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Dementia diagnosis in seven languages: the Addenbrooke's Cognitive Examination-III in India

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Running title

Dementia diagnosis in seven languages: ACE-III in India

Abstract

Objective: With the rising burden of dementia globally, there is a need to harmonise dementia research across diverse populations. The Addenbrooke's Cognitive Examination-III (ACE-III) is a well-established cognitive screening tool to diagnose dementia. But there have been few efforts to standardise the use of ACE-III across cohorts speaking different languages. The present study aimed to standardise and validate ACE-III across seven Indian languages and to assess the diagnostic accuracy of the test to detect dementia and mild cognitive impairment (MCI) in the context of language heterogeneity.

Methods: The original ACE-III was adapted to Indian languages: Hindi, Telugu, Kannada, Malayalam, Urdu, Tamil, and Indian English by a multidisciplinary expert group. The ACE-III was standardised for use across all seven languages. 757 controls, 242 dementia, and 204 MCI patients were recruited across five cities in India for the validation study. Psychometric properties of adapted versions were examined, and their sensitivity and specificity were established.

Results: The sensitivity and specificity of ACE-III in identifying dementia ranged from 0.90 to 1, and sensitivity for MCI ranged from 0.86 to 1 and specificity from 0.83 to 0.93. Education, but not language was found to have an independent effect on ACE-III scores. Optimum cut-off scores were established separately for low education (≤10 years of education) and high education (>10 years of education) groups. Examination of the ACE-III validity results on the new independent sample, show good diagnostic validity, indicating usefulness of the ACE-III as a diagnostic tool.

Conclusions: The adapted versions of ACE-III have been standardised and validated for use across seven Indian languages, with high diagnostic accuracy in identifying dementia and MCI in a linguistically diverse context.

Key words: Dementia; Mild cognitive impairment; Languages; Screening test; Cognition

Introduction

Recent studies report that a major proportion (58%) of the people with dementia reside in low and middle income countries (LMICs) and by 2030 and 2050 will increase to 63% and 68% respectively (Prince, Comas-Herrera, Knapp, Guerchet, & Karagiannidou, 2016). However, prevalence rates vary significantly both between LMICs (2.7%-8%) (Alladi & Hachinski, 2018) and within countries like India (Alladi et al., 2011; Das, Pal, & Ghosal, 2012; Kalaria et al., 2008; Prince et al., 2013). In addition to sociodemographic and environmental factors, the within and between-country variability in prevalence has been attributed to a limited availability of harmonised and standardised methodologies and variable screening instruments (Alladi & Hachinski, 2018; Das et al., 2012; Mungas, Reed, Haan, & Gonzalez, 2005; Prince et al., 2003). Therefore standardising diagnostic tools for dementia is important to determine prevalence rates accurately and to establish risk and protective factors for dementia. Common testing tools are also crucial in the setting of sociocultural diversity to develop multicentric cohorts of dementia patients that can be studied systematically.

Linguistic variability is one of the major challenges for the development of common diagnostic tools for a heterogeneous setting. In India, Hindi is the most widely spoken language (43.63%), followed by Bengali (8%), Telugu (6.7%), Tamil (5.7%), Urdu 4.2%, Kannada 3.6%, Malayalam 2.9% and others (Census of India, 2011). 10.6% of the Indian population speak English for professional and commercial communication, especially in inter-state contexts (Census of India, 2011). Indian languages are also official languages in other South Asian countries: Bangladesh, Pakistan, Sri Lanka and in Singapore. With global immigration, Indian languages are also increasingly being encountered among the Indian diaspora in the developed world (United Nations Department of Economic and Social Affairs Population Division, 2017). In the context of linguistic heterogeneity, it is important to have

clinical instruments in several languages, both for Indian as well as for global dementia research efforts.

The major cognitive screening instruments validated in different languages in LMICs include the Addenbrooke's Cognitive Examination-Revised (ACE-R), Addenbrooke's Cognitive Examination-III (ACE-III), Mini Mental State Examination (MMSE), Montreal Cognitive Assessment (MoCA), Mini Cog, Picture-based Memory Intelligence Scale, and the revised Hasegawa Dementia Scale (HDS-R) (Mathuranath et al., 2007; Rosli, Tan, Gray, Subramanian, & Chin, 2016; Yang, Chey, Kim, & Kim, 2002). Among the brief cognitive tests, MMSE, ACE-R and ACE-III have been adapted and validated for use in India, but typically in only one or two languages, thereby limiting wider applicability (Alladi et al., 2016; Mathuranath et al., 2007; Mathuranath et al., 2004; Sharma, Chaudhary, Sheth, & Dalal, 2018).

ACE-III is one of the widely used cognitive screening tools for dementia, focusing on five specific cognitive domains: attention, memory, fluency, language and visuospatial abilities (Hsieh, Schubert, Hoon, Mioshi, & Hodges, 2013; Mirza, Panagioti, Waheed, & Waheed, 2017). The first version of ACE was developed at Cambridge memory clinic (Mathuranath, Nestor, Berrios, Rakowicz, & Hodges, 2000) as a bedside test to detect dementia and its subtypes in particular Alzheimer's disease, Fronto-temporal syndromes and Parkinsonian syndromes with dementia (Bak et al., 2005). In 2006, the ACE was revised to ACE-R, to develop a sensitive tool and also to facilitate ease of administration, across cultural usage and translation (Mioshi, Dawson, Mitchell, Arnold, & Hodges, 2006). Hsieh (2013) updated ACE-R into ACE-III by removing MMSE component and modifying some items to improve diagnostic utility of the instrument (Hsieh et al., 2013). This version has been validated in several languages and is widely recognised and a well-established screening tool to detect dementia and Mild Cognitive Impairment (MCI) (Habib & Stott, 2017). Given

the need for a common screening tool to diagnose dementia uniformly in India, we aimed to develop a culturally relevant version of ACE-III for the Indian context and standardise the instrument across commonly used Indian languages. The objective of the study was to standardise and validate ACE-III for Indian languages: Hindi, Telugu, Kannada, Malayalam, Urdu, Tamil, and Indian English, and to establish the sensitivity and specificity of the Indian versions to detect dementia and MCI.

Methods

Participants

A total of 1203 participants were recruited: 757 were controls, 242 were diagnosed with dementia and 204 were MCI patients. Five cities from different parts of India participated in this study 1) Telugu, Hindi, Urdu and Indian English data were collected from Hyderabad; 2) Hindi data was also collected from Delhi; 3) Malayalam data was obtained from Trivandrum; 4) Kannada data from Bangalore; and 5) Tamil language data was obtained from Puducheri.

Controls were randomly drawn from volunteers from senior citizen centres of the cities as well as healthy family carers of patients visiting neurology and geriatric clinics of the hospitals. An experienced neurologist examined every participant, interviewed a reliable family caregiver, and reviewed the demographic and cognitive history, and medical records of the control participants to determine their eligibility for participation in the study. Structured written proforma and interview was used to include participants in the study. The inclusion criteria for the healthy controls included: age >50 years, formal education of at least three years, no history of cognitive or behavioural complaints, no history of head injury, drug abuse, severe alcoholism, major psychiatric and neurological illness. Patients with dementia were recruited from memory clinics and neurology outpatient clinics of the participating

centres. Dementia was diagnosed based on DSM-IV criteria by experienced neurologists in all centres using a standard diagnostic protocol that consisted of a structured clinical interview, administration of a global cognitive screening test MMSE, and Clinical Dementia Rating (CDR) scale to assess severity of dementia ("American Psychiatric Association: Diagnostic and Statistical Manual of Mental Disorders, ed 4.," 1994; Folstein, Folstein, & McHugh, 1975; Morris, 1993). The diagnosis of dementia subtypes was done based on standard criteria (McKhann et al., 2011; Rascovsky et al., 2011; Román et al., 1993). Patients with moderate and severe dementia (CDR ≥2) were excluded from the study. MCI was diagnosed according to the modified Petersen criteria (Petersen, 2004) based on clinical history and performance on standard neuropsychological tests of memory, language, visuospatial and executive function. Each centre used neuropsychological tests for which normative data were locally available in the respective language (Alladi et al., 2011; George & Mathuranath, 2007; Mathuranath et al., 2007; Rao, Subbakrishna, & Gopukumar, 2004). Patients with dementia and MCI were excluded from the study for the following other reasons: presence of psychiatric or neurological symptoms (for example, depression, head injury), which might additionally affect the performance on the test. Further, patients with inadequate/incomplete demographic and clinical data were also excluded.

The number of subjects included were; 357 for Hindi, 278 for Telugu, 107 for Kannada, 45 for Malayalam, 139 for Urdu, 53 for Tamil and 224 for Indian English. Table-1 provides the number of controls and patients across diagnostic groups (dementia and MCI). MCI data were not available for Malayalam and Tamil. The total sample was stratified based on the common Indian state education system (National Policy on Education, 1992). Completion of primary and secondary school (4 to 10 years of formal education) was considered as low education group and completion of senior secondary school and above (≥10 years of formal education) was categorised as high education group, making it a 7

(languages) × 2 (educational attainment) between-group design. Minimally educated/illiterates (0-4 years of formal education) were not included in the present study. Majority of the items in ACE-III are literacy dependant and adaptation of the test for illiterates will need to undertaken separately. Of the 242 dementia patients, 136 were diagnosed with Alzheimer's disease, 52 with vascular dementia; 32 with Frontotemporal dementia, 12 with Lewy body dementia, and 10 with mixed dementia.

Adaptation of Addenbrooke's Cognitive Examination-III

In accordance with the original ACE-III, the Indian versions correspond to five different cognitive functions: attention (subscore: 18), memory (subscore: 26), fluency (subscore: 14), language (subscore: 26), visuospatial (subscore: 16) summing up to a total of 100.

Applicability of the original version of ACE-III to Indian adults and elderly population was discussed among a multidisciplinary expert group of behavioral neurologists, neuropsychologists, speech-language-pathologists, and local language experts. Culturally appropriate modifications were formulated based on the clinical and research experience of the authors. The guidelines of cross cultural adaptation by Guillemin, Bombardier & Beaton (1993) were followed (Guillemin, Bombardier, & Beaton, 1993).

Every item in the five domains of the test was evaluated for cultural relevance, translatability, comparable difficulty and adaptability with an aim of tapping the domain referred to in the original version. At the initial stage, the Indian English version was developed and piloted on a sample of 20 controls. Following this, a literal word to word translation of Indian English version of ACE-III was done in different Indian languages, followed by back translation by linguists and psychologists who were proficient in the respective languages. Based on the pilot group performance; ambiguities in the adapted items were discussed and resolved. The following changes were made in each of the domain:

Fluency: Given that language fluency among Indian elderly population is lower compared to the western populations, as reported in prior validation studies of ACE-R (Alladi et al., 2016; Mathuranath et al., 2003), the scores for letter and animal fluencies in all seven languages were rescaled using the percentile distribution of raw scores similar to the Malayalam version of ACE (Table-2) (Mathuranath et al., 2004). In this section, a corresponding equivalent of 'P' was substituted for the Indian languages.

Memory: In the memory recall and recognition sections, the address was replaced with ones that had geographical relevance while maintaining the comparable syllable length. In retrograde memory section, questions on famous people were replaced with questions about Indian politicians, movie actors, and the name of Father of the Nation: Mahatma Gandhi.

Language: The naming section in language domain was modified to account for the cultural influences that impact picture naming. A pilot study that included 30 pictures was conducted and the final 12 were chosen based on picture naming properties such as naming, familiarity, image agreement and visual complexity (Figure 1) (George & Mathuranath, 2007). The 30 pictures were taken from ACE-III original version, Snodgrass and Vanderwart (1980) and some were drawn by an artist (Snodgrass & Vanderwart, 1980). In the repetition section, the words and proverbs were replaced by the words with equivalent meaning, or in cases where this proved difficult, they were substituted by words and proverbs matched in length and complexity as determined by linguistic experts. In the reading section, irregular words were replaced with regular words of comparable frequency and word length, as the selected Indian languages do not typically include irregular or silent words (Singh, 2006).

Visuospatial: Fragmented letters in the visuospatial section were replaced with corresponding phonetic alphabets in each Indian language. Other items such as copy of figures and dot counting were retained.

A common administration and scoring guide was developed and psychologists were trained to ensure standardised test assessment in seven Indian languages. The choice of language for testing was determined using a language use and proficiency questionnaire. Subjects with ≥70% on proficiency and language choice scores in any of the seven languages on language use questionnaire (LUQ; Vasanta, Suvarna, Sireesha, & Raju, 2010) were tested in the respective language. If the subjects were fluent in multiple languages, the LUQ was administered on the subjects themselves in healthy controls and on family caregivers in patients with MCI and dementia.The language in which the subject was most proficient in, was selected for administration of ACE-III.

Average time taken to complete the test was 10-15 minutes in control subjects and 10-25 minutes in patients with dementia and MCI depending on the severity of the disease.

Reliability and Validity of ACE-III

Reliability: Inter-rater reliability was assessed in 15 controls for the Hindi, Telugu, and Indian English versions of ACE-III (Table-3). To measure test-retest reliability, alternate versions of ACE-III were re-administered on 15 control subjects in a gap of two months to avoid practice effect. Internal reliability was also measured in the Hindi, Telugu and Indian English versions.

Validity: The Indian versions of ACE-III were validated for diagnosing dementia and MCI. To indicate accuracy of the test in diagnosing dementia, area under curve (AUC) were obtained from receiver operating characteristic (ROC) curve analysis across languages. Optimum sensitivity and specificity of the Indian versions of ACE-III in diagnosing patients with dementia and MCI were established along with the corresponding cut-off values. Analysis was also carried out to investigate how well the ACE-III distinguishes between MCI and dementia diagnosis.

Since ROC curves tend to overfit in the sample used for training the model, the performance is often lower when applied to a new sample. To address this, we carried out a second validation study of ACE-III by applying the cut-offs of the ACE-III to a new independent sample (n=434) across seven languages. This data was pooled from the other ongoing clinical and research work from respective centres and the common cut-off values were applied to the new independent sample.

The study was approved by the Institutional Research Ethics Committee. Informed consent was obtained from all the participants and their family caregivers.

Statistical analysis

Statistical analysis was conducted using SPSS 20 for Windows and MedCalc 18.11.6. Student t-test and ANOVA were used to measure the differences between control and patient groups. Bonferroni correction was used when multiple comparisons were performed. Chi-square test was done to assess the group differences for categorical variables. Cronbach's alpha coefficient was calculated for the internal consistency. Pearson correlation was used to compute correlation among ACE-III total score, age and education. AUC, sensitivity, and specificity were determined using ROC curve analysis. Inter-rater and test-retest reliability was measured using Cohen’s kappa coefficient and alpha coefficient of correlation respectively. A univariate general linear model (GLM) was used to evaluate the independent effect of age, education and language on test performance. Interaction effects of education with age and language were also calculated by using univariate GLM. Effect sizes were calculated using the Hedges’g formula where 0.20, 0.50, and 0.80 represent small, medium, and large effects.

Results

Total study sample consisted of 1203 subjects. The mean age of controls, dementia, and MCI groups were 64.7±7, 65.7±8.7 and 65.8±9.2 years respectively ($F_{2,2000} = 2.77$, $p = 0.063$). Corresponding mean years of education in controls, dementia and MCI groups were 13.8±3.6, 13.3±4, and 13.4±3.9 years ($F_{2,2000} = 2.71$, $p=0.067$). 64.1% (485) of controls, 68.6% (166) of dementia group, 68.1% (139) of MCI group were men. 78.2% (592) of controls, 78.5% (190) of dementia, 83.3% (170) of MCI group, were recruited from urban areas. The demographic details of subjects, ACE-III total and sub-domain scores across seven languages and diagnostic groups are presented in Table-1. ACE-III total scores and sub-domain scores in all the seven languages were higher in controls compared to patients with dementia and MCI. Furthermore, ACE-III scores of MCI subjects were higher in comparison with dementia patients.

Internal reliability of the Hindi, Telugu and Indian English versions of ACE-III was found to be good according to the standard criteria ($\alpha > 0.86$). Inter-rater reliability and test-retest reliability in these languages was high ($\alpha > 0.89$) (Table-3).

Among controls, high education group ($M = 90.1$, $SD = 4.7$) had higher test scores compared to low education group ($M = 92.9$, $SD = 4.5$), $p < 0.0001$, Hedges' $g = 0.62$). Therefore, optimum cut-off scores were established separately for high and low education groups. Optimum cut-off values for diagnosing dementia in low education group were 80-83 and 82-85 in high education group (Table-4). Cut-off values for identifying MCI ranged from 84-86 in low education group and 87-89 in high education group (Table-5).

The sensitivity and specificity of ACE-III in identifying dementia ranged from 0.90 to 1.00 across different languages (Table-4). The sensitivity of the instrument in identifying MCI ranged from 0.86 to 1, and the specificity ranged from 0.83 to 0.93 (Table-5). Area under curve was derived from ROC curve analysis and was in the range of 0.917 to 1 across

languages (Tables 4 and 5). When we combine the subjects across all languages, area under curve for dementia diagnosis in low education group was 0.989 and in high education group 0.990 (Figure-2). The sensitivity and specificity of ACE-III in distinguishing between MCI and dementia ranged from 0.73 to 0.83 with an area under curve 0.860.

We explored the relationship between sociodemographic variables and performance on ACE-III. Among controls, age, years of education and language had significant influence on ACE-III performance (age: $r = -.091$, $p < 0.012$; education: $r = .270$, $p < 0.0001$; language $F_{6,750} = 9.15$, $p < 0.0001$). Performance declined along with the increase in age, whereas education had a positive influence on the performance across languages. When we compared ACE-III total scores across languages some differences were found to be significant. The mean score of the Tamil version of ACE-III was lower (88 ±4.5) and the mean score of the Malayalam version was higher (94.2±2.9) compared to other languages. Gender ($F_{1,755} = 0.01$, $p < 0.921$, Hedges' $g = 0.021$) and place of dwelling ($F_{1,755} = 0.02$, $p < 0.901$, Hedges' $g = 0.020$), did not have any influence on ACE-III total scores. GLM analysis showed that only education had an independent effect on ACE-III performance ($F_{8,748} = 4.93$, $p < 0.027$) while age ($F_{8,748} = 0.91$, $p = 0.341$) and language ($F_{8,748} = 1.72$, $p = 0.114$) did not. In addition, examination of the interaction effects of age ($F_{1,755} = 2.17$, $p = 0.141$) and language ($F_{6,750} = 0.319$, $p = 0.927$) with years of education confirmed the independent effect of education on the performance of ACE-III. Since language did not independently affect subjects' test performance, we propose common cut-off points for all seven languages (Table-6).

Analysis of the second validation results of ACE-III as a diagnostic tool in the new independent sample show sensitivity and specificity levels in the range of 0.87 to 0.92 for dementia and 0.71 to 0.91 for MCI across education groups and is presented in supplementary tables 1 and 2.

Discussion

Diagnosis of cognitive impairment and dementia in socio-linguistically heterogeneous communities requires the availability of cognitive screening instruments that have been adapted to multiple languages spoken by the local population. The present study was undertaken to adapt, standardise and validate the cognitive screening instrument ACE-III in seven languages commonly used in India and create a tool that could be used to accurately screen dementia and MCI in a linguistically diverse context. The psychometric properties of seven language versions of ACE-III met standardised test requirements suggesting that the test adaption and standardisation was successful across languages. Results exhibited good sensitivity, specificity in diagnosing dementia and MCI.

Accounting for cultural differences and linguistic characteristics of different populations, without altering the principal concepts or aims of the original screening tool, are crucial for the development of a common instrument to diagnose dementia. In this study, a systematic process of adaptation of ACE-III, that included involvement of a multidisciplinary expert group, incorporation of culturally relevant stimuli, translation, back-translation, rescaling of scores and piloting ensured the development of a culturally appropriate cognitive screening instrument.

ACE-III in India has been adapted and validated into one Indian language, Gujarati (Sharma, Chaudhary, Sheth, & Dalal, 2018). Our version of ACE-III is largely similar to the Gujarati version of ACE-III. Local names and addresses of the respective regions have been used in the memory subtest, and corresponding phonetic alphabets in the respective Indian language are used in the visuospatial task “identification of fragmented letters”. In the language domain of ACE-III, we followed a detailed and systematic process of adaptation in the language domain of ACE-III, that included “centering” and a pilot study to standardise

the test across seven languages simultaneously, thereby allowing for compatibility across linguistically diverse populations.

The Hindi, Telugu and Indian English versions of ACE-III met the requirement of psychometric properties showing high internal consistency, inter-rater reliability and test-retest reliability. To examine diagnostic accuracies of ACE-III, we measured the sensitivity and specificity of the Indian versions of ACE-III for the diagnosis of dementia and MCI. The ability of the tests to detect dementia accurately was good, with high sensitivity (0.90-1.00) and high specificity (0.94-1.00) at the optimum cut-off points ranging from 80-85. ACE-III also had good sensitivity and specificity for MCI, within a range of 0.83-1.00 at corresponding cut-off values of 84-89, comparable to English ACE-III (88/82), Chinese ACE-III (83), German ACE-R (82, 83), French ACE-R (83, 89), Japanese ACE-R (80), Greek ACE-R (85), and Spanish ACE-R (88, 85) (Habib & Stott, 2017; Hsieh et al., 2013; Wang et al., 2017). Some studies from Thailand, Brazil, Korea, Malaysia and Italy yielded lower cut-off scores, and this difference could be attributed to the lower education levels or older age of patients in these studies (Habib & Stott, 2017; Kan et al., 2019). Diagnostic utility of the Indian versions of ACE-III was further confirmed by higher AUCs in diagnosing dementia (0.976-1) and MCI (0.917-0.963), consistent with previous studies (Habib & Stott, 2017). ACE-III is moderately able to distinguish between dementia and MCI diagnosis, with sensitivity and specificity levels ranging from 0.73 to 0. 83 with an area under curve of 0.860 which is reasonably good, but indicates that ACE-III cannot in itself be claimed as a highly reliable tool to distinguish MCI from dementia.

Examination of the ACE-III validity results on the new independent sample show lesser sensitivity and specificity levels compared to the sample used in training model. However, the results still show a good diagnostic validity covering above 0.863 area under

curve. Therefore the results with the new independent sample validate the use of ACE-III as a diagnostic tool.

Education was found to have an independent effect on the test performance, as reported in earlier studies (Carvalho, Barbosa, & Caramelli, 2010; dos Santos Kawata et al., 2012; Takenoshita et al., 2019), necessitating separate cut-off scores for low and high education groups. Our results emphasise the importance of education adjusted cut-off scores in reducing bias in interpretation of scores (Kittner et al., 1986). Language did not have an independent effect on performance of the subjects; therefore it was feasible to establish a common threshold point for the Indian versions of ACE-III in the diagnosis of MCI and dementia across the seven languages. This finding is of importance, since it demonstrates that ACE-III can be effectively used as a common screening instrument across different languages.

The following are the potential limitations of this study (i) As we have chosen availability sampling method, which corresponds to the previously published literature in the adaptation and validation of the tests, this method might contribute to selection bias of the participants; (ii) Sample size in controls and patients with dementia and MCI in some languages such as Kannada, Malayalam and Tamil is small/not collected due to limited resources and lack of personnel to collect the data in these centres limiting the assessment of internal consistency and reliability in these languages; (iii) Accuracy analysis of ACE-III across different subtypes of dementia was not explored mainly due to small sample size in each dementia subtype; (iv) The healthy controls in the present study could be a super normal sample and easier to distinguish from MCI/dementia. Hence results may not necessarily hold equally good in case of unselected clinical populations. To address these limitations of the present study, future clinical and community studies will be required to elicit further insights regarding the use of ACE-III as a screening instrument.

To conclude, the major contribution of the study is that it provides a cognitive screening tool that can be used to uniformly diagnose cognitive impairment in people speaking different languages from both rural and urban populations located across India. The development of a common diagnostic tool will facilitate harmonisation of dementia research across diverse populations and catalyse the development of preventive and treatment strategies for larger cohorts of dementia from diverse demographic and geographic backgrounds.

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Table 1. Demographic and cognitive profile of Hindi, Telugu, Kannada, Malayalam, Urdu, Tamil, and Indian English speaking subjects

Language and diagnosis	n	Age	Male n, %	Years of Education	Education groups (≤10 vs >10), n	ACE-III Total (Max: 100)	Attention (Max: 18)	Memory (Max: 26)	Fluency (Max: 14)	Language (Max: 26)	Visuospatial (Max: 16)
Hindi-Controls	241	65.5±5.5	143, 59.3%	13.7±3.3	69, 172	92±5	17.5±1	23.5±3	10.8±2	25.3±1.3	15.4±1.1
Hindi-Dementia	59	67.6±5.3	41, 69.5%	13.9±3.7	21, 38	65±11	13.2±3.1	13.5±4.1	6.4±2.5	22.8±2.8	11±3.1
Hindi-MCI	57	65.7±7.5	39, 68.4%,	13.8±3.2	16, 41	78.2±7.8	16.5±3.2	16.2±4.5	7.6±2	24.8±1.3	13.1±2.7
Telugu-Controls	162	63.1±6.3	107, 66%	12.7±3.4	42, 120	92 ±4.8	17.2±1.2	24.2±1.8	10.9±2	25.1±1.3	14.6±1.7
Telugu-Dementia	72	65±10.8	50, 69.4%	12.7±3.9	41, 31	67.1±13.7	13.1±3.7	15.1±6.1	6.2±2.3	22.5±2.9	11.2±3.8
Telugu-MCI	44	63.6±10.3	33, 75%	13.3±4.5	16, 28	83.2±5.2	16±1.8	20.8±3.1	8±2	24.3±2.5	14.1±2.4
Kannada-Controls	56	68.2±11.6	35, 62.5%	11.9±3.8	26, 30	92.5±4.6	17.4±1.4	22.6±4.2	11.3±1.4	25.4±1.2	15.4±1
Kannada-Dementia	17	62.9±11	10, 58.8%	13.5±3.7	8, 9	52.9±19.3	11.1±3.6	11.3±7.6	4.1±2.7	17.2±5.5	9.2±4.6
Kannada-MCI	34	71±7.6	21, 61.8%	10.8±2.9	18, 16	79.2±7.1	15 ±3.2	16.5±3.8	8.1±2.2	25±1.8	14.5±2.7
Malayalam-Controls	30	66.1±7.4	18, 60%	13.2±3.4	8,22	94.2±2.9	17.9±0.4	23.7±1.9	10.9±1.4	25.7±0.7	15.9±0.6

Malayalam-Dementia	15	67.5±5.7	10, 66.7%	12.3±3.7	10,5	49.5±19.2	10.8±4.5	8.1±5.2	3.3±2.6	17.9±6.5	9.2±4
Urdu-Controls	74	63.2±6	39, 52.7%	13.8±4.4	18, 56	90.8±4.5	16.4±1.9	23.7±2.3	11±2	24.9±1.8	14.7±1.6
Urdu-Dementia	33	66.2±10.5	22, 66.7%	13±4.2	18, 15	60.6±14.4	11.3±3.8	11.4±6	5.5±2.6	20.8±3.8	11.1±4.7
Urdu-MCI	32	61.8±6.3	14, 43.8%	11.8±3.7	21, 11	79.7±4.5	13.9±2.4	20.2±3.6	9.3±2	23±2.6	13±1.8
Tamil-Controls	26	59.4±9.6	14, 53.8%	13.2±3.5	9, 17	88±4.5	16.2±2	22.4±3	10.4±2.1	24.4±1.3	14.5±1.6
Tamil-Dementia	27	62.1±10.5	19, 70.4%	11.4±4.2	19, 8	61.4±18	11.9±4.1	12.9±5.8	7.3±2.4	20.1±4.6	8.9±4.6
Indian English-Controls	168	65±6.4	129, 76.8%	16±2.4	0,168	93.7±3.8	17.6±0.9	24.1±1.9	11.3±2.1	25.3±1.1	15.3±1.1
Indian English-Dementia	19	69±6.9	14, 73.7%	17.4±2.4	0,19	71.9±9.8	14.1±3	14±5.2	7.5±3.4	22.7±3.4	13.1±2.2
Indian English-MCI	37	66.8±9.2	32, 86.5%	16.8±2.5	0,37	86.7±2.8	17.1±1	21.3±2.6	8.6±2.2	24.9±1.2	14.8±1.7

Table 2. Percentile distribution of raw scores and revised scaled scores of 591 controls on letter and category fluency

	Raw score of letter fluency	Revised scaling of letter fluency	**Scaled score**	Raw score of category fluency	Revised scaling of of category fluency
Mean (SD)	9.2 (3.2)			13.0 (3.2)	
1st percentile	1	1	**1**	2	1-2
5th percentile	3	2	**2**	6	3-5
25th percentile	6	3-5	**3**	9	6-7
50th percentile	8	6-7	**4**	11	8-10
75th percentile	11	8-10	**5**	14	11-13
95th percentile	14	11-14	**6**	17	14-16
99th percentile	15	>14	**7**	20	>16

Table 3. Internal, inter-rater and test-retest reliability (alpha coefficients) of ACE-III in Hindi, Telugu, and Indian English language versions

Language	Internal reliability	Inter-rater reliability	Test-retest reliability
Hindi	0.86	0.92	0.89
Telugu	0.90	0.94	0.91
Indian English	0.92	0.95	0.94

Table 4. Sensitivity and specificity of ACE-III in Indian languages in diagnosing dementia at optimum cut off values

Language	Education ≤ 10				Education>10			
	AUC[a]	Cut-off value	Sensitivity	Specificity	AUC	Cut-off value	Sensitivity	Specificity
Hindi	0.997	80	0.95	0.97	0.991	82	0.92	0.97
Telugu	0.976	82	0.93	0.91	0.985	83	0.90	0.96
Kannada	1	81	1	0.96	0.998	82	1	0.97
Malayalam	1	82	1	1		85	1	1
Urdu	0.991	83	1	0.94	0.977	84	0.93	0.95
Tamil	0.995	80	0.95	1	0.996	82	1	0.94
Indian English	--	--	--	--	0.996	84	0.95	0.98

[a]AUC-area under curve

Table 5. Sensitivity and specificity of ACE-III in Indian languages in diagnosing MCI at optimum cut off values

Language	Education≤10				Education>10			
	AUC[a]	Cut-off value	Sensitivity	Specificity	AUC	Cut-off value	Sensitivity	Specificity
Hindi	0.961	84	0.94	0.93	0.939	87	0.88	0.89
Telugu	0.917	86	0.94	0.83	0.919	87	0.86	0.92
Kannada	0.963	86	1	0.92	0.961	88	0.94	0.90
Urdu	0.938	86	0.95	0.83	0.948	87	0.91	0.91
Indian English	--	--	--	--	0.926	89	0.89	0.86

[a]AUC-area under curve

Table 6. Common ACE-III cut-off values with sensitivity and specificity levels in diagnosing dementia and MCI

	Education ≤ 10			Education>10		
	Cut-off value	Sensitivity	Specificity	Cut-off value	Sensitivity	Specificity
Dementia	82	0.97	0.92	84	0.98	0.96
MCI	86	0.96	0.82	89	0.92	0.81

Figure legends

Fig 1a Picture naming of original ACE-III

Fig 1b Picture naming of Indian version of ACE-III

Fig 2 ROC curve of the ACE-III in diagnosing (a) Dementia (b) MCI

Supplementary tables: 3 tables

Supplementary table 1. Demographic profile and ACE-III total scores of new study sample of Hindi, Telugu, Kannada, Malayalam, Urdu, Tamil, and English speaking subjects

Supplementary table-2. Application of the ACE-III validation study cut-off scores to a new sample with sensitivity, specificity and area under curve in diagnosing dementia and MCI

Supplementary table-3: Language wise application of the ACE-III validation study cut-off scores to the study sample with sensitivity, specificity and area under curve in diagnosing dementia and MCI

Supplementary table 1. Demographic profile and ACE-III total scores of new study sample of Hindi, Telugu, Kannada, Malayalam, Urdu, Tamil, and English speaking subjects

Language and diagnosis	n	Age	Male n, %	Years of Education	Education groups (≤10 vs >10), n	ACE-III Total (Max: 100)
Hindi-Controls	30	63.3±6.6	21, 70.0%	12.1±2.8	15, 15	89.1±6.1
Hindi-Dementia	16	69.4±11.0	11, 68.8%	13.4±3.1	5, 11	60.2±15.7
Hindi-MCI	29	61.6±8.0	16, 55.2%	12.3±3.1	15, 14	77.6±7.4
Telugu-Controls	30	66.9±7.2	13, 43.3%	11.5±4.0	15, 15	90.8±5.2
Telugu-Dementia	27	63.5±6.7	20, 74.1%	11.8±5.5	12, 15	70.7±13.5
Telugu-MCI	18	64.3±10.0	11, 61.1%	10.9±3.4	12, 6	81.3±6.4
Kannada-Controls	30	67.7±8.7	15, 50.0%	11.0±3.7	15, 15	91.8±5.9
Kannada- Dementia	30	62.5±7.2	22, 73.3%	11.5±3.4	16, 14	62.0±13.2
Kannada-MCI	27	68.0±7.6	14, 51.9%	11.2±3.6	13, 14	81.0±5.3
Malayalam-Controls	29	62.1±5.1	14, 48.3%	11.7±2.8	15, 14	89.6±5.7
Malayalam-Dementia	27	69.8±7.2	21, 77.8%	11.8±3.6	13, 14	65.7±12.5
Urdu-Controls	20	62.7±4.6	10, 50.0%	11.5±4.3	10, 10	89.7±5.7
Urdu-Dementia	15	66.0±7.0	8, 53.3%	13.8±4.1	6, 9	66.7±13.2
Urdu-MCI	16	66.8±7.2	10, 62.5%	12.8±3.9	8, 8	81.3±6.5
Tamil-Controls	29	65.5±5.7	19, 65.5%	11.8±3.9	13, 16	91.9±6.3
Tamil-Dementia	19	60.4±5.0	11, 57.9%	9.0±3.6	11, 8	69.9±7.9
Indian English-Controls	16	62.5±5.7	7, 43.8%	14.1±3.2	0, 16	93.1±5.0

Indian English-Dementia	13	68.3±5.6	7, 53.8%	17.2±2.2	0, 13	66.3±15.1
Indian English-MCI	13	72.0±5.4	7, 53.8%	15.9±1.8	0, 13	84.8±4.5

Supplementary table-2. Application of the ACE-III validation study cut-off scores to a new sample with sensitivity, specificity and area under curve in diagnosing dementia and MCI

	Education ≤ 10				Education>10			
	Cut-off value	Sensitivity	Specificity	Area under curve	Cut-off value	Sensitivity	Specificity	Area under curve
Dementia	82	0.92	0.89	0.976	84	0.89	0.87	0.969
MCI	86	0.83	0.78	0.863	89	0.91	0.71	0.892

Supplementary table-3: Language wise application of the ACE-III validation study cut-off scores to the study sample with sensitivity, specificity and area under curve in diagnosing dementia and MCI

		Education ≤ 10				Education>10			
	Language	Cut-off value	Sensitivity	Specificity	Area under curve	Cut-off value	Sensitivity	Specificity	Area under curve
Dementia	Hindi	82	0.95	0.96	0.997	84	0.95	0.95	0.991
	Telugu	82	0.93	0.91	0.976	84	0.90	0.96	0.985
	Kannada	82	1.00	0.96	1.00	84	1.00	0.93	0.998
	Malayalam	82	1.00	1.00	1.00	84	1.00	1.00	1.00
	Urdu	82	0.94	0.94	0.991	84	0.93	0.95	0.977
	Tamil	82	1.00	0.90	0.995	84	1.00	0.81	0.996
	Indian English	--	--	--	--	84	0.95	0.98	0.996
MCI	Hindi	86	0.94	0.84	0.961	89	0.90	0.88	0.939
	Telugu	86	0.94	0.83	0.917	89	0.93	0.83	0.919
	Kannada	86	1.00	0.92	0.963	89	0.94	0.90	0.961
	Urdu	86	0.95	0.83	0.938	89	1.00	0.86	0.948
	Indian English	86	--	--	--	89	92.0	0.82	0.926

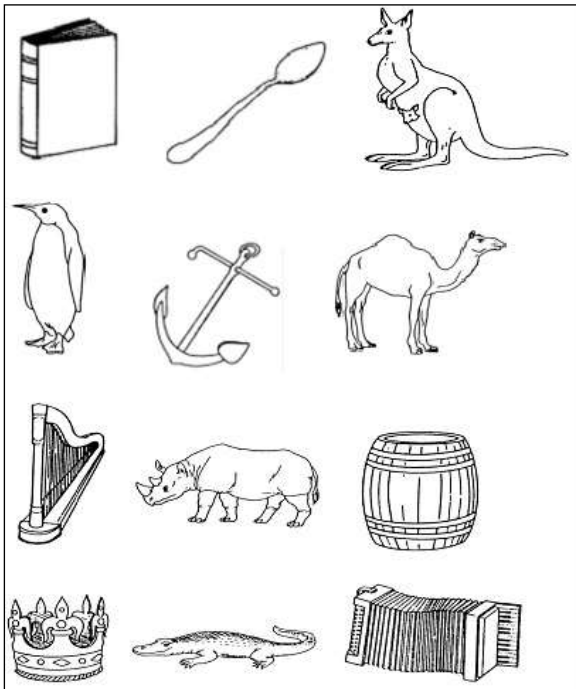


Figure 1a. Picture naming of original ACE-III

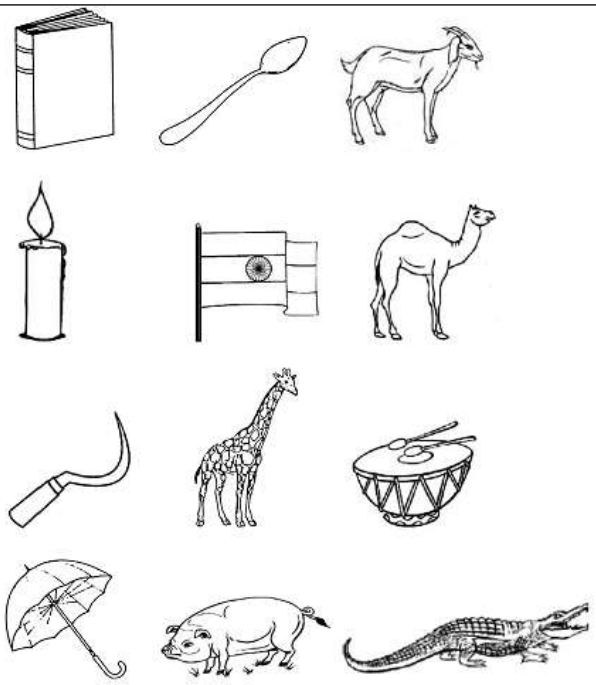


Figure 1b. Picture naming of Indian version of ACE-III

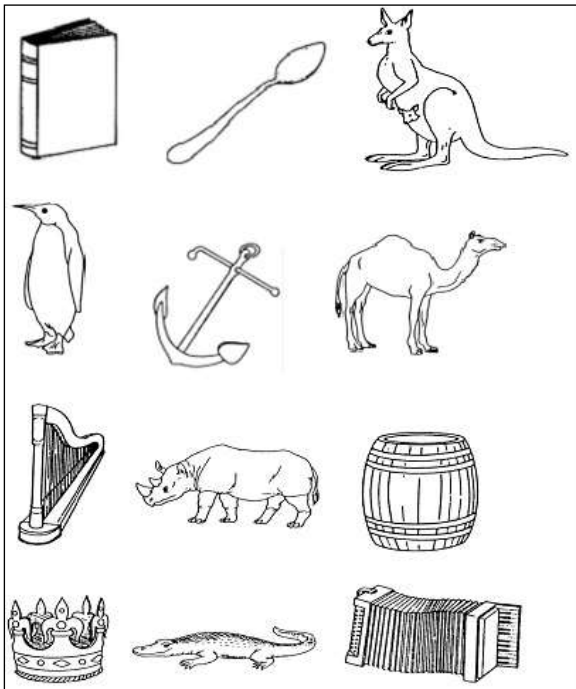


Figure 1a. Picture naming of original ACE-III

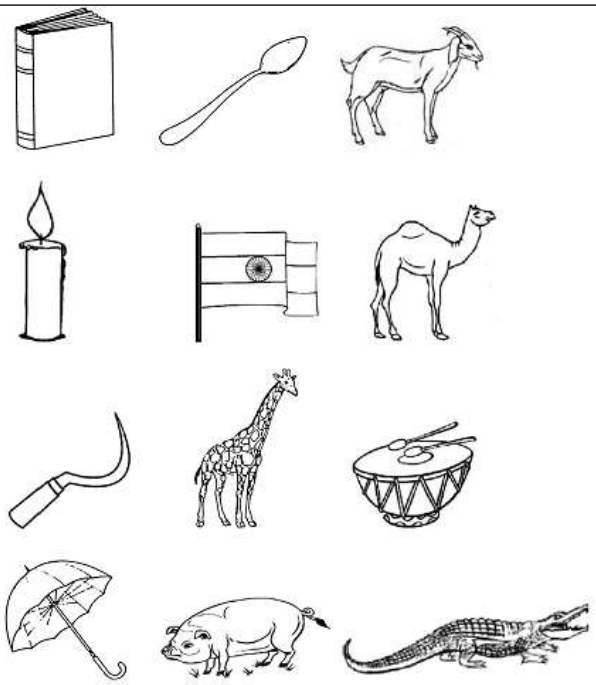
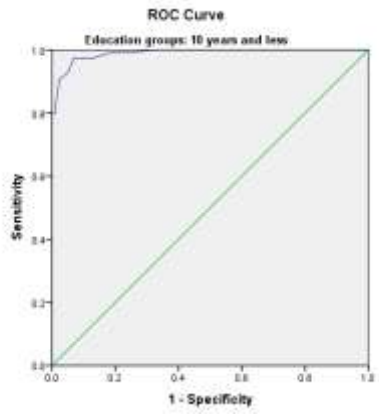
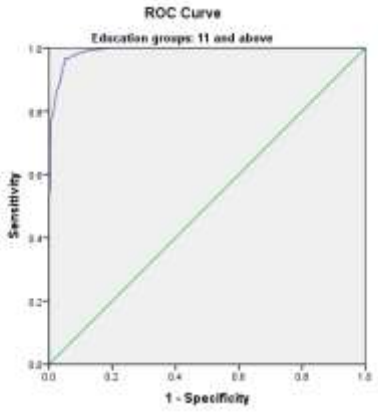


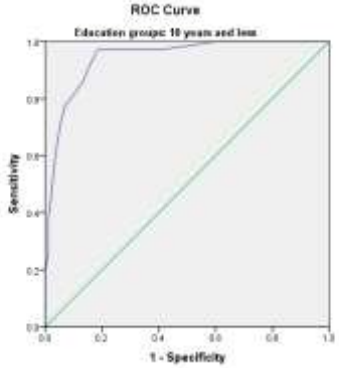
Figure 1b. Picture naming of Indian version of ACE-III

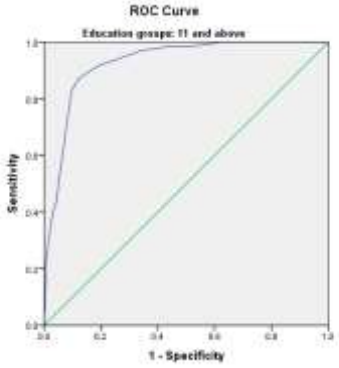




(a) (b)

Figure 2: ROC curve of the ACE-III in diagnosing dementia in (a) ≤ 10 years of education (b) >10 years of education





(a) (b)

Figure 2: ROC curve of the ACE-III in diagnosing MCI in (a) ≤ 10 years of education (b) >10 years of education