure of diagnostic accuracy from the area under the curve (AUC) metric and sensitivity and specificity values for a range of cut-off scores. Predicative values and likelihood ratios were also calculated.

Correlation analyses were performed on the healthy control group to examine the influence of age, education, and gender on test performance. The results showed education has the strongest influence on performance, followed by gender. Age only showed a significant effect when the other variables were controlled for. Normative data was provided on this basis through banding and regression approaches.

Overall, the results show the Bengali ACE-III demonstrates excellent diagnostic accuracy for the detection of dementia, however has a lower accuracy for the detection of Mild Cognitive Impairment (MCI). This should reflect how it is used in practice. Due to the influence of demographic factors clinicians should utilise the normative data when interpreting test scores to enhance diagnostic accuracy.

1.0 Introduction and Background:

1.1 Dementia

Dementia is an umbrella term for a group of progressive, neurological conditions that primarily affect older people. The most common form of dementia is Alzheimer's disease (AD), followed by vascular dementia (VaD), dementia with Lewy bodies (DLB), and frontotemporal dementia (FTD). The boundaries between different forms of dementia can be indistinct and mixed dementia, that has features from more than one cause, is also common (Prince & Jackson, 2009).

Dementia is characterised by the gradual deterioration of multiple cognitive functions, including: memory, learning, language, comprehension, orientation and judgement from a previously attained level, that impairs the ability to maintain activities of daily living (ICD 10, 2016). The type of dementia determines the cognitive functions that are impaired, which can result in distinct profiles of impairment (Braaten, Parsons, McCue, Sellers & Burns 2006). For example, AD is associated with a disproportionate decline in memory relative to other functions, while FTD is generally associated with a decline in language functions (Levy & Chelune, 2007).

Consequently, dementia is a major cause of disability and dependency in the older population. This imposes a profound burden on the individual, their families who are likely to be responsible for the majority of caregiving, and on society, which bears the direct costs of both formal and informal care and losses of income and productivity (Prince et al, 2015).

To date, an estimated total of 47.8 million people suffer from dementia globally. This estimate is projected to rise to 131 million people by 2030, as the combined effects of demographic development and improvements in life expectancy are increasing the proportion of older people, and thus those at risk of dementia, in the population. With this, the burden of dementia is likely to become a significant public health challenge (Prince et al, 2015), particularly in low-middle income countries where there is an absence of adequate policy and health care systems are under-resourced (Shetty, 2012; Ferri & Jacob, 2017).

This challenge is further compounded by the current lack of effective disease modifying treatments available for dementia (Livingston et al, 2017). However, an increasing body of research suggests that the burden placed on the patient, caregiver, and society can be reduced through therapeutic and educational interventions if implemented early in the disease course. The evidence, albeit limited, indicates such interventions can improve short and long-term outcomes, reduce psychological distress, delay institutionalisation, and enable the autonomous planning of future medical, financial and legal decisions (Smith et al, 2018). This highlights the importance of making an early diagnosis of dementia.

1.2 Cognitive Screening Tests

There is no single test to diagnose dementia, and the process can potentially be complex and time-consuming. In order to increase efficiency and maximise available healthcare resources, a stepped approach to diagnosis is recommended (National Collaborating Centre for Mental Health, 2007).

The first step towards making an early diagnosis is cognitive screening. This typically takes place in a primary care setting where the majority of persons experiencing symptoms initially present (Robinson, Tang & Taylor, 2015).

Cognitive screening involves the administration of a brief test to provide an objective measure of the major cognitive functions known to be affected by dementia. The presence or absence of cognitive impairment can be detected when test performance is compared against the published cut-off scores (Cullen, O'Neill, Evans, Coen & Lawlor, 2007), in which scores below this threshold indicate impairment.

The emphasis on detecting cognitive impairment must also support differential detection of other key sources of cognitive impairment such as mild cognitive impairment (MCI). MCI exhibits similar symptoms as dementia but does not result in major impairment of the patient's activities of daily living (Petersen et al, 1999). The detection of MCI is important as it poses an increased risk state for progression to dementia (Mitchell & Shiri-Feshki, 2009).

Detection of cognitive impairment thus enables the appropriate monitoring of patients with MCI and the referral of patients who require a more comprehensive clinical assessment to specialist services such as memory clinics (Block, Johnson-Greene, Pliskin & Boake, 2017).

Cognitive screening tests also have a place in specialist services where their assessment of multiple cognitive functions can be used to establish a more in-depth profile of impairment. Examination of the profiles of impairment can provide an indication of the subtype of dementia and support further, targeted, diagnostic evaluations (Velayudhan et al, 2014).

There are a number of cognitive screening tests that perform these functions. The most widely used is the Mini Mental State Examination (MMSE). However, the MMSE is associated with numerous shortcomings including limited assessment of visuospatial and executive functions and is strongly influenced by levels of educational attainment (Devenney & Hodges, 2016). In addition, the MMSE has recently incurred licencing costs, which has led to other well accepted tests gaining increased use. These include: The Clock Drawing Test, Mini-Cog, Memory Impairment Screen, General Practitioner Assessment of Cognition, Abbreviated Mental Test, Addenbrooke's Cognitive Examination, Montreal

Cognitive Assessment, and Rowland Universal Dementia Assessment Scale (Cullen et al, 2007; Ismail, Rajji & Shulman, 2010).

The usefulness of these tests for detecting cognitive impairment is dependent on their diagnostic accuracy. This is reflected in the psychometric properties, and in particular in measures of sensitivity and specificity (Cullen et al, 2007). Sensitivity is a measure of the number of people with the condition of interest who are correctly identified as impaired (true positives), and specificity is a measure of people without the condition of interest who are correctly identified as not impaired (true negatives).

However, it is uncommon for screening tests to have both perfect sensitivity and specificity (=1) and it is generally perceived that screening tests with higher sensitivity, at the expense of specificity, are of more value in the aforementioned settings to ensure all potential cases are detected (Larner, 2017). This poses the risk of misclassifying a healthy person as impaired (false positive), which can be associated with distress, stigma or unnecessary treatment (Milne, 2010; Borson et al, 2013).

Moreover, it is well established that cognitive performance is influenced by demographic variables such as age, gender, education, and culture (Ardila, Ostrosky-Solis, Rosselli & Gomez, 2000). This influence is mirrored in performance on cognitive screening tests (Mortensen & Gade, 1993; Ardila, 1995) and can lead to false conclusions about an individual's cognitive ability, thus affecting the overall diagnostic accuracy of the test. It is therefore important to take these variables into account when interpreting test results.

The influence of age, gender, and education can be addressed using relevant normative data (Mitrushina, Boone, Razani & D'Elia, 2005). However, as will be discussed in the following section the influence of culture on test performance is multi-dimensional and to adequately control for it requires a more complex approach such as test adaptation.

1.3 Culture and Cognitive Testing

Culture can be understood as a 'set of learned traditions and living styles, shared by the members of a society. It includes the ways of thinking, feeling and behaving' (Harris, 1983) and therefore provides an important context for cognitive testing.

This context can be understood by considering four aspects of culture; patterns of abilities, cultural values, familiarity, and language as described by Ardila (2018);

> **Patterns of abilities** refers to the differences that can arise in the expression of cognitive functions between different cultural settings. Cognitive functions are known to be universal, however the way they are used in specific situations is learnt and thus subject to the influence of culture.

Cultural values considers the relevance or meaning given to the conditions and strategies used for cognitive testing. This may vary depending on the normality of testing situations to a particular culture. For example, the relationship between the examiner and examinee and the associated concept of background authority may be different between cultures.

Familiarity relates to the test conditions and strategies required as above, but also to the items included in the test. Certain test items may be less commonly known in cultures, compared to where the test was developed, and therefore less appropriate to assess cognitive abilities.

Language exerts multiple influences on test performance. Language can have an effect on both understanding of the test, and cognitive ability via effects mediated by its complex linguistic properties.

Consequently, cognitive tests that are primarily developed for Western, middle class, and literate populations cannot be readily applied across cultures without introducing cultural biases. These cultural differences may mask genuine differences in cognitive ability. They have been classified as: construct, method and item. (Ardila, 1995; van de Vijver & Tanzer, 2004).

For example, evidence indicates that when cognitive tests, developed in North America, are administered to individuals from diverse cultures, without consideration of these biases, a significantly high number of false positives are given (Norman et al, 2011; Daugherty, Puente, Fasfous, Hidalgo-Ruzzante & Pérez-Garcia, 2017).

1.4 Adaptation

A preferred strategy to address some of these biases is cultural adaptation (Fernandez & Abe, 2017). Cultural adaptation refers to a procedure in which an instrument, developed for one cultural setting, is transferred for use in another cultural setting while preserving its psychometric properties (International Test Commission, 2017). This is generally achieved through the translation of the culturally appropriate components of the test to the target language, and modification of the components where translation is not sufficient to address cultural differences (Malda et al, 2008).

There are clear advantages associated with test adaptation. It represents a cheaper and quicker method than the generation of new tests, which can take several years of research and development. In addition, it enables a more thorough evaluation of the adapted test to provide a strong evidence base, as it can be compared to the original version (Hambleton & Patsula, 1998; Borsa, Damásio & Banderia, 2012).

A number of cognitive tests have been successfully adapted to different cultures (Fernandez & Abe, 2017). For instance, the Addenbrookes Cognitive Examination (ACE) and its revisions, the ACE-R and

ACE-III (Mathuranath, Nestor, Berrios, Rakowicz & Hodges, 2000; Mioshi, Dawson, Mitchell, Arnold & Hodges, 2006; Hsieh, Schubert, Hoon, Mioshi & Hodges, 2013).

1.5 Addenbrooke's Cognitive Examination

The ACE is a brief cognitive screening tool, developed at the Memory Clinic at Addenbrooke's Hospital, Cambridge, UK for fluent English speakers with an understanding of UK cultural norms. The primary objectives of the ACE were to detect dementia related cognitive impairment and differentiate between subtypes of dementia, namely AD and FTD (Mathuranath et al, 2000).

The ACE was designed to meet these objectives through the assessment of five key cognitive domains and involved the incorporation of the MSSE. This produced sub-scores for domains of attention/ orientation, memory, verbal fluency, language, and visuospatial functions. The overall level of cognitive function was obtained through the sum of sub-scores to produce a total score out of 100, with a higher score denoting better overall cognitive function.

The evaluation of the ACE revealed two cut-off scores to indicate the presence of cognitive impairment. The cut-off of 88/100 provided an excellent sensitivity of 0.93 and an adequate specificity of 0.71. The lower cut-off of 83/100 had a sensitivity of 0.82 and a specificity of 0.96.

The ACE was followed by the development of the ACE-R (Mioshi et al, 2006). The ACE-R continued to assess the five cognitive domains and produce a total score out of 100, while incorporating the MMSE. However, content modifications were made to the language, memory and visuospatial domains to facilitate cross-cultural translation, and to improve sensitivity by replacing tests that were too easy or too difficult.

Subsequently, the evaluation of the ACE-R in an English-speaking sample, revealed superior diagnostic properties compared to the original ACE. The cut-off scores were identified as 88/100 and 82/100 to provide sensitivity and specificity values of; 0.94 and 0.89, and 0.84 and 1 respectively.

Unfortunately, in light of copyright issues associated with the MMSE, it was necessary to remove this component from the ACE-R and substitute it with similar test items. A comparison of sub-domain scores obtained before and after substitution demonstrated that internal reliability was high (Cronbach alpha coefficient = 0.88), indicating that the MMSE was successfully replaced.

This resulted in the formation of the ACE-III at the Frontier FTD Research Group, Sydney, N.S.W., Australia, the most current version of this cognitive screening test (Hsieh et al, 2013) (see Appendix 7.1).

The ACE-III has carried forward from previous versions the assessment of the five cognitive domains to produce sub-domain scores that together, total 100. Within the setting it was developed, evaluation of the ACE-III demonstrated it continues to provide high measures of sensitivity and specificity. The cut-off score of 88/100 provides a perfect sensitivity, of 1, indicating all cases of cognitive impairment are identified and an excellent specificity of 0.96. The lower published cut-off score of 82/100 provides a sensitivity of 0.93 and a specificity of 1.

Overall, the ACE, ACE-R, and ACE-III are acceptable to patients and easy to use, due to the lack of specialised equipment required and fairly brief administration time of 15-20 minutes. Consequently, they have been validated for use in both settings of modest dementia prevalence such as primary care, and high prevalence such as specialist services (Larner & Mitchell, 2014; Velayudhan et al, 2014).

These clinically useful properties have been a key driver for the adaptation of ACE and ACE-R to different cultures. This has widened access to dementia diagnosis and subsequent management and care in countries where English is not the majority language (Habib & Scott, 2017).

The focus of present studies is on adaptation of the ACE-III. The relatively recent publication of ACE-III limits the number of available adaptations, however so far adaptations have been published for; Spain, Thailand, and China, which have shown a comparable diagnostic accuracy to the index study (Matias-Guiu et al, 2015; .(Charernboon, Jasin & Lerthattasilp, 2016; Wang et al, 2017

Recently, the ACE-III has been adapted for a Bengali-speaking population in India by Dr. Dutt and colleagues (see Appendix 7.2). A systematic approach was taken to identify culturally appropriate and culturally inappropriate items. Items that were deemed appropriate, and the test instructions, were translated into Bengali and back translated. Items that were deemed inappropriate were adapted. This resulted in the adaptation to the name and address, famous names, letter fluency, word repetition, proverb repetition, naming, reading and incomplete letters components of the test. The details of the adaptation process will be reported elsewhere.

Bengali is one of twenty-two official languages spoken in India and it is spoken by an estimated 97 million people, primarily in the state of West Bengal (Census India, 2011). Therefore, the development of this tool has far reaching implications.

1.6 Cognitive Screening in India

At present it is recognised there is a paucity of good cognitive screening tools available in India (Porrselvi & Shankar, 2017). Prince (2009) suggests that one reason for this is the lack of awareness of dementia, which is often attributed to normal ageing. This is problematic as the effects of demographic development and improvements in life expectancy are causing a profound increase of the ageing

population in this setting, leading to an increasing prevalence of dementia (Dias & Patel, 2009). The lack of cognitive screening tools impedes diagnosis, thus obstructing pathways to management and care.

The availability of the Bengali ACE-III will facilitate the detection of cognitive impairment and increase access to an early dementia diagnosis in the Bengali speaking population. This will help address the burden imposed by dementia for a large proportion of the total population of India.

1.7 Aims and Objectives

The validity of adapted cognitive screening tests cannot be assumed to be the same as the original test (Borsa et al, 2012). For this reason, the aim of the present study was to examine the validity of the Bengali ACE-III before it can be routinely used in clinical practice. The hypothesis that the adaptation would achieve comparable psychometric properties to the original ACE-III was therefore tested.

This aim was addressed through the analysis of patient and control data collected by Dr. Dutt and colleagues, to examine the diagnostic accuracy of the Bengali ACE-III for the detection of cognitive impairment caused by MCI or dementia.

The study also investigated the effect of demographic variables: education, age, and gender on test performance and appropriate strategies for utilising normative data were established to improve clinical utility.

2.0 Methods:

2.1 Participants

Participants were recruited and evaluated between June 2015 and June 2017. All participants were native Bengali speakers, literate, aged 40 years and above and able to give informed consent to participate. Exclusion criteria for all participants were a lack of capacity to give informed consent, severe psychiatric disorder (e.g. schizophrenia, bipolar disorder), or a severe language disorder likely to impact ability to understand task instructions.

Demographic factors: age, gender and years of education were collected for all participants and recorded against an individual subject number.

2.1.1 Patients

Patient participants were recruited from among consecutive referrals for neuropsychological assessment at the Apollo Gleneagles Hospital, Kolkata and Duttanagar Mental Health Centre in Kolkata, India. Patients with a diagnosis of Mild Cognitive Impairment (MCI); diagnosed based on Peterson criteria

(Petersen et al, 1999), Alzheimer's Disease (AD) diagnosed according to NINCDS-ADRDA criteria (Mc Khann et al, 1984), Vascular Dementia according to NINDS-AIREN criteria (Román et al, 1993) and Mixed Dementia were included. Diagnosis was made by an independent neurologist in conjunction with the neuropsychologist without reference to the Bengali ACE-III results. Scores on the clinical dementia rating scale were also obtained (Hughes, Berg, Danziger, Coben & Martin, 1982). Only patients who scored 1 or below, indicating a mild case, were included in the final patient sample as these patients are the ones that present a greater diagnostic challenge.

2.1.2 Controls

Healthy controls were recruited through purposive sampling of: family members or friends of patients attending the clinic, family members of other patients attending the hospital, volunteer hospital staff, members of the community and acquaintances of the relatives who volunteered for the study.

2.2 Ethics

This study was approved by Duttanagar Mental Health Centre Institutional Research Ethics Committee (DMHC IREC) (see Appendix 7.2) and carried out in accordance with the Declaration of Helsinki. Written informed consent was taken from the healthy controls, patients and their family members before taking part in the study.

2.3 Instruments

All participants were administered the Bengali ACE-III by blinded researchers. Scores in memory, attention, language, fluency, and visuospatial subdomains were derived and summed to generate an ACE-III total score out of 100. All scores were recorded against the corresponding subject number.

2.4 Statistical Analysis

Statistical analysis was performed using IBM® Statistical Package for the Social Sciences (SPSS) version 24 for Windows. The significance value of $p < 0.05$ was accepted as significant.

2.4.1 Diagnostic Accuracy

The first set of analyses aimed to investigate the diagnostic accuracy of the Bengali ACE-III.

Prior to carrying out diagnostic accuracy analyses the distribution of data was tested for normality visually using histograms and through skewness and kurtosis indices. Skewness and kurtosis values between -1 and +1 were considered acceptable.

Parametric or non-parametric tests were then conducted as appropriate to compare the mean of: ACE-III total, years of education, age, and gender between the patient group and the control group.

Where a significant difference of education, age, or gender was present between patient and control groups linear regression models including disease status were applied to examine the effect of these variables, relative to disease status, on ACE-III score. Where demographic variable effects on ACE-III total were found to be significant patient-control matching based on the calculation of a propensity scores followed by nearest neighbour matching was used to generate datasets without mean differences between groups for significant variables.

The diagnostic accuracy of the Bengali ACE-III was then examined through the construction of a series of Receiver Operating Characteristic (ROC) curves for the patient-control matched samples. The area under the curve (AUC) was obtained to measure the overall test accuracy of the Bengali ACE-III for discriminating between: controls and all patients, controls and dementia patients, controls and MCI patients, and between MCI patients and dementia patients. AUC values of > 0.9 indicate a high accuracy, 0.71-0.9 as moderate accuracy, or 0.5-0.7 as low accuracy (Swets, 1988).

Analysis of the ROC curves was also used to determine the sensitivity and specificity of different cut-off scores. The optimal cut-off scores were selected using the maximum Youden Index (sensitivity + specificity -1) in order to maximise the number of true positives, and minimise the number of false positives (Youden, 1950).

Positive and negative predicative values (PPV, NPV) were calculated, as below, for a range of disease prevalence rates to demonstrate the performance of the cut-off in different settings. This included the estimated prevalence of cases in the clinic from which patients were recruited in the present study.

$$PPV = \frac{sensitivity\ x\ prevalence}{sensitivity\ x\ prevalence + (1 - specificity) x\ (1 - prevalence)}$$

$$NPV = \frac{specificity\ x\ (1 - prevalence)}{(1 - sensitivity) x\ prevalence + specificity\ x\ (1 - prevalence)}$$

Positive and negative likelihood ratios (LR+, LR-) (LR+=sensitivity/1-specificty) (LR-=1-sensitivity/specificity) were also derived, to observe the diagnostic value provided by the optimal cut-off score, and compared to standards obtained from Larner (2015, p. 54).

2.4.2 Normative Data Analysis

The second set of analyses examined the influence of demographic variables on Bengali ACE-III performance using the control group data.

As above, in order to determine whether parametric or non-parametric analyses were appropriate the distribution of the control group data was tested for normality.

Coefficients of correlation were then calculated between the ACE-III total score, age and years of education to determine the direction and strength of their correlation. To investigate the relationship between ACE-III total score performance and gender a Mann-Whitney U test was performed. Where the influence of demographic variables on ACE-III total score resulted in significance, two methods were used to address this issue.

The first method was to derive normative data based on bands stratified by demographic factors which were found to have a significant influence test performance. The control group population percentiles of ACE-III scores were then derived for each band and the 5^{th} percentile point was applied as a cut-off score to the patient sample to see the percentage of patients correctly classified.

The second method was to develop regression-based normative data (Crawford & Howell, 1998). The aim of this approach was to use multiple linear regression modelling to derive an equation to predict control test scores based on the demographic variables that influence test performance.

Prior to regression analysis, a number of preparatory steps were required. Where data are not normally distributed a BoxCox transformation is used to generate a normally distributed regression data set. This regression data set was then analysed in relation to demographic variables to generate Pearson's (r) correlation coefficients and scatterplots. Examination of these scatterplots was used to determine if linear or higher order dependencies of demographic variables should be considered for the regression model.

A hierarchal regression approach was then performed in which the demographic variables were entered in descending order of their r values. A regression model was chosen based on the examination of regression output parameters. The significance of r^2 change was used to determine the demographic variables included in the model. Multicollinearity effects between variables in the model were also examined using the variance inflation factor (VIF) and compared to a critical value of 10.

The standardised coefficients produced by the regression model were used to develop a regression equation, to calculate predicted scores, based on the demographic variables. Predicted scores were then derived for the control population and the difference between the predicted and obtained scores were calculated. This discrepancy score was then converted to standardised Z and T scores to ease interpretation, and the frequencies were obtained in order to determine the percentile distribution.

The regression equation was then applied to the patient population and converted to Z and T scores using the mean and standard deviation from the control population. The fifth percentile T score derived from the control population was then used to examine what proportion of the patient group fell below this cut-off.

3 Results:

3.1 Characteristics of the Sample

The total sample included 464 participants, composed of 305 healthy controls and 159 patients (MCI=34, AD=51, VaD=60, Mixed=15). The descriptive statistics for this sample are summarised in Table 1.

	Healthy Controls (n=305)					*Patients (n=159)*				
	Min-Max	*Mean*	*SD*	*Skewness*	*Kurtosis*	*Min-Max*	*Mean*	*SD*	*Skewness*	*Kurtosis*
Age (Years)	40-88	59.24	10.91	0.162	-0.808	47-87	69.24	8.20	-0.184	-0.095
Education (Years)	1-21	11.81	4.87	-0.264	-0.747	5-21	14.11	2.92	-0.561	0.940
ACE-III Total (/100)	24-99	78.44	13.42	-1.220	1.446	20-89	56.22	16.63	0.095	-0.851

Table 1 Descriptive statistics for whole sample

3.2 Diagnostic Accuracy

As can be seen in Table 1, the distribution analysis of the control and patient groups indicate the ACE-III total score was not normally distributed within the control group. A Kruskal-Wallis test was therefore used to compare the ACE-III total score between groups. The distribution of both mean age and education years fell within the accepted range of indices for skewness and kurtosis for both the control group and the patient group and hence independent student t-tests were used for comparisons. Gender was tested as a categorical variable using the chi-squared test.

Upon comparison, a significant difference ($p<0.001$) was observed for all variables between the control group and the patient group.

Linear regression analysis was therefore applied which revealed that when education, age, gender, and disease status were considered together, the largest predictor of ACE-III total was disease status, contributing to an r^2 value of 0.34 ($p<0.001$). This was followed by education and gender which collectively, contributed to a r^2 change of 0.235 ($p<0.001$). Age did not produce a significant r^2 change in any model. This can be observed in in Table 2.

Predictors	R^2	R^2 *Change*	*F Change*	*Sig. F Change.*
Disease status	0.344	0.344	242	.000
Disease status and education	0.569	0.225	240	.000
Disease status, education, and gender	0.579	0.010	11.31	.001

Table 2 Linear regression output table for the predictor variables of Bengali ACE-III total score

Subsequently, the patient group and the control group were matched by years of education and gender using propensity score matching, as detailed in the methods. As a result, 146 healthy control participants were removed. The demographic information for the revised, matched sample is provided in Table 3.

Total Sample n=318

	Healthy Controls (n=159)					*Patients (n=159)*				
	Min-Max	*Mean*	*SD*	*Skewness*	*Kurtosis*	*Min-Max*	*Mean*	*SD*	*Skewness*	*Kurtosis*
Age (Years)	48-88	66.87	8.09	-0.104	-0.237	47-87	69.24	8.20	-0.184	-0.095
Education (Years)	2-21	13.76	4.246	-0.646	0.317	5-21	14.11	2.92	-0.561	0.940
ACE-III Total (/100)	37-97	82.65	10.30	-1.823	4.387	20-89	56.22	16.63	0.095	-0.851

Table 3 Descriptive statistics for patient-control matched sample

Following matching, there were no significant differences of mean education (p=0.390) or gender (p=0.138) between the control and patient group as indicated by an independent students t-test and chi squared test. A significant difference of age remained (p=0.01), however as shown by the linear regression age did not make a significant contribution to the ACE-III score (p=0.364) and thus does not pose confounding effects. A comparison of ACE-III total score between the matched groups using a Mann-Whitney test indicated the difference was still significant (p<0.001).

Subsequent ROC curve analyses were matched by the same techniques. No significant differences in confounding demographic variables were seen.

Healthy Controls vs Patients

The ROC curve shown in Figure 1 demonstrates the ability of the Bengali ACE-III total score to discriminate between all patients (i.e. MCI and dementia patients) and healthy controls. The AUC shows a value of 0.909 indicating excellent diagnostic accuracy.

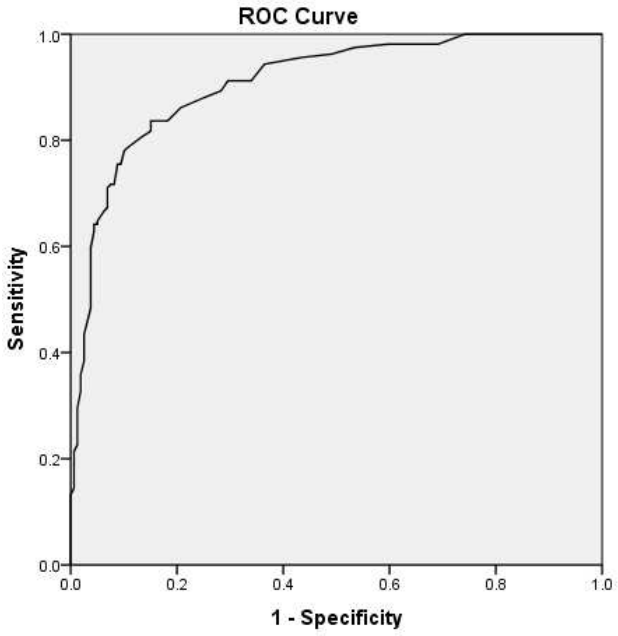

Figure 1 ROC curve for patients with cognitive impairment and healthy controls

The optimal cut-off score derived from the maximum Youden index of 0.69 is 76. This cut-off provides a good balance of sensitivity of 0.84 and specificity of 0.85. The LR+ value of 5.54 and LR- value of -0.19 show a moderate diagnostic gain is achieved from using this cut-off score.

The PPV and NPV for a range of prevalence rates are presented in Table 4, where it can be seen that the diagnostic performance of the cut-off score of 76 is impacted by disease prevalence.

Prevalence	*5%*	*10%*	*20%*	*40%*	*81%* *
PPV	0.23	0.38	0.58	0.79	0.96
NPV	0.99	0.98	0.96	0.89	0.55

*Table 4 PPV/NPV for a range of specified prevalence rates. * indicates prevalence of cognitive impairment in the setting used for the present study*

As shown in Table 4, as the prevalence increases, so does the PPV value. This indicates it is more likely a score that falls below the cut-off of 76 is due to true cognitive impairment in higher prevalence settings, in comparison to low prevalence settings. The opposite trend is observed for the NPV values. As the prevalence increases, the NPV decreases. This means in higher prevalence settings it is less likely a score above the cut-off indicates healthy cognition.

Healthy Controls vs Dementia Patients (no MCI)

The diagnostic accuracy of the Bengali ACE-III was then examined in its ability to discriminate between dementia patients (i.e. excluding MCI) and healthy controls. The ROC curve, shown in Figure 2, provides an AUC of 0.952 demonstrating excellent diagnostic accuracy.

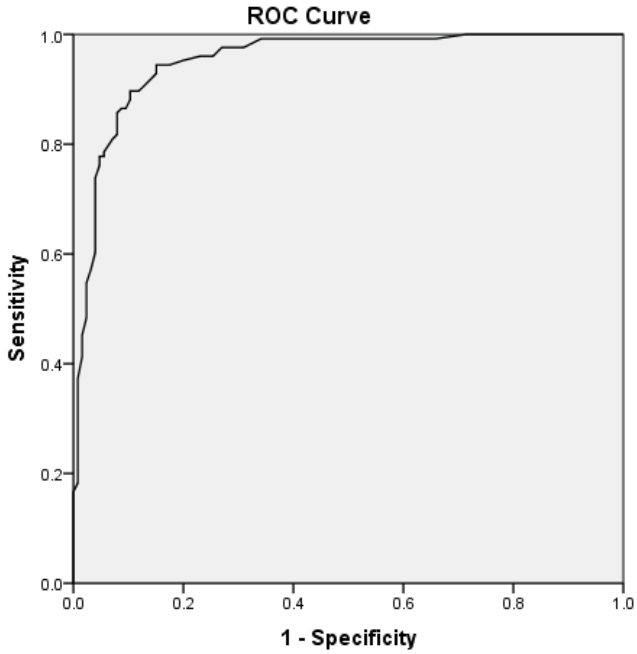

Figure 2 ROC curve for patients with dementia and healthy controls

The optimal cut-off score for the detection of dementia was identified as 72 from the maximum Youden Index of 0.79. This cut-off score provides both good sensitivity and specificity values of 0.897 and 0.897. The LR+ and LR- values of 8.71 and 0.11 indicate a moderate-large diagnostic gain is achieved when using this cut-off point.

The PPV and NPV for a range of prevalence rates are presented in Table 5, where it can be seen the PPV and NPV show the same trend as shown above, in Table 4.

Prevalence	*5%*	*10%*	*20%*	*40%*	*65%* *
PPV	0.31	0.49	0.68	0.85	0.94
NPV	0.99	0.99	0.97	0.93	0.82

*Table 5PPV/NPV for a range of specified prevalence rates. * indicates the estimated prevalence of dementia patients in the setting used for the present study.*

Healthy Controls vs MCI

The next analyses examined the ability of the Bengali ACE-III to discriminate between patients with MCI and healthy controls. The ROC curve, shown in Figure 3, gives an AUC of 0.748 demonstrating a fair diagnostic accuracy.

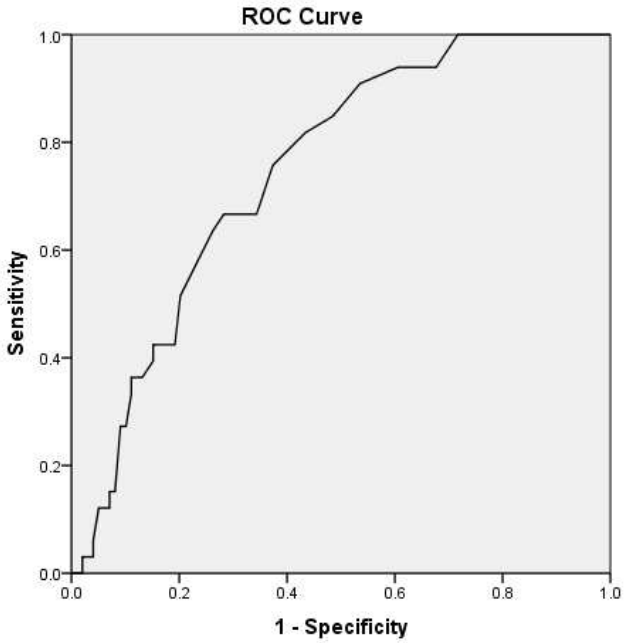

Figure 3 Bengali ACE-III ROC curve for patients with MCI and healthy controls

The maximum Youden Index of 0.39 indicates the optimal cut-off score to detect MCI is 81. This cut off provides lower values of sensitivity and specificity of 0.67 and 0.717 respectively. The LR+ and LR- values of 2.36 and 0.46 suggest that this cut-off score offers a small-unimportant diagnostic gain.

MCI vs Dementia (AD, VAD, Mixed)

The final ROC curve analysis comparing MCI and patients (AD, VAD and mixed dementia) is presented in Figure 4. The AUC value of 0.915 indicates the ACE-III total score provides excellent discrimination between MCI patients and dementia patients.

The maximum Youden Index of 0.71 gives a cut-off score of 68, with good corresponding sensitivity and specificity values of 0.87 and 0.85 respectively. The LR+ of 5.71 and LR- of 0.16 signify there is a small-moderate value in using this cut off score.

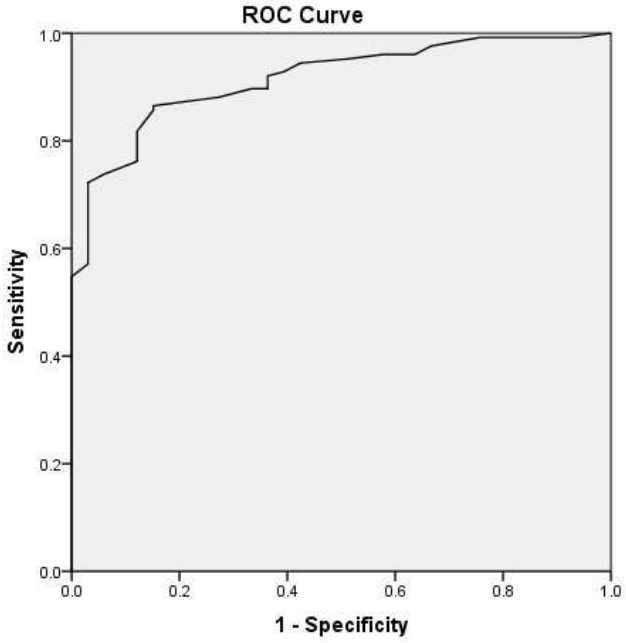

Figure 4 Bengali ACE-III ROC curve for MCI patients and dementia patients

3.3 Normative Results:

3.3.1 Descriptive Statistics

All 305 participants from the control group completed the Bengali ACE-III and were used for the normative analysis. The demographic information and ACE-III total score of this sample are presented below in Table 6.

	Male n= 152			*Female n=153*			*All n=305*		
	Min-Max	*Mean*	*SD*	*Min-Max*	*Mean*	*SD*	*Min-Max*	*Mean*	*SD*
Age (Years)	40-88	61.57	11.55	40-83	56.92	9.72	40-88	59.24	10.91
Education (Years)	2-21	12.47	4.76	1-21	11.14	4.91	1-21	11.81	4.87
ACE-III Total (/100)	36-99	81.00	11.67	24-97	75.89	14.55	24-99	78.44	13.42

Table 6 Descriptive statistics for healthy control group

As can be seen in Table 6, the ACE-III total score ranged from 24-99. The examination of the distribution of ACE-III total scores across the control group indicated scores were not normally distributed (Skewness: -1.220; Kurtosis: 1.446). This is illustrated in Figure 5. The following analyses therefore used non-parametric tests.

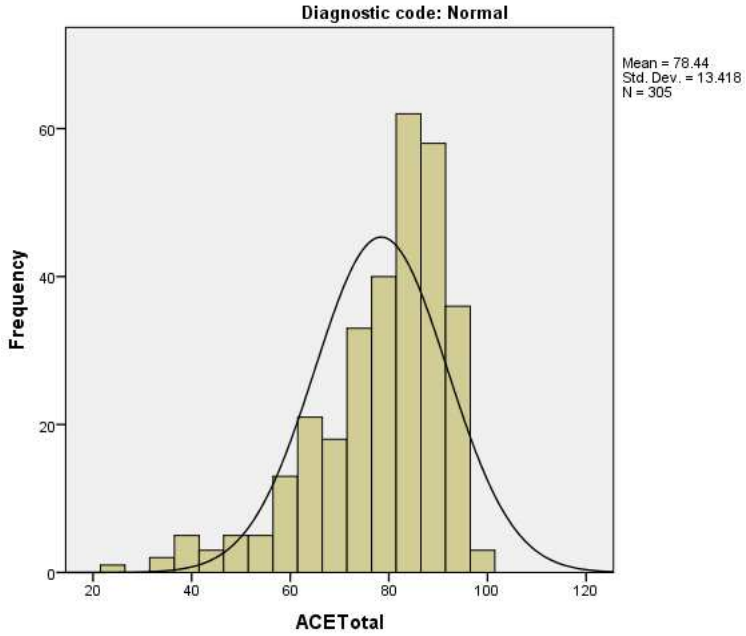

Figure 5 Histogram illustrating the distribution of the Bengali ACE-III total score across the control group

3.3.2 Influence of Demographics

The correlation analysis between age, education, gender and ACE- III total score highlighted a significant and strong positive relationship between years of education and ACE-III total score (rho=0.802, p<0.001). In contrast, age did not correlate significantly with ACE-III total (rho=0.110, p=0.055). However, as the influence of age was close to reaching significance and as age is known to affect cognition it was included in subsequent regression analysis.

A Mann-Whitney U test showed there was a significant difference in ACE-III total score between male and females (p=0.002) indicating there is an influence of gender on test performance.

Cross correlations between gender, education, and age were assessed in subsequent statistical analysis.

3.3.3 Norms

The strong influence of years of education, followed by gender on Bengali ACE-III performance indicated the importance of devising normative scores that account for this influence. The normative results produced using the stratification of ACE-III total score by discrete education bands and gender, and regression are described below.

Education and Gender Banding

The results obtained from education and gender banding are presented in Tables 7 and 8. The education bands were derived by merging data from a range of years of education, as illustrated in the table. It can

be seen that total ACE-III total score increases from the lower education bands to the higher education bands.

FEMALE	*Percentiles*	*5*	*10*	*25*	*50*	*75*	*90*	*95*
Education Bands	*Sample Size*							
1 (1-4)	17	24	38	44	50	62	65	x
2 (5-8)	32	38	49	58	65	73	78	80
3 (9-12)	42	64	68	73	77	83	87	88
4 (13-15)	35	74	76	83	87	91	93	95
5 (16-21)	27	80	83	84	90	92	94	96

Table 7 Percentile distribution of ACE-III total score (/100) for education bands 1-5 of the female control participants. The numbers in brackets are the years of education included in each band

MALE	*Percentiles*	*5*	*10*	*25*	*50*	*75*	*90*	*95*
Education Bands	*Sample Size*							
1 (1-4)	13	36	36	43	64	69	74	x
2 (5-8)	21	53	59	66	72	78	83	86
3 (9-12)	36	66	71	77	83	85	89	89
4 (13-15)	50	69	78	81	88	90	94	95
5 (16-21)	32	81	82	86	91	93	95	97

Table 8 Percentile distribution of ACE-III total score (/100) for education bands 1-5 of the male control participants. The numbers in brackets are the years of education included in each band

Regression-based Norms

As previously observed in Figure 5, the ACE-III total score was not normally distributed across the control group. As the score was strongly skewed it was decided to normalise the data using a Box-Cox transformation procedure, in which the total score was transformed to the power 3.3686. The distribution of data after transformation is shown in Figure 6 where it can be seen to be normally distributed (Skewness -0.245 Std. Error 0.140; Kurtosis -0.786 Std. Error 0.278).

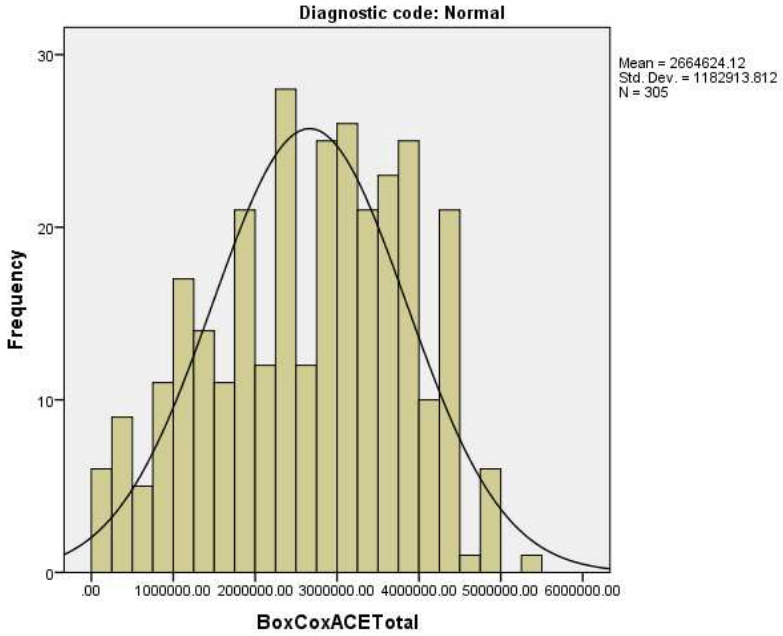

Figure 6 Histogram of the distribution of ACE-III total scores after transformation across the control group

Following transformation, scatterplots were generated, as illustrated in Figure 7 and Figure 8. As expected the scatterplot of transformed ACE-III against age showed little observable correlation. In contrast the scatterplot of transformed ACE-III against education shows nonlinear behaviour that plateaus at higher education levels, for this reason both education and education^2 were considered for regression.

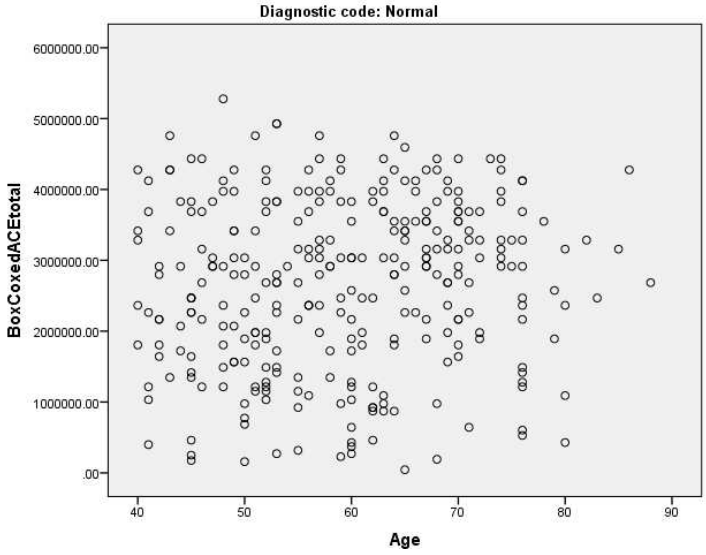

Figure 7 Scatterplot of age against the transformed ACE-III total of the healthy control group

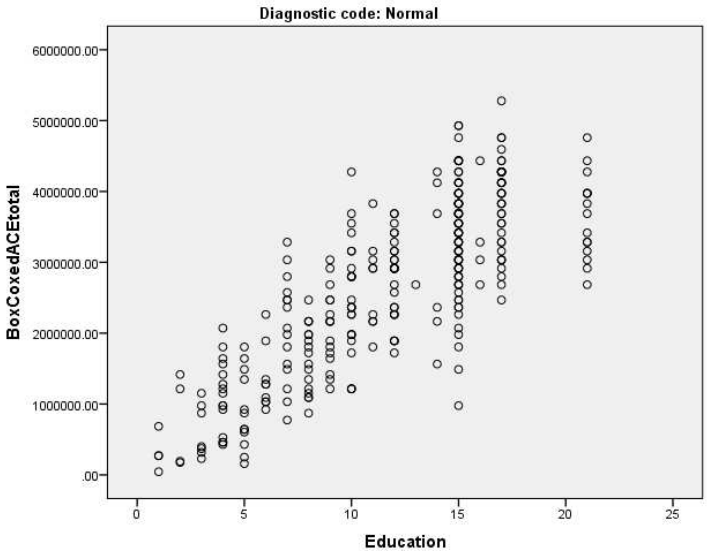

Figure 8 Scatterplot of education against the transformed ACE-III total of the healthy control group

To determine the order of demographic variables to be entered in the hierarchical regression, a correlation analysis was performed against the transformed ACE-III total score. The results are presented in Table 9, in the order entered.

Demographic Variables	*Pearson's r*	*Sig. (2-tailed)*
Education	0.808	0.000
Education^2	0.754	0.000
Gender	0.201	0.000
Age	0.095	0.097

Table 9 Coefficients of correlation between demographic variables and transformed ACE-III total score

Addition of each variable to the hierarchical regression model demonstrated a significant r^2 change. A total r^2 value of 0.684 was obtained for the final model, indicating 68% of the variance observed in the ACE-III total score amongst the control group can be attributed to these demographic variables. The coefficients of the final regression model are shown in Table 10.

	Unstandardized Coefficients (β)	*Std. Error*	*Sig.*	*VIF*
Constant	69244	274378.891	x	x
Education	334974	34287.510	0.000	18.970
Education squared	-6218	1496.150	0.000	19.022
Gender	221923	79096.457	0.005	1.066
Age	-7686	3668.190	0.037	1.087

Table 10 Regression model output

It should be noted that the addition of age to the model only improved the r^2 from 0.680 to 0.684, although this change was significant age remains a minor contributor to variance.

The variable inflation values (VIF) are also shown in Table 10. As would be expected the variance inflation values for education and education squared are high, but both are included as adding education squared produces a significant increase in the r^2 value of the model (Prof John Crawford, Personal Communication).

The regression equation, using the coefficients from Table 10, is reported as below:

> Predicted transformed ACE= 69244 + (334974 x years of education) + (-6218 x years of education squared) + (221923 x gender code) + (-7686 x age)

Using this equation, predicted values for the transformed ACE-III total score, adjusted for the influence of education, gender, and age, were generated for the control group. The difference between the transformed ACE-III total and the predicted transformed ACE-III total was calculated for each control and converted to standardised Z scores using the mean difference of -0.0151 and Std. Deviation 664576. The Z scores were then converted to T scores and the 5th percentile cut-off point was identified as 34.

3.3.4 Implementation of Normative Data

The normative data produced from both education banding and multilinear regression was then evaluated in its capacity to correctly classify patients as impaired using the 5th percentile cut off points.

Tables 11 and 12 present the percentage of patients who were correctly classified as impaired using the 5th percentile cut-off score determined for education bands 1-5 of the control group, as reported earlier (Tables 7 & 8).

MALE *Education Band*	*5th percentile cut off ACE-III score (/100)*	*Number of participants in band (all patients)*	*Percent correctly classified %*	*Number of participants in band (dementia only)*	*Percent correctly classified %*
1	36	X	X	X	X
2	53	6	50	4	100
3	66	25	68	18	78
4	69	67	75	54	89
5	81	21	81	15	93

Table 11 5th percentile cut-off scores obtained from the male education banded control group and their capability to identify patients

FEMALE *Education Band*	*5th percentile cut off ACE-III score (/100)*	*Number of participants in band (all patients)*	*Percent correctly classified %*	*Number of participants in band (dementia only)*	*Percent correctly classified %*
1	24	X	X	X	X
2	38	1	X	1	X
3	64	13	85	12	92
4	74	18	83	14	100
5	80	8	100	8	100

Table 12 5th percentile cut-off scores obtained from the female education banded control group and their capability to identify patients

Alternatively using the regression-based norms, after the calculation of predicted scores for the patient group and the conversion to standardised scores, the 5th percentile t-score cut-off of 34 identified 81% of all patients as impaired and 92% of dementia patients.

4 Discussion:

The results demonstrate the diagnostic accuracy of the newly adapted Bengali ACE-III, the key demographic factors that influence test performance and the utility of normative based corrections. These results will be discussed in the context of the aim of this study; to examine the validity of the Bengali adaptation of the ACE-III.

4.1 Diagnostic Accuracy

As with many prior adaptation studies of the ACE, ACE-R, and ACE-III the diagnostic accuracy will be discussed in relation to the index study, and potential root causes for discrepancies in performance will be suggested.

Overall, the results from the ROC curve analysis using the matched control-patient sample show that the Bengali ACE-III has excellent diagnostic accuracy for the detection of cognitive impairment. The AUC of 0.907 indicates an almost 91% probability that a patient with cognitive impairment would obtain a lower total score than a control with healthy cognitive function. The cut-off score for the detection of cognitive impairment was identified as 76, to provide a sensitivity of 0.84 and a specificity of 0.85.

This level of accuracy is primarily arising from the tests ability to discriminate between healthy controls and patients with dementia, rather than healthy controls and patients with MCI.

The observed diagnostic accuracy of the test for the discrimination of healthy controls from patients with dementia shows a larger AUC value of 0.952, indicating an improvement compared to testing all patients. As would be expected, the cut-off score for the detection of dementia was lower at 72. This cut-off provides better sensitivity and specificity values, of 0.897 and 0.897, and shows better diagnostic gain.

In addition, whilst the PPV values are good using the cut-off score proposed for all patient screening and the cut-off for dementia only screening, it is pertinent to note that an important improvement in NPV is observed in the case of dementia only. At the estimated prevalence rate for all patients in the setting of the present study, the NPV is only slightly better than chance in comparison to 82% for dementia patients.

In contrast, the AUC demonstrating the ability of the test to discriminate between healthy controls and patients with MCI is much lower at 0.747, which shows moderate-poor accuracy. It can also be seen that the optimal cut-off score of 83 provides much lower sensitivity and specificity values of 0.76 and 0.64 respectively, indicative of the greater challenge involved in identification.

This suggests that most useful clinical application of the Bengali ACE-III is for the identification of patients with dementia. Thus having important implications in the pathway to management and care.

Further support for the utility of the Bengali ACE-III in detecting dementia comes from the findings that the test provides excellent discrimination between MCI patients and dementia patients, as indicated by the AUC of 0.915. This is a promising finding, as in clinical practice the diagnostic challenge is to distinguish people with dementia from people who may have some cognitive difficulties (which could arise from mood disorder etc) but do not meet criteria for dementia, as opposed to distinguishing from healthy controls.

The use of the Bengali ACE-III to detect dementia will therefore be the focus of the current discussion. It's use for the detection of MCI should be approached with caution as the sensitivity and specificity values indicate a high number of false negatives and false positives will occur, bringing with it the adverse consequences of misclassification.

4.1.1 Comparison with the Index Study

As stated in section 1.5, the index study of the ACE-III reported two cut-offs of 82 and 88, for the detection of dementia (Heish et al, 2013). In comparison, the optimal cut-off from the present study of 72 is considerably lower than both. There are several possible explanations for this discrepancy.

One possible explanation is that the cut-off score from the present study was derived from a patient population which included AD, VAD, and Mixed dementia whereas the comparable cut-off scores from the index study came from patients with AD and FTD.

It could be suggested that the diverse profiles of impairment associated with the different types of dementia, as described in Section 1.1, will affect performance on sub-domain tests. Due to the different weighting of the sub-domains in derivation of the total score, dementias that are characterised by impairment of more heavily weighted domains or across multiple domains, my lead to a lower total score thus decreasing the cut-off.

Another possible explanation for this discrepancy between studies relates to the challenge of adaptation. Despite the systematic approach taken, adaptation may result in test items that are not equivalent between the original ACE-III and the Bengali ACE-III. It could be that the adapted items are more difficult, resulting in lower scores.

This is reflected in the comparison of mean total scores of the control groups between studies, in which the mean total score for the Bengali ACE-III is 78.4 compared to the original ACE-III score of 95.4. Yoshida et al (2011) also provided such an explanation for the lower cut-off scores obtained in the Japanese adaptation of the ACE-R.

Even after careful adaptation, cultural aspects as addressed in Section 1.3, may remain to contribute to the lower cut-off score. For instance, it has been suggested that due to the provision of healthcare in a medical model in India, psychological methods involving pen and paper tests such as the ACE-III are approached with suspicion and lack of motivation. This can reduce performance and lead to a lower total score in comparison to Western countries, where the index study was conducted, where there is a familiarity with psychological testing (Kumar and Sadasivan, 2016).

Further, it is understood that elderly populations from non-Western countries, such as India, have less exposure to testing situations than Western countries. This lack of familiarity can result in test anxiety or an absence of a test-taking attitude, both of which ultimately lead to poorer test performance (Chandra et al, 1998; Tripathi, Kumar, Bharath, Marimuthi & Varghese 2014).

Since the primary experience of testing is within the education system it would be reasonable to suggest that the level of familiarity with testing may be attributed to differences in educational experiences between settings. The present study included a much greater range of education than the index study, however a simple comparison between the two shows the mean years of education are similar. It could therefore be suggested that the lower cut-off score might be attributed to the quality of education rather than the quantity.

It is recognised that the quality of education in India is poorer than that of developed countries. This can be attributed to lower government spending, resulting in an under-resourced education system characterised by: poor infrastructure, fewer learning materials, and higher pupil to teacher ratios than countries in which the government devote high priority to education (Kingdon, 2007; UNESCO 2014; 2017).

Previous research has found that poorer quality education leads to an inferior performance on neuropsychological tests (Manly, Jacobs, Touradji, Small & Stern, 2002; Chin, Negash, Xie, Arnold & Hamilton, 2012), thus providing support for this explanation for the lower cut-off score in the present study compared to the index study.

Future research is required to determine the extent to which quality of education influences performance on the Bengali ACE-III. If this is the case it has important implications for the provision of appropriate normative data as the quality of education is highly variable within the setting of intended use; between private and government, and rural and urban schools (Agrawal, 2014).

4.2 Normative Data

The objective of the normative data analysis was to identify the demographic variables that influence Bengali ACE-III total score, and to improve clinical utility by exploiting understanding of these influences through the production of normative data.

The results from the present study show demographic variables have a significant influence on the Bengali ACE-III total score. In this discussion comparisons will be made with studies of other adaptations since the index study of the ACE-III did not investigate the effects of demographic variables on test performance (Hsieh et al, 2013).

The demographic variable with the strongest influence on Bengali ACE-III total score was education. Such education effects are consistent with other adaptations such the Spanish and Thai versions of the ACE-III (Matias-Guiu et al, 2015; Charernboon et al, 2016) and with larger normative studies such as the Portuguese, Spanish and Icelandic adaptations (Machado, Baeta, Pimentel & Peixoto, 2015; Matias-Guiu et al, 2016; Jóakimsdóttir,2016).

In contrast, other adaptations such as the Chinese ACE-III have reported no education effects (Wang et al, 2017). However, this could be attributed to the smaller sample size and the restricted range of years of education included, in which the standard deviation was 1.3 years compared to 4.9 years in the present study.

The results also show small but statistically significant gender effects. The effects of age could only be measured when other variables were controlled for, but then also showed significance.

The significant influence of age on Bengali ACE-III performance is supported by the majority of the literature surrounding the ACE, ACE-R, and ACE-III, while the findings on gender are mixed. The current finding that male participants obtain a higher total score than female participants has also been observed by dos Santos Kawata et al (2012), while other studies have found gender effects are limited to subdomain performance (Matias-Guiu et al, 2016), or have found no effects (Nieto, Galtier, Hernandez, Velasco & Barroso, 2016).

In the present study two approaches were used to address this demographic influence: banding and regression. Although both approaches use an understanding of the effects of demographic variables on test performance in the control population, they vary in their ease of use, efficacy, and statistical rigour.

The banding of data based on demographic variables offers a simpler approach, in which printed tables can allow classification of patients with no score adjustments required, and hence is easier for the clinician to understand and apply. However, a drawback is that correcting for multiple, interacting demographic variables results in complex tables. In addition, strong demographic effects require multiple, more detailed bands in order to provide useful clinical information which necessitates the collection of a large amount of normative data.

Due to the observed strong effect of education, followed by gender it was deemed suitable to band the data on this basis. As illustrated in Tables 7 & 8, after banding for education and gender the 5th percentile cut-off scores derived from the control population varied from 24 to 80 for female and 36 to 81 for male, depending on education band. This highlights the very strong effects of education and the lesser effects of gender on cut off scores.

The improvements in diagnostic accuracy gained from this approach can be demonstrated through the comparison of the percentage of the patient population correctly identified using these 5th percentile cut-off points.

Prior to banding, the 5th percentile cut-off correctly identified 35% of all patients, and 44% of dementia patients. Once banded, the results show a vast improvement in the number of patients correctly identified in the higher education bands for both males and females. Tables 12 and 13 show these improvements but also highlight the highly variable size of patient populations available. For instance, the utility of the education bands for identifying patients with lower educational attainment couldn't be determined due to a lack of such patients in the present study.

Moreover, the sample size of the control population in each band, from which the cut-offs were derived, varied from a maximum of 50 to a minimum of 13. Such small sample sizes can affect the precision of the 5th percentile cut-off score and the measures of diagnostic accuracy obtained, thus revealing a weakness in this study for the use of banding.

On the other hand, the regression approach provides continuous corrections and a number of influences can be addressed at once. In contrast to the simplicity of banding, regression uses careful statistical treatment of the data. A benefit of such treatment is that all normative data is used to generate the regression, unlike banding where as noted, the sample sizes can become small.

The application of the 5th percentile T score derived from the control population to the patient population also showed a vast improvement in diagnostic accuracy, in which 81% of all patients and 92% of dementia patients were correctly classified.

These results are comparable with the results obtained for the male patients in band 5, but show an improved ability to detect patients than the bands for lower years of education as shown in Table 12. Surprisingly, when compared to the female education bands in Table 13, the regression cut-off appears inferior. This is likely to be related to the limited accuracy associated with these bands, due to the small sample size, as previously discussed.

4.3 Implications for Clinical Practice

Thus, due to the limitations associated with banding in the present study, the regression cut-off of 34 offers the most robust approach to provide normative data for the Bengali ACE-III.

This cut-off score is useful for clinicians to determine the degree to which the total score truly reflects impaired performance and help correctly classify patients. Whilst capable of delivering improved results, regression-based normative data may require an additional level of understanding from clinicians.

In practice, this does not require the use of the sophisticated software that was required for its derivation, however a number of basic calculations are still required to obtain the final T-score. Where calculations are performed manually, additional care is required to prevent misclassification due to calculation error. The excel file provided (see Appendix 7.3), containing macros to automate these calculations represents a solution to this potential error.

It must be considered that the added time required to perform such calculations may present practical implications in busy clinical practice. This is especially pertinent in India, where the deficiency of neuropsychologists leads to a high number of referrals and heavy workload (Kumar and Sadasivan, 2016). In such case, it would therefore be suitable to use the cut-off score derived from the ROC curve analysis of 72. Although the sensitivity and specificity values are slightly lower than the T-score cut-off, it also demonstrates good diagnostic properties making it acceptable for clinical practice.

However, the use of this cut-off is limited to patients with higher levels of educational attainment as the sample from which it was derived contained few participants with lower levels of education. The

diagnostic accuracy of this cut-off for patients of this nature therefore cannot be assumed and the T-score cut-off is more appropriate despite the additional time required.

It is important to note that these cut-off scores should be used with discretion, and clinical judgement also plays an important part in making a correct classification.

4.4 Limitations and Future Studies

The present study has several limitations. It is useful to consider these limitations when implementing the Bengali ACE-III in practice, and to identify areas of future research.

As discussed, a limitation of the present study is related to the sample. The sample size is too small to provide precise normative data through banding; thus it must be used in clinical practice with a great deal of caution. It would be useful for future work to address this, as such a simple approach would prove useful in LMIC settings such as India where there may not be widespread access to resources that allow for the regression approach, especially in rural areas.

In addition, the range of demographic factors were not distributed equally amongst the sample, and there was little representation of participants with few years of education. This had implications in determining the diagnostic accuracy for both the banded data, and the ROC curve cut-off for patients of this nature.

Another limitation to note is the collection of demographic variables. In the present study, the demographic variables were restricted to age, years of education, and gender. This overlooks the potential influence of other demographic variables shown to influence cognition such as complexity of lifetime occupations or socio-economic status (Andel, Vigen, Mack, Clark & Gatz, 2006; Zhang et al, 2014). Further, the investigation of socio-economic status may provide an insight into the role of quality of education on Bengali ACE-III performance, which as suggested, will have important implications in the provision of normative data.

The use of a case-control study design, for the diagnostic accuracy analyses, must also be considered as a limitation. Although it is recognised that case-control designs are valuable for early investigations of diagnostic tests (Ritjes, Reitsma, Vandernbroucke, Glas & Bossuyt, 2005), the application of extensive exclusion criteria and presence of cognitively healthy controls is not reflective of clinical practice (Larner, 2015). It therefore cannot be assumed how test will perform in clinical settings, where the diagnostic challenge is greater. For instance, previous studies that have avoided a case-control design have found lower cut-off scores for the ACE to be more suitable in day-to-day practice (Larner, 2007).

The present study has provided some evidence for this, in which the cut-off to detect dementia amongst MCI patients was identified as 68. However, this evidence is based upon a small sample from which it would be unwise to draw definitive conclusions. A future study using a larger sample, representative of clinical practice would be useful to further understand if revisions need to be made to the cut-off scores established in this study. For such future research the advantages that have already been gained in the present study from normative data can be applied to mitigate demographic effects.

A further limitation is the patient sample was confined to MCI, AD, VaD, and Mixed dementia. This means conclusions cannot be drawn about the utility of the Bengali ACE-III in detecting other types of dementia such as FTD or DLB. In addition, this restricted patient population prevents the assessment of the ability of the Bengali ACE-III to differentiate between AD and FTD subtypes of dementia, as previously demonstrated by Mathuranath, et al (2000).

5. Conclusion

The aim of the present study was to examine the validity of the Bengali ACE-III for detecting cognitive impairment, investigate the influence of age, education, and gender on test performance, and produce appropriate normative data to improve clinical utility.

This study has shown that the Bengali ACE-III is a valid tool for the detection of AD, VaD, and Mixed dementia in moderate to high prevalence settings. It is therefore suitable for use in clinical practice where it will increase access to an early dementia diagnosis for the Bengali speaking population in India. This has significant implications in addressing the increasing individual, familial, and societal burden posed by dementia through the implementation of timely interventions.

The optimal cut-off score for the detection of dementia was identified as 72. This cut-off is lower than the cut-off defined in the index ACE-III study and the exploration of reasons for this discrepancy suggest that despite adaptation, cultural aspects remain to influence test performance.

Although this cut-off demonstrates clinically favourable properties, the production of alternative cut-off scores using normative data was deemed important due to the observed strong effects of education, and small but significant effects of gender and age on Bengali ACE-III performance. The T-score cut-off produced using regression modelling represents a robust alternative cut-off that can be utilised to improve diagnostic accuracy, at the expense of being more time consuming. Further studies are required before the cut-offs obtained from the banded data can be used in practice. Additional studies would also enable other limitations of the current study to be addressed.

The Bengali ACE-III does not demonstrate clinically useful properties for the detection of MCI and therefore its use in practice for this purpose should be approached with care. The adverse

consequences of not detecting MCI are less severe than those of dementia, however such consequences may be mitigated with good clinical judgment and clinical follow up.

Despite this, this study has addressed a gap in the lack of robust screening cognitive screening tests for the Bengali speaking population in India and has increased access to dementia diagnosis, leading to pathways of management and care.

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7. Appendices:

7.1 Addenbrooke's Cognitive Examination III

ADDENBROOKE'S COGNITIVE EXAMINATION – ACE-III
English Version A (2012)

Name:
Date of Birth:
Hospital No. or Address:

Date of testing: ____/___/___
Tester's name:_____
Age at leaving full-time education:_____
Occupation: _____
Handedness: _____

ATTENTION

➢ Ask: What is the	Day	Date	Month	Year	Season	**Attention** [Score 0-5]
➢ Ask: Which	No./Floor	Street/Hospital	Suburb	State	Country	**Attention** [Score 0-5]

ATTENTION

➢ Tell: "I'm going to give you three words and I'd like you to repeat them after me: lemon, key and ball." After subject repeats, say "Try to remember them because I'm going to ask you later".
➢ Score *only* the first trial (repeat 3 times if necessary).
➢ Register number of trials: _____

Attention [Score 0-3]

ATTENTION

➢ Ask the subject: "Could you take 7 away from 100? I'd like you to keep taking 7 away from each new number until I tell you to stop."
➢ If subject makes a mistake, do not stop them. Let the subject carry on and check subsequent answers (e.g., 93, 84, 77, 70, 63 – score 4).
➢ Stop after five subtractions (93, 86, 79, 72, 65): ____ ____ ____ ____ ____

Attention [Score 0-5]

MEMORY

➢ Ask: 'Which 3 words did I asked you to repeat and remember?' _____ _____ _____

Memory [Score 0-3]

FLUENCY

➢ **Letters**
Say: "I'm going to give you a letter of the alphabet and I'd like you to generate as many words as you can beginning with that letter, but not names of people or places. For example, if I give you the letter "C", you could give me words like "cat, cry, clock" and so on. But, you can't give me words like Catherine or Canada. Do you understand? Are you ready? You have one minute. The letter I want you to use is the letter "P".

Fluency [Score 0 – 7]

≥ 18	7
14-17	6
11-13	5
8-10	4
6-7	3
4-5	2
2-3	1
0-1	0
total	correct

➢ **Animals**
Say: "Now can you name as many animals as possible. It can begin with any letter."

Fluency [Score 0 – 7]

≥ 22	7
17-21	6
14-16	5
11-13	4
9-10	3
7-8	2
5-6	1
<5	0
total	correct

MEMORY

➢ Tell: "I'm going to give you a name and address and I'd like you to repeat the name and address after me. So you have a chance to learn, we'll be doing that 3 times. I'll ask you the name and address later."

Score only the third trial.

Memory
[Score 0 – 7]

	1st Trial	*2nd Trial*	*3rd Trial*
Harry Barnes 73 Orchard Close Kingsbridge Devon	_____ _____ ___ _____ _____ _____ _____	_____ _____ ___ _____ _____ _____ _____	_____ _____ ___ _____ _____ _____ _____

MEMORY

➢ Name of the current Prime Minister.....
➢ Name of the woman who was Prime Minister .....
➢ Name of the USA president.....
➢ Name of the USA president who was assassinated in the 1960s.....

Memory
[Score 0 – 4]

LANGUAGE

➢ Place a pencil and a piece of paper in front of the subject. As a practice trial, as the subject to "**Pick up the pencil and then the paper**." If incorrect, score 0 and do not continue further.

➢ If the subject is correct on the practice trial, continue with the following three commands below.
- Ask the subject to "**Place the paper on top of the pencil**"
- Ask the subject to "**Pick up the pencil but not the paper**"
- Ask the subject to "**Pass me the pencil after touching the paper**"

Language
[Score 0-3]

LANGUAGE

➢ Ask the subject to write two (or more) complete sentences about his/her last holiday/weekend/Christmas. Write in complete sentences and do not use abbreviations. Give 1 point if there are two (or more) complete sentences about the one topic; and give another 1 point if grammar and spelling are correct.

Language
[Score 0-2]

LANGUAGE

➢ Ask the subject to repeat: **'caterpillar'; 'eccentricity; 'unintelligible'; 'statistician'**
Score 2 if all are correct; score 1 if 3 are correct; and score 0 if 2 or less are correct.

Language
[Score 0-2]

LANGUAGE

➢ Ask the subject to repeat: **'All that glitters is not gold'**

Language
[Score 0-1]

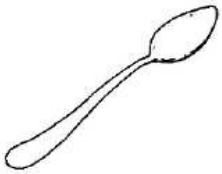
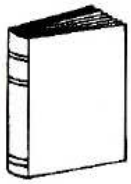
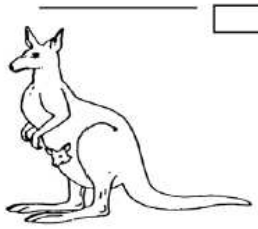
➢ Ask the subject to repeat: **'A stitch in time saves nine'**

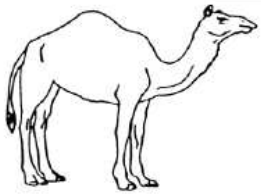
Language
[Score 0-1]

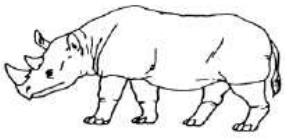
LANGUAGE

➢ Ask the subject to name the following pictures:

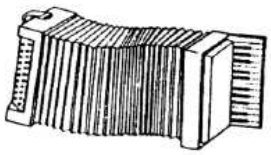
Language
[Score 0-12]







LANGUAGE

➢ Using the pictures above, ask the subject to:

Language
[Score 0-4]

- Point to the one which is associated with the monarchy .....
- Point to the one which is a marsupial .....
- Point to the one which is found in the Antarctic .....
- Point to the one which has a nautical connection .....

LANGUAGE

➢ Ask the subject to read the following words: (Score 1 only if all correct)

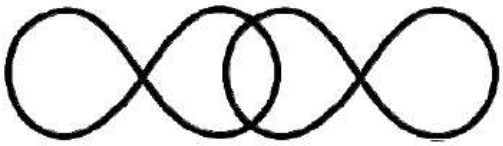
Language
[Score 0-1]

sew
pint
soot
dough
height

VISUOSPATIAL ABILITIES

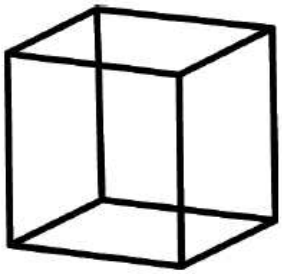
➢ Infinity Diagram: Ask the subject to copy this diagram:

Visuospatial
[Score 0-1]



➢ Wire cube: Ask the subject to copy this drawing (for scoring, see instructions guide).

Visuospatial
[Score 0-2]



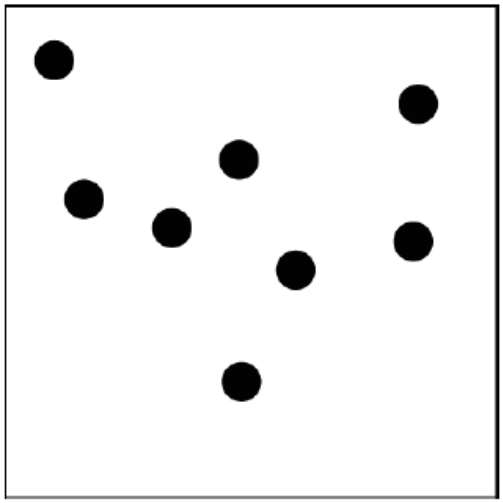
➢ Clock: Ask the subject to draw a clock face with numbers and the hands at ten past five. (For scoring see instruction guide: circle = 1, numbers = 2, hands = 2 if all correct).

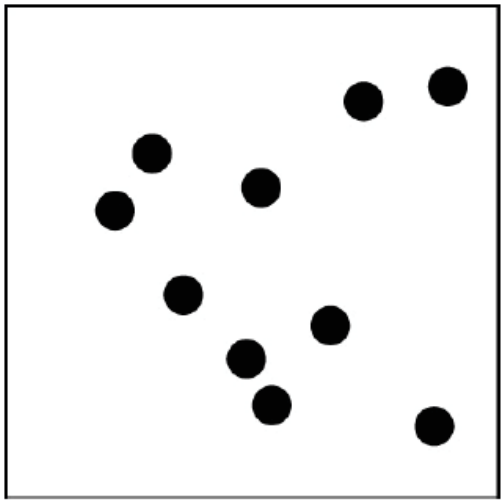
Visuospatial
[Score 0-5]

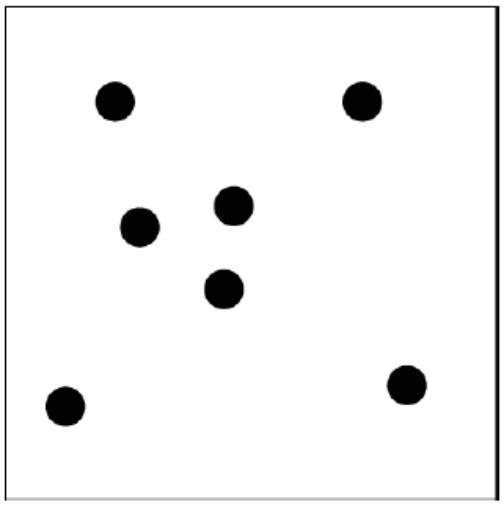
VISUOSPATIAL ABILITIES

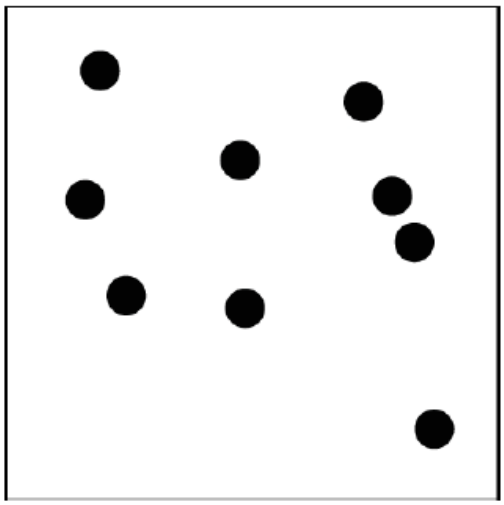
- Ask the subject to count the dots without pointing to them

Visuospatial
[Score 0-4]





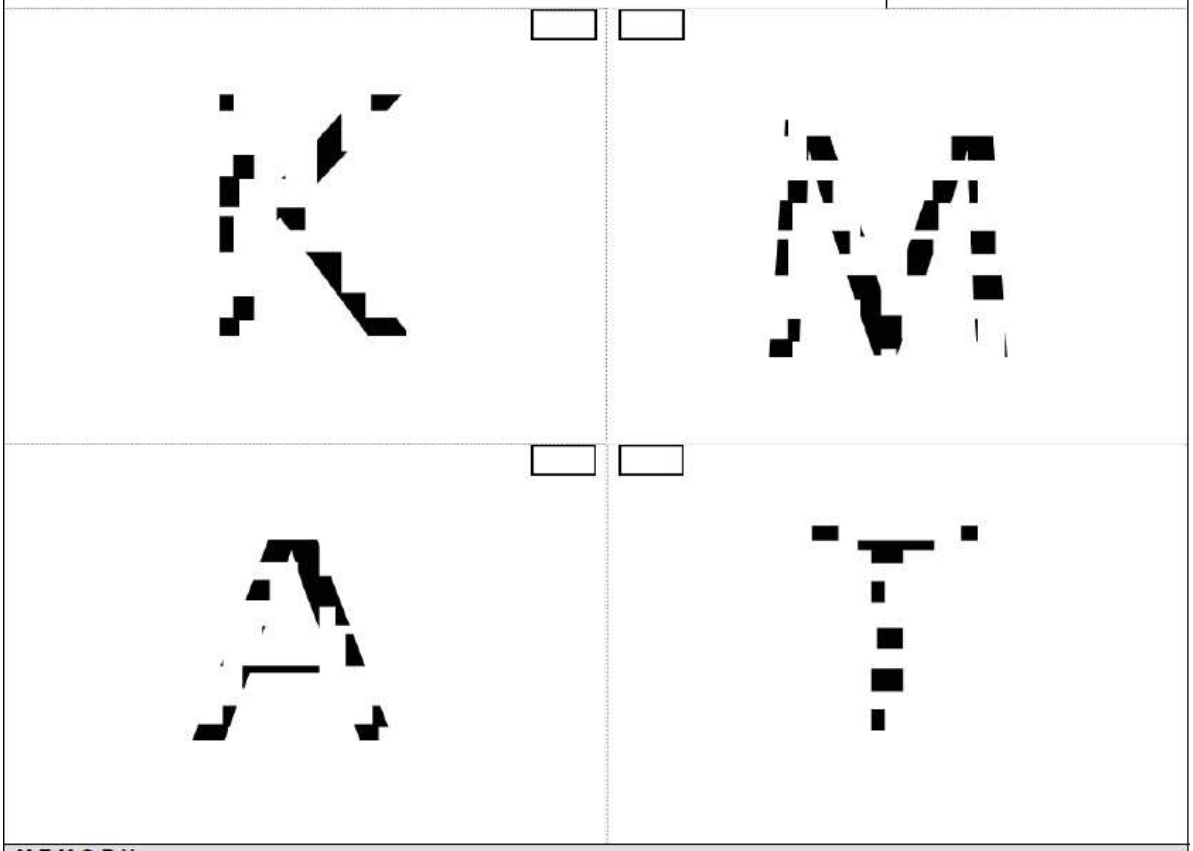




VISUOSPATIAL ABILITIES

➢ Ask the subject to identify the letters

Visuospatial [Score 0-4] ☐



MEMORY

➢ Ask "Now tell me what you remember about that name and address we were repeating at the beginning"

Harry Barnes	....	**Memory** [Score 0-7] ☐
73 Orchard Close	....	
Kingsbridge	.....	
Devon	.....	

MEMORY

➢ This test should be done if the subject failed to recall one or more items above. It all items were recalled, skip the test and score 5. If only part was recalled start by ticking items recalled in the shadowed column on the right hand side; and then test not recalled items by telling the subject "ok, I'll give you some hints: was the name X, Y or Z?" and so on. Each recognised item scores one point, which is added to the point gained by recalling.

Memory [Score 0-5] ☐

Jerry Barnes	☐	Harry Barnes	☐	Harry Bradford	☐	recalled	☐
37	☐	73	☐	76	☐	recalled	☐
Orchard Place	☐	Oak Close	☐	Orchard Close	☐	recalled	☐
Oakhampton	☐	Kingsbridge	☐	Dartington	☐	recalled	☐
Devon	☐	Dorset	☐	Somerset	☐	recalled	☐

SCORES

TOTAL ACE-III SCORE	/100
Attention	/18
Memory	/26
Fluency	/14
Language	/26
Visuospatial	/16

7.2 Bengali Addenbrookes Cognitive Examination III

ADDENBROOKE'S COGNITIVE EXAMINATION - ACE-III

Bengali Version (2016)

Aparna Dutt, Ranita Nandi, P.Sulakshana Rao, Pallavi Bhargava, T.G.Subha, Arpita Bose, Amitabha Ghosh & Jonathan J Evans

Name :
Date of Birth :
Hospital No or Address :
Age (Yrs.) :
Education :
Languages :

Date of testing : .....
Tester's Name : .....
Age at leaving full-time education : .....
Occupation : .....
Handedness : .....

ATTENTION

➤ Ask ঃ এটা কোন/আজ কত	দিন	তারিখ	মাস	সাল	ঋতু	**Attention** [Score 0-5]
➤ Ask ঃ এটা কোন/কত	তলা	হাসপাতাল /রাস্তা	শহর/জেলা	রাজ্য	দেশ	**Attention** [Score 0-5]

ATTENTION

➤ Tell the subject ঃ "আমি আপনাকে তিনটে শব্দ বলব, আমার বলা হয়ে গেলে, আপনি শব্দগুলো বলবেন— লেবু, চাবি, বল। এই শব্দগুলো মনে রাখার চেষ্টা করুন, আমি কিছুক্ষণ পর আবার জিজ্ঞেস করবো।"

Score only the first trial (repeat 3 times if necessary).
Register number of trials .....

Attention [Score 0-3]

ATTENTION

➤ Ask the subject ঃ "একশো (১০০) থেকে সাত (৭) বাদ দিলে কত হয়?" After the subject responds, "আপনি এরকম করে প্রতিবার সাত (৭) বাদ দিতে থাকবেন, ঠিক আগের উত্তরটার থেকে যতক্ষণ না আমি থামতে বলবো।"
➤ If subject makes a mistake, do not stop them. Let the subject carry on and check the subsequent answers (i.e. 93, 84, 77, 70, 63 — Score 4)
➤ Stop after five subtractions (93, 86, 79, 72, 65) ....

Attention [Score 0-5]

MEMORY

➤ Say ঃ কিছুক্ষণ আগে "আমি কোন তিনটে শব্দ কবার আপনাকে বলেছিলাম এবং মনে রাখতে বলেছিলাম?"
....

Memory [Score 0-3]

FLUENCY

➤ অক্ষর
Say ঃ আমি আপনাকে একটি অক্ষর বলব, সেই অক্ষরটা দিয়ে যত রকমের বাংলা শব্দ বলতে পারেন বলুন। আপনি কোনো লোকের বা জায়গার নাম বলতে পারবেন না। উদাহরণ ঃ যদি আমি আপনাকে 'ল' অক্ষর দিয়ে শব্দ বলতে বলি, তাহলে আপনি বিভিন্ন শব্দ যেমন 'লাল, লোভ, লিখন' বলতে পারেন। কিন্তু আপনি 'ল' দিয়ে শব্দ যেমন 'লক্ষ্মী বা লক্ষ্ণৌ বলতে পারবেন না। আপনি কি বুঝেছেন? আপনি তাহলে 'প' দিয়ে যত বাংলার শব্দ হতে পারে বলে যান, আপনার কাছে '১' মিনিট সময় আছে।

Fluency [Score 0-7]

					>14	7
					12-13	6
					10-11	5
					8-9	4
					7-3	3
					6-2	2
					4-5	1
					3-0	0
					Total	Correct

➤ জন্তু
Say ঃ "এবার আপনি যতগুলো জন্তুর নাম জানেন বলুন, সেটা যে কোনো অক্ষর দিয়ে শুরু হতে পারে।"

Fluency [Score 0-7]

					>22	7
					20-21	6
					18-19	5
					16-17	4
					14-15	3
					12-13	2
					10-11	1
					<9	0
					Total	Correct

MEMORY

➤ Tell ঃ আমি আপনাকে একটি নাম ঠিকানা বলব, ''আমার বলা হয়ে যাবার পর আপনি আবার নাম ও ঠিকানা বলবেন যাতে আপনি সেটা মুখস্থর সুযোগ পান। আমি এরকম করে আপনাকে তিনবার নাম আর ঠিকানা বলবো এবং পরে আপনাকে আমি জিজ্ঞাসা করবো।''

Score only the third trial

Memory [Score 0-7] ☐

	1st Trial	2nd Trial	3rd Trial
অমল মিত্র	....	....	....
৫২ বেলতলা রোড	....	....	....
শিবপুর	.....	.....	.....
বর্ধমান	.....	.....	.....

MEMORY

➤ ১৯৪৮ সালে কোন ভারতীয় স্বাধীনতা সংগ্রামীকে হত্যা করা হয়েছিল?
➤ ভারতের প্রথম রাষ্ট্রপতির নাম বলুন।
➤ ভারতের প্রথম মহিলা রাষ্ট্রপতির নাম বলুন।
➤ মহাত্মা গান্ধীকে কে হত্যা করেছিল?

Memory [Score 0-4] ☐

LANGUAGE

➤ Place a pencil and a piece of paper in front of the subject. As a practice trial, ask the subject ''**পেন্সিল তুলুন তারপর কাগজটা তুলুন।**'' If incorrect, score 0 and do not continue further.
➤ If the subject is correct on the practice trial, continue with the following three commands below.
- Ask the subject to ''**কাগজটা পেন্সিলের ওপরে রাখুন**''
- Ask the subject to ''**পেন্সিলটা তুলুন কিন্তু কাগজটাকে নয়**''
- Ask the subject to ''**পেন্সিলটা আমায় দিয়ে দিন কাগজটাকে ছোঁয়ার পর**''

Language [Score 0-3] ☐

LANGUAGE

➤ Tell ঃ যে কোনো একটি বিষয়ের ওপর আপনি মন থেকে দুই বা তার বেশি পূর্ণ বাক্য লিখুন। বিষয়টা হতে পারে আপনার কাটানো কোনো দুর্গাপুজো/বেড়াতে যাওয়া/রবিবার কিভাবে কাটান। আপনি পূর্ণ বাক্য লিখবেন এবং পুরো শব্দ লিখবেন।

Give 1 point if there are two (or more) complete sentences about the one topic; and give another 1 point if grammar and spelling are correct.

Language [Score 0-2] ☐

LANGUAGE

➤ Tell ঃ ''আমি আপনাকে একটা শব্দ বলবো। আমার বলা হয়ে যাবার পর আপনি সেটা আবার বলবেন। এরকম করে আমি কয়েকটা শব্দ বলবো আর প্রতিবার শোনার পর আপনি শব্দটা আবার বলবেন।''

Tell ঃ **'অপব্যবহার'; 'আজ্ঞানুবর্তী'; 'অনালোচনীয়'; 'স্থিতিস্থাপক'**

Score 2 if all correct; 1 if 3 are correct; and score 0 if 2 or less are correct.

Language [Score 0-2] ☐

LANGUAGE

➤ Tell ঃ "আমি আপনাকে একটা বাক্য বলবো। আমার বলা হয়ে যাবার পর আপনি সেটা আবার বলবেন।"
"কড়ায় কড়া কাহনে কানা"

Language
[Score 0-1]

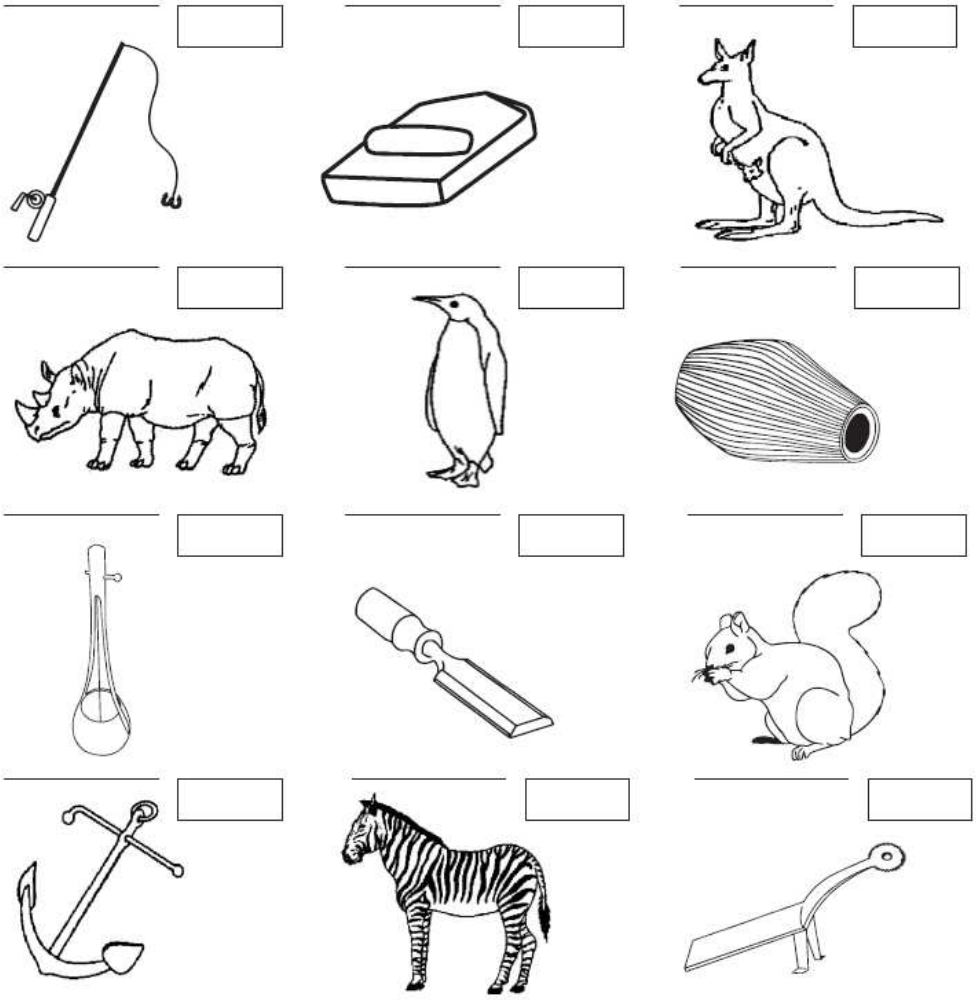
➤ Tell ঃ "আমি আপনাকে আবার একটা বাক্য বলবো। আমার বলা হয়ে যাবার পর আপনি সেটা আবার বলবেন।"
"হাকিম নড়ে তো হুকুম নড়ে না"

Language
[Score 0-1]

LANGUAGE

➤ Tell ঃ আপনি নীচের ছবিগুলির নাম বলুন।

Language
[Score 0-12]



LANGUAGE

➤ Using the pictures above, tell the subject উপরের এই ছবিগুলির মধ্যে কোনটা—

- জাহাজের সাথে জড়িত .....
- অ্যাটল্যান্টিক মহাসাগরে পাওয়া যায় .....
- ছুতোর মিস্ত্রিরা ব্যবহার করে .....
- অস্ট্রেলিয়াতে দেখা যায় .....

Language
[Score 0-4]

LANGUAGE

➤ Tell : ''এই শব্দগুলো পড়ুন'' [Score 1 only if all corrected]

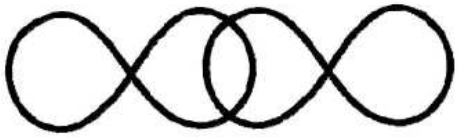
Language
[Score 0-1]

রশ্মি
বিল্ব
ধ্বনি
ভস্ম
শ্বেত

VISUO SPATIAL ABILITIES

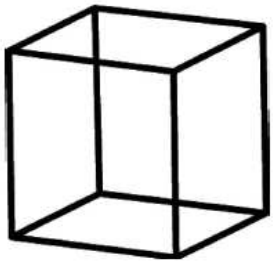
➤ Infinity Diagram: Tell: ''এই ছবিটা দেখে আঁকুন''

Visuospatial
[Score 0-1]



➤ Wire cube: Tell: ''এই ছবিটা দেখে আঁকুন'' (for scoring, see instructions guide).

Visuospatial
[Score 0-2]



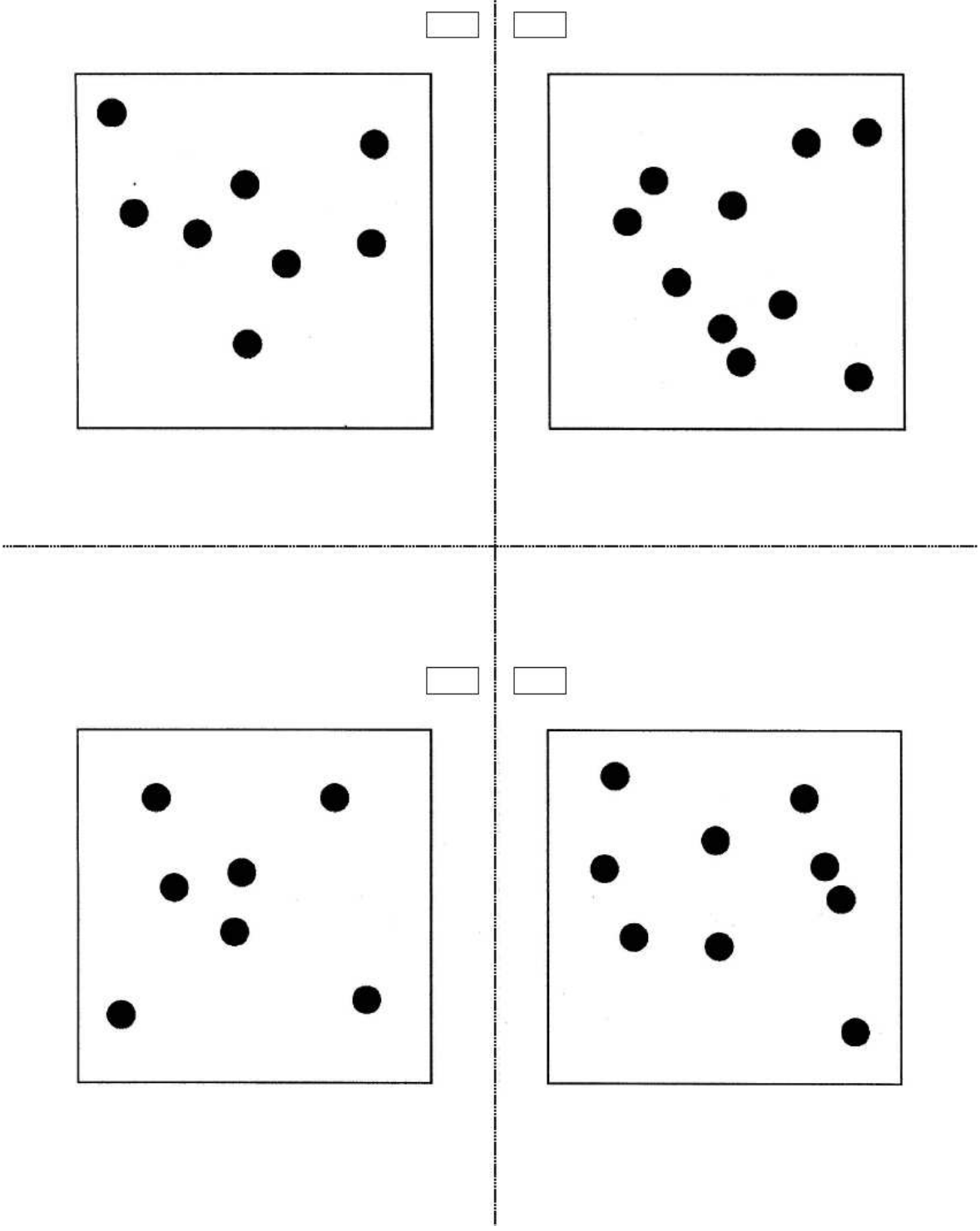
➤ Say : একটা গোল করে ঘড়ির ছবি আঁকুন সব নম্বর সহ। তারপর ঘড়ির ছোট কাঁটা আর বড় কাঁটা এমনভাবে আঁকুন যাতে বোঝা যায় পাঁচটা বেজে দশ হয়েছে।
For scoring see instruction guide: circle = 1, numbers = 2, hands = 2 if all correct.

Visuospatial
[Score 0-5]

VISUOSPATIAL ABILITIES

➤ Tell : "এক-একটা বাক্সে কটা করে বিন্দু আছে, আঙুল না ব্যবহার করে গুণে বলুন।"

Visuospatial
(Score 0-4)
☐



7.3 Ethics Approval

DUTTANAGAR MENTAL HEALTH CENTRE DMHC

INSTITUTIONAL RESEARCH ETHICS COMMITTEE

Dear Dr Aparna Dutt,

The Institutional Research Ethics Committee (IREC) of Duttanagar Mental Health Centre (DMHC) has reviewed and discussed your application to conduct the study entitled "Adaptation and Validation of the Addenbrooke's Cognitive Examination III (ACE III) Bengali version for Literate Individuals"at Duttanagar Mental Health Centre, Kolkata.

The IREC conducted a scientific and ethical review of the following documents in the meeting held on 12th June 2015 at 12pm in Duttanagar Mental Health Centre, Kolkata.

i. Research Protocol
ii. Informed Consent Form (ICF) for Healthy Volunteers
iii. Informed Consent Form (ICF) for Patients
iv. Demographic Sheet – for healthy volunteers and patients
v. Mini Mental State Examination (MMSE)/ Bengali Mental State Examination (BMSE)
vi. Addenbrooke's Cognitive Examination III (ACE-III)
vii. Neuropsychological Assessment Protocol
viii. Hospital Anxiety and Depression Scale (HADS)
ix. Geriatric Depression Scale (GDS)

We are pleased to inform you that the full ethical approval has been granted to your study.

Approval no	**DMHC IREC/01/2015**
Approval date	12 June 2015
Expiry date	12 June 2017
IREC Decision	**Approved**

DUTTANAGAR MENTAL HEALTH CENTRE, DUTTANAGAR, KOLKATA – 700 077
Phone: (033) 25572482/65052244 Email: dmhc@vsnl.com web: www.dmhc.co.in

DUTTANAGAR MENTAL HEALTH CENTRE

DMHC

The following members of the ethics committee were present at the IREC meeting

Srl No.	Name	Designation	Role in the EC
1	Dr Anil Bhuson Dutt	Consultant Psychiatrist	Chairperson
2	Mr Namit Biswas	Retd Spl. Secretary, Family Welfare, West Bengal	Member Secretary
3	Dr Kishan Pradhan	General Secretary Calcutta Heart Clinic & Hospitals, Kolkata	Clinician
4	Dr Dharitri Dutt	Physician National Institute of Cholera and Enteric Diseases	Clinician
5	Mr Sumanta Chaudhury	Retired Colonel, Indian Army	Ethicist
6	Dr Samaresh Choudhuri	Retd Professor & Head, Dept. of Biotechnology, School of Tropical Medicine, Kolkata	Medical Scientist
7	Dr Swapna Choudhuri	Professor, Department of Laboratory Medicine, School of Tropical Medicine, Kolkata	Medical Scientist
8	Mr Y M Nandy	Lawyer, Calcutta High Court	Legal expert
9	Mrs Rati Basu	School Teacher, Shantiniketan, West Bengal	Lay Person

Please follow the standard conditions:

a. conduct the project strictly in accordance with the proposal submitted and granted ethics approval, including any amendments made to the proposal required by the IREC
b. report the IREC about any change in the protocol
c. provide a progress report to the IREC annually
d. provide a 'final report' after completion of the project
e. advise in writing if the project has been discontinued.

You may now commence your project.

ETHICS COMMITTEE APPROVED Duttanagar Mental Health Centre

With Best Wishes

Yours Sincerely,

Mr. Namit Biswas
Member Secretary
Institutional Research Ethics Committee
Duttanagar Mental Health Centre
Kolkata

Mr Namit Biswas
Member Secretary
Institutional Research Ethics Committee (IREC)
Duttanagar Mental Health Centre, Kolkata

DUTTANAGAR MENTAL HEALTH CENTRE, DUTTANAGAR, KOLKATA – 700 077
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7.4 T Score Excel File

T score calculator.xlsx

7.5 Journal of Neuropsychology Guidelines

• Contributions must be typed in double spacing with wide margins. All sheets must be numbered.

• Manuscripts should be preceded by a title page which includes a full list of authors and their affiliations, as well as the corresponding author's contact details. You may like to use this template. When entering the author names into Editorial Manager, the corresponding author will be asked to provide a CRediT contributor role to classify the role that each author played in creating the manuscript. Please see the Project CRediT website for a list of roles.

• The main document must be anonymous. Please do not mention the authors' names or affiliations (including in the Method section) and refer to any previous work in the third person.

• Tables should be typed in double spacing, each on a separate page with a self-explanatory title. Tables should be comprehensible without reference to the text. They should be placed at the end of the manuscript but they must be mentioned in the text.

• Figures can be included at the end of the document or attached as separate files, carefully labelled in initial capital/lower case lettering with symbols in a form consistent with text use. Unnecessary background patterns, lines and shading should be avoided. Captions should be listed on a separate sheet. The resolution of digital images must be at least 300 dpi. All figures must be mentioned in the text.

• All articles should be preceded by an Abstract (see point 3 for guidelines), giving a concise statement of the intention, results or conclusions of the article.

• For reference citations, please use APA style. Particular care should be taken to ensure that references are accurate and complete. Give all journal titles in full and provide DOI numbers where possible for journal articles.

• SI units must be used for all measurements, rounded off to practical values if appropriate, with the imperial equivalent in parentheses.

• In normal circumstances, effect size should be incorporated.

• Authors are requested to avoid the use of sexist language.

• Authors are responsible for acquiring written permission to publish lengthy quotations, illustrations, etc. for which they do not own copyright.

https://onlinelibrary.wiley.com/page/journal/17486653/homepage/forauthors.html

7.6 Dissertation Proposal Outline

Proposed title: Evaluation of the Bengali Addenbrooke's Cognitive Examination

Matriculation number:

Supervisor: Professor Jonathon Evans

Brief summary of existing literature:

The Addenbrooke's cognitive examination (ACE) was developed in 2000 (Mathuranath, et al., 2000) and has since been revised in 2004 (Mioshi et al., 2006). It is a highly sensitive and specific tool for detecting cognitive impairment (Larner & Mitchell, 2014) and is used for detection and assessment.

ACE examines five domains of cognitive function; attention and orientation, memory, fluency, language, and visuospatial skills. It is scored out of 100 and takes 15-20 minutes to administer.

Performance on ACE can be influenced by culture. Culture is a confounding factor that can influence the perception of content and the contents relevance or familiarity. The effect of language barriers must be taken into consideration (Ganguli et al, 1996). This reduces its applicability for use in other cultures.

Thus, it is important to control for culture by designing culturally adapted tests. There have been many adaptations of ACE-R however the extent of translation and adaptation varies.

Aims, research questions and hypotheses:

This project aims to analyse pilot data from the Bengali adaptation of ACE to determine its reliability and validity.

- Sensitivity and specificity between participants with cognitive impairment or healthy participants compared to original ACE scores
- Cut off scores when considering the differences in education in India

Hypothesis: There will be no significant difference in scores from the Bengali ACE compared to the original ACE-III

Proposed methodology: A statistical analysis tool will be used to conduct regression based analysis to investigate associations and differences between demographic groups

Potential barriers:

Proposed timetable:

- December 2017: Submission of draft research proposal to Professor Jonathon Evans
- February-April 2017: Data analysis
- May-July 2017: Write up

Plan for obtaining ethics: This project involves the analysis of data, for which ethics was already obtained