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Sensitivity of the Mini-Mental State Examination, Montreal Cognitive Assessment and the Addenbrooke's Cognitive Examination III to everyday activity impairments in dementia: An exploratory study

RUNNING TITLE: Sensitivity to everyday activities

Clarissa M. Giebel ^{1,2,*} and David Challis ³

¹ School of Health Sciences, University of East Anglia, Norwich, UK

² School of Psychological Sciences, University of Manchester, Manchester, UK

³ Personal Social Services Research Unit, University of Manchester, Manchester, UK

** Correspondence should be addressed to: Clarissa Giebel, Queen's Building, School of Health Sciences, University of East Anglia, NR4 7TJ, Norwich, UK. Telephone: +44 1603 593259; Email: C.giebel@uea.ac.uk*

ABSTRACT

Objective: The Mini-Mental State Examination (MMSE) is one of the most frequently used cognitive measures for dementia severity, and linked to deficits in everyday functioning. Recently, the Montreal Cognitive Assessment (MoCA) and the Addenbrooke's Cognitive Examination III (ACE-III) increasingly substitute for the MMSE. However, there are no specific cut offs in the ACE-III for mild dementia. The objectives of this exploratory study were to assess the sensitivity of each scale to everyday functioning and to examine the cut offs between mild and moderate dementia on the ACE-III.

Methods: People with mild dementia completed the MMSE, MoCA and ACE-III, whilst informal carers completed the Revised Interview for Deteriorations in Daily Living Activities for Dementia to rate their relative's initiative and performance of instrumental activities of daily living, and the Katz activities of daily living scale. Data were analysed using correlation analysis, raw score comparisons, Cohen's kappa and Receiver Operating Characteristics analysis.

Results: Thirty-three dyads completed the measures. The ACE-III was the most sensitive tool for everyday functioning performance, whilst its language sub-scale was specifically related to initiation of activities. The most suitable cut off on the ACE-III between mild and moderate dementia was 61.

Conclusions: Findings suggest ACE-III more efficiently identifies everyday functional impairments. Further research is required to confirm these exploratory analyses of the cut off between mild and moderate dementia on the ACE-III. Both functional impairment and stage of dementia are needed in the diagnostic process and in the clinical assessment of people with dementia.

Key words: dementia, activities of daily living, cognition, diagnosis

Word count: 3,657

Introduction

Dementia represents a major global health and social care burden (Alzheimer's Disease International, 2015). Whilst some studies have recently suggested a decline in age-specific dementia risk (Matthews *et al.*, 2013; Schrijvers *et al.*, 2012), timelier diagnosis is a critical aspect in clinical practice to address the progression of the condition. One way to improve timelier diagnosis is to increase knowledge about the early symptoms of the disease, such as everyday functioning. People with dementia (PwD) experience more difficulties with complex instrumental activities of daily living (IADLs) in the early stages, including managing finances and preparing a hot meal, than with basic activities of daily living (ADLs), including feeding and dressing (Pocnet *et al.*, 2013). Impairments in everyday functioning are linked to cognitive deficits (Lau *et al.*, 2015; Vermeersch *et al.*, 2015), although the exact cognitive underpinnings of these activities remain largely unknown (Giebel *et al.*, 2015a). This is because reports primarily focus on global cognitive tools, such as the Mini-Mental State Examination (MMSE) (Folstein *et al.*, 1975), the Montreal Cognitive Assessment (MoCA) (Nasreddine *et al.*, 2005) and the Addenbrooke's Cognitive Assessment III (ACE-III) (Hsieh *et al.*, 2013), and global IADL and ADL impairments (i.e. Fauth *et al.*, 2013). However, there is relatively little evidence about the relationship between cognition and specific individual activities. Given that ADLs deteriorate differently across the dementia stages (Giebel *et al.*, 2015b), evidence on global relationships appears too broad to indicate which of these three tools allows for better identification of IADL and ADL deficits.

Another aspect often lacking in everyday function assessment, particularly in relation to cognition, is the initiative to perform an activity. Initiating an activity is a required first step prior to its performance (Bier *et al.*, 2013), and it might link to

cognition differently than performing the task. Prospective memory as an example of cognition also comprises steps of initiating and planning an activity and then subsequently remembering to perform the activity. Indeed, prospective memory is found to be related to one particular daily activity – medication adherence (Insel *et al.*, 2016). This further suggests that initiating an activity can be an important cornerstone of everyday functioning, with links to this separation in cognition. One particular tool that allows assessing these different stages for a range of activities, including modern activities of computer use, is the revised Interview for Deteriorations in Daily Living Activities in Dementia (R-IDDD) (Giebel *et al.*, 2014).

Timelier diagnosis may be enhanced by employing the most sensitive measure to assess early cognitive deficits. Reflecting recent guidelines, cognitive assessments will increasingly incorporate the ACE-III (Hsieh *et al.*, 2013). With the MMSE being one of the most established cognitive tools, for which there are existing cut offs to distinguish mild from moderate from severe dementia, it is important to compare the cut offs for the different stages of dementia with more recently introduced tools. These new tools are increasingly replacing the MMSE in clinical practice and in research, as it is suggested that these are more sensitive to early cognitive problems in dementia (Ballard *et al.*, 2013; Nasreddine *et al.*, 2005). Van Steenoven and colleagues (2014) converted raw MoCA scores into MMSE scores, thereby suggesting that a score of 15 on the MoCA is equivalent to a score of 21 on the MMSE, a frequently employed cut off to distinguish mild from moderate dementia. However, the most recent tool, the ACE-III, has received little attention in this regard, with studies having focused on overall dementia diagnosis (Hsieh *et al.*, 2013; Jubb & Evans, 2015). Thus, no study to date has compared the cut off scores for mild to moderate dementia on the ACE-III with the MMSE and the MoCA, but only with former ACE scales (Hsieh *et al.*, 2013).

The first aim of this study was to explore which global cognition scale is most strongly associated with everyday functioning in mild dementia. Improved knowledge on how these scales relate to everyday activities could be beneficial in the diagnosis process. We know that cognition is linked to functional decline, so a cognitive tool sensitive to functional decline would allow for the joint assessment of cognition and functioning. With the MoCA and the ACE, a forerunner of the ACE-III, suggested to be more sensitive to cognitive performance in dementia (Mathuranath *et al.*, 2000; Nasreddine *et al.*, 2005), it was hypothesised that these two tools would also be more sensitive to everyday functioning. The second aim was to assess cut offs for the ACE-III for the lower end of mild dementia. Providing such cut offs has important implications for clinical practice, with the MMSE being replaced by the MoCA and the ACE-III. In particular, this exploratory study may offer important insights for the follow-up assessments of people diagnosed with dementia, as clinicians will be better equipped in assessing the cognitive decline during these follow-ups.

Method

Participants

Participants were recruited by staff at memory clinics in Greater Manchester and through the Greater Manchester NIHR Clinical Research Network. People with mild dementia were eligible for the study if they had a diagnosis of dementia; an MMSE score of 21 or above, a MoCA score of 15 or above or an ACE-III equivalent estimated to be above 65 by clinical staff, including clinical neuropsychologists, based on extensive experience in clinical assessments and in comparison to MMSE and MoCA assessments performed in their clinical practice; and had an informal carer. The last cognitive test score upon which the referral to the study was based

was no older than six months. Ethical approval was obtained from the NRES Committee North West – Greater Manchester East, and recruitment took place from January 2014 to September 2015.

Measures

Addenbrooke's Cognitive Examination III (ACE-III)

The ACE-III (Hsieh et al., 2013) is a newer version of the established ACE-II and ACE-R and a slightly longer cognitive assessment than the MMSE and MoCA. The questionnaire covers areas of memory, language, fluency, attention and visuospatial abilities. A maximum score of 100 can be obtained, with higher scores indicating better memory and cognitive performance. Hsieh et al. (2013) showed that the ACE-III has good sensitivity and specificity in the assessment of cognitive deficits in people with Alzheimer's disease and fronto-temporal dementia.

Mini-Mental State Examination (MMSE)

The MMSE (Folstein et al., 1975) is a brief cognitive screening tool that has validated norms for mild, moderate and severe dementia. The maximum score is 30, and a cut off of 21 and above is indicative of mild dementia (Perneckzy et al., 2006), although reports vary on the cut off for mild dementia (Mioshi et al., 2007; Nagaratnam et al., 2014; Perry et al., 2000).

Montreal Cognitive Assessment (MoCA)

The MoCA (Nasreddine et al., 2005) is a brief test of cognitive performance which is frequently used to ascertain the severity of dementia as well as to differentiate patients with early dementia from those with mild cognitive impairment (Freitas et al.,

2013; Smith *et al.*, 2007). This cognitive screening tool has eight categories which address visuospatial and executive functioning; naming; memory; attention; language; abstraction; delayed recall and orientation. For each correct answer, one point is given. A maximum of 30 points can be scored, which indicates no cognitive impairment. A score below 26 indicates mild dementia (Nasreddine *et al.*, 2005), although a cut off between mild and moderate dementia has not been established. The MoCA has high test-retest reliability in people with Alzheimer's (Freitas *et al.*, 2013) and higher classification accuracy than the MMSE (Larner, 2012).

Everyday functioning assessment

Everyday functioning was assessed with the Revised Interview for Deterioration in Daily Living Activities (R-IDDD) (Giebel *et al.*, 2014; Teunisse *et al.*, 1991). The R-IDDD measures the initiative and performance of 15 and 19 activities, which can be rated on a scale from '0' (never lacking the initiative/never any difficulties) to '4' (always lacking the initiative/always difficulties). The R-IDDD is based on the original IDDD, which despite its good construct validity showed poor concurrent validity and was suggested to lack further activities (Voigt-Radloff *et al.*, 2012). Thus, the R-IDDD contains additional IADLs, which describe subtle everyday activities, such as *following familiar routes or monitoring own day*.

Procedure

Testing took place either at the participant's home or in a quiet room at the University of Manchester. After written informed consent was obtained, PwD were administered all three measures, whilst informal carers completed the R-IDDD. Testing lasted approximately 30 minutes.

Data analysis

Demographic characteristics and test performances were explored using frequency analysis. To explore which scale was most suitable to also detect everyday activity deficits, the associations between individual activities on the initiative and performance scale of the R-IDDD and the MMSE, MoCA and the ACE-III were analysed using bivariate correlation analysis. For the investigation of different cut off scores, scatter plots were calculated to compare the raw scores between the MMSE and the ACE-III and between MoCA and the ACE-III. This exploration was based on similar conversion analyses by Law *et al.* (2013). Furthermore, Cohen's kappa statistic (Cohen, 1960) was calculated to compare the inter-scale agreements. Kappa can range from -1 to +1, with negative values indicating worse than chance agreement, and positive values indicating poor to very good agreement. Receiver Operating Characteristic (ROC) analysis was employed to measure the accuracy of different cut offs (65 and 61) on the ACE-III compared to the MMSE and the MoCA. For all analyses, SPSS version 22 was used.

Results

The sample comprised 39 PwD, and their informal carers. A total of six PwD were found not to be eligible when global cognition was tested, because of deteriorations beyond the cut offs since their last testing by clinical staff. Hence, the total sample comprised 33 PwD and their carers. The majority of PwD was male (54.5 percent) and the mean age was 76 years (+/-7.5). PwD had received on average 12 years of education (+/-3) with a range of 7 to 20 years, with the majority having a diagnosis of Alzheimer's disease (N=19), whilst there were also cases of mixed dementia (N=4),

vascular (N=2), fronto-temporal (N=1), Parkinson's (N=1) and Lewy Body dementia (N=1). Five PwD had an unknown type of diagnosis. Carers were primarily female (72.7 percent) and had a mean age of 63 (+/-14). Most carers were spouses (60.6 percent), with 33.3 percent of carers being the PwD's child. The mean score on the MMSE was 24.3 (+/-3.0) with scores ranging from 17 to 29; on the MoCA it was 20.3 (+/-4.1) with scores ranging from 12 to 28, and on the ACE-III 70.6 (+/-12.7) with scores ranging from 42 to 96.

Sensitivity to everyday activity decline

Few activities on the R-IDDD initiative and performance scales were associated with the MMSE, MoCA and the ACE-III (Table 1). Overall, there were more significant associations between the performance of activities and the cognitive scales than with initiative. *Medication management* and *following familiar routes* emerged as being significantly associated with cognition, both for initiative and performance. Initiating *medication management* was negatively associated with the MMSE and MoCA, indicating increasing lack in motivation with poorer cognitive functioning. Initiating *following familiar routes* was associated with the MMSE and the ACE-III. The performance of *following current affairs* was significantly associated with all three scales, whilst actively *monitoring the day* was related to the ACE-III. Several other activities on both scales approached significance, such as both the MMSE and ACE-III with initiating to *following current affairs*, the MoCA with initiating to *prepare a meal*, and the MoCA and ACE-III with performance total.

To explore whether specific sub-components of cognition were more strongly associated with the initiative to perform activities than overall global cognition, further correlation analyses with the subscales of the ACE-III were conducted. Language

was most strongly correlated with initiative ratings, including *dressing* (-.361, p=.039); *finance management* (-.355, p=.046); *following familiar routes* (-.522, p=.004); *following current affairs* (-.489, p=.004) and initiative total (-.416, p=.016). Visuo-spatial abilities and memory were associated with *cleaning* (-.373, p<.05) and *following familiar routes* (-.393, p<.05) respectively.

[insert Table 1 here]

Conversion scores for the ACE-III

Figure 1 shows the relationship between the raw scores on the MMSE and the ACE-III, and on the MoCA and the ACE-III. According to the raw scores, a score of 21 on the MMSE approximately equals a score of 61 on the ACE-III. For the MoCA, a score of 15 approximately equals a score of 59 on the ACE-III. The Pearson correlation coefficient between the MMSE and ACE-III was .64. The regression equation was

$$\text{ACE-III} = 4.56 + 2.72 * \text{MMSE}$$

The Pearson correlation coefficient between MoCA and ACE-III was .71. The regression equation was

$$\text{ACE-III} = 25.27 + 2.24 * \text{MoCA}$$

Cohen's kappa statistics between the MMSE and the ACE-III showed that both scales showed poor agreement (k=.195, p=.151) using a cut off of 65 on the ACE-III, and moderate agreement (k=.436, p=.009) using the cut off of 61 suggested by the raw score analysis and regression equation. Cohen's kappa statistics between the MoCA and the ACE-III showed that both scales showed poor agreement (k=.118, p=.151) using a cut off of 65, and fair agreement (k=.369, p=.006) using the cut off of

59 suggested by the raw score analysis and regression equation. Fair agreement was also reported for a cut off of 61 ($k=.298$, $p=.016$).

Figures 2 and 3 show the ROC curve for distinguishing between mild and moderate dementia on the ACE-III in comparison to scores on the MMSE and MoCA. For an ACE-III cut off of 65, the area under the curve (AUC) was estimated at .82 (95%CI: .67-.97) for the MMSE and at .80 (95%CI: .64-.95) for the MoCA, both of which were significantly different from AUC 0.5 ($p_{MMSE}=.004$; $p_{MoCA}=.008$). For an ACE-III cut off of 61, the AUC was estimated at .83 (95%: .64-1.0) for the MMSE and at .95 (95%CI: .88-1.0) for the MoCA, both of which were significantly different from an AUC of 0.5 ($p_{MMSE}=.020$; $p_{MoCA}=.002$). A ROC analysis for a cut off of 59 on the ACE-III was not conducted, because this cut off was found to be too low for the MMSE, and there could not be two cut off values on the ACE-III equaling the same established cut off on other scales.

[insert Figures 1-3 here]

Discussion

This is one of the first pilot studies exploring the relationship between cognition and everyday activity initiative and performance. Our hypothesis for the first objective was only partially supported, in that the data indicated that the ACE-III was the most sensitive tool to everyday functioning performance. However, the MMSE was equally sensitive for the performance and initiative, thereby contradicting our hypothesis, whilst the MoCA was found to be less sensitive than the MMSE. This is an exploratory analysis however, so conclusions need to be considered carefully.

Upon closer examination, the cognitive scales were found to be most sensitive to the performance of everyday activities. That does not suggest that exploring the relationship between initiating activities and cognition is less relevant, but that the performance is better captured by the types of cognition assessed. Possibly, loss of initiative is related to certain types of cognition that are not sufficiently addressed by these measures. However, there are other factors that affect everyday functioning, such as depression or the environment (dePaula *et al.*, 2015; Gitlin *et al.*, 2001), which may have a larger impact on initiating everyday tasks compared to cognition. Indeed, upon further analysis, several activities on the initiative scale were found to most strongly correlate with the language subscale on the ACE-III. Dementia is characterised by subtle language deficits, which vary between different types of dementia (Blair *et al.*, 2007; Forbes-McKay & Venneri, 2005). The relationship between language and initiating activities may suggest a breakdown in communication, so that carers perceive their PwD as less proactive. For *finance management* and *following current affairs* in particular, both of which were found to be associated with language, it may be the case that difficulties with language (and thus in the actual comprehension) may inhibit PwD from initiating the activity in the first place. In light of proxy as opposed to self-reports of everyday functioning, there is a possibility that carer burden might have biased these reports and associations with language (Zanetti *et al.*, 1999). However, the sample comprised only people in the mild stage of dementia and their carers, in which carer burden is not as dominant as in the later stages (Mioshi *et al.*, 2013). Considering that the limited research into cognition and everyday functioning generally focuses on executive functioning or short-term memory (Brown *et al.*, 2011; Ramsden *et al.*, 2008), this study highlights the possible need for further investigation of the semantic underpinnings of engaging in activities. For clinical practice, this suggests that some areas of everyday

functioning might be improved by speech and language therapy. For everyday life, this might suggest that carers should be more sensitive to the communication abilities of their relatives and possibly consider their non-verbal communication also.

In addition to the sensitivity of a cognitive scale to everyday functioning, it is relevant to clarify the cut off between different stages of dementia to aid classification. The data suggest that the initial cut off of 65 on the ACE-III was too conservative, as it incorrectly categorised several cases of people with mild dementia to have moderate dementia. Instead, a cut off of 61 was found most suitable based on several exploratory analyses. This cut off was more representative of MoCA scores with a greater improvement on the AUC compared to the MMSE. It is important to note that this cut off analysis is subject to limitations, based on the small sample size, and on the low number of non-cases (people classified to have moderate dementia), therefore making it an exploratory study. To increase the power of the analysis, the sample would need to include a greater number of non-cases. However, other published research in dementia and Parkinson's disease has employed ROC analysis on similarly small samples (i.e., Frank *et al.*, 2000; Hobson *et al.*, 2014). Furthermore, there may have been a slight ordering effect in this study, as the order of assessment was kept the same for each participant, with the MoCA and the ACE-III being administered after the MMSE. This may have biased the results in that participants may have been slightly more exhausted during the third test, or, on the contrary, may have performed better due to practice effects. A larger study would allow for randomly ordering the tests to remove ordering effects. Moreover, in a recent investigation into the early detection of dementia, Jubb and Evans (2015) suggested that the cut off for dementia on the ACE-III was dependent on the years of education. In the present study however, correlation analysis between years of education and the 19 performance items on the R-IDDD has shown no

significant associations. Furthermore given the small number of participants in this exploratory study, it was not considered feasible to split the sample into PwD with low and high education. However, this study provides a stepping stone and guidance for future research.

Different studies employ different cut offs for mild dementia, which range from 18 to 22 (Mioshi *et al.*, 2007; Perry *et al.*, 2000). The cut off of 21 on the MMSE was chosen as it has been applied in many other studies (Giebel *et al.*, 2014; Monaci & Morris, 2012; Nagaratnam *et al.*, 2014). This is not a direct limitation of the study, but the cut off score analysis focused on this particular score to equate with the ACE-III, so if future studies were to employ a different cut off this would result in slightly different ACE-III score equivalents. To take account of the variation in MMSE cut offs for mild dementia, one solution would be to employ the percentile ranking method, so as to compare each MMSE score with a suitable ACE-III equivalent.

Whilst this study highlights that the ACE-III is clearly the most suitable out of the three global cognitive tools because of its sensitivity to everyday function, it is slightly longer than the MMSE and the MoCA. Most likely it is this increased length and specificity of different types of cognition that increase the tool's sensitivity to everyday function. However, considering that particularly people with suspected dementia, and those with a diagnosis, usually receive a large battery of neuropsychological assessments, this slightly increased length of the ACE-III might be considered as a minor limitation. Furthermore, in view of the small sample size of this exploratory study, multiple tests of associations with the initiative and performance might have increased the Type I error. However, the purpose of this study was to provide an exploratory insight into these associations, and applying Bonferroni correction to the correlation analysis would have increased the Type II error considering the number of tests of associations performed. Given the overall

benefits of the tool however, the ACE-III appears to be the best tool to employ in clinical practice.

Conclusions

Findings from this study can have implications for clinical practice. Although the study is exploratory based on its small sample size, it suggests that the ACE-III is the most sensitive measure to everyday activity performance in dementia. Therefore, performance on the ACE-III might be linked to levels of everyday dependence. This can be helpful in clinical assessments or care home admissions where the PwD might struggle communicating or no proxy is available. Furthermore, the study offers novel insights into the most suitable cut off between mild and moderate dementia on the ACE-III. In light of the increased use of the ACE-III in clinical practice, the findings can directly assist in the assessment of dementia, such as during check-up visits for the progress of the disease. Future research should explore the entire spectrum of dementia in a larger sample, by not only focusing on the distinction between mild and moderate, but also between moderate and severe dementia.

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Key points

- The ACE-III is the most sensitive tool to everyday activity impairments in dementia compared with the MMSE and the MoCA.
- Language is particularly associated with initiating activities.
- A cut off of 61 on the ACE-III was found to be most suitable to distinguish mild from moderate dementia. Future research needs to explore the cut offs in a larger sample.

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