Title: Cognitive assessment in stroke: Feasibility and test properties using differing approaches to scoring of incomplete items

Running title: Brief cognitive screening tools, feasibility and non-completion

Keywords: feasibility, screening, sensitivity, specificity, stroke

Keypoints:

- Feasibility of completion of cognitive screening tests should not be assumed. In the stroke population we studied, most participants needed assistance to complete tests and even “short” assessments had substantial rates of non-completion.

- Where a multi-item cognitive test is only partially compete, the method used to account for the missing scores will impact on potential screen positive rates and diagnostic properties of the test.

- Clinicians and researchers need to have explicit protocols for dealing with partial test completion, We recommend a method that makes greatest use of the available data.

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Objectives: Cognitive screening is recommended in stroke, but test completion may be complicated by stroke related impairments. We described feasibility of completion of three commonly used cognitive screening tools and the effect on scoring properties when cognitive testing was entirely/partially incomplete.

Methods: We performed a cross-sectional study, recruiting sequential stroke patient admissions from two University Hospital stroke rehabilitation services. We assessed Folstein's Mini-Mental State Examination (MMSE); Montreal Cognitive Assessment (MoCA); Addenbrooke's Cognitive Examination (ACE-III). The multidisciplinary team gave an independent diagnostic formulation. We recorded numbers fully/partially completing tests, assistance and time required for testing. We calculated test discrimination metrics in relation to clinical assessment using four differing statistical approaches to account for incomplete testing.

Results: We recruited 51 patients. Direct assistance to complete cognitive tests was required for 33 (63%). At traditional cut-offs, the majority screened "positive" for cognitive impairment (ACE-III:98%; MoCA:98%;MMSE:81%). Comparing against a clinical diagnosis, ACE-III and MoCA had excellent sensitivity but poor specificity. Partial completion of cognitive tests was common (ACE-III:14/51, MMSE:22/51; MoCA:20/51 fully complete), greatest non completion was for test items that required copying or drawing. Adapting analyses to account for these missing data gave differing results, MMSE sensitivity ranged from 0.66-0.85 and specificity ranged from 0.44-0.71 depending on the approach employed.

Conclusions: For cognitive screening in stroke, even relatively brief tools are associated with substantial incompletion. The way these missing data are accounted for in analyses impacts on apparent test properties. When choosing a

cognitive screening tool, feasibility should be considered and approaches to handling missing data made explicit.

Introduction

Specialist stroke societies and clinical guidelines recommend routine cognitive screening of all stroke survivors (Hachinski *et al* 2006). Various approaches to screening have been described but there is no consensus on the optimal assessment for use in stroke (Lees *et al* 2012). Although stroke specific assessments are available (Demeyere *et al* 2015), most centres still use tools developed for non-stroke settings: Folstein's Mini Mental State Examination (MMSE) (Folstein *et al* 1975); the Montreal Cognitive Assessment (MoCA) (Nasreddine *et al* 2005); and iterations of the Addenbrooke's Cognitive Examination (ACE) (Crawford *et al* 2012).

Each of these tools has advantages and limitations. MMSE has traditionally been the favoured assessment for hospital and research work and there is considerable experience with this test (Creavin *et al* 2016). However, MMSE is perceived to provide limited assessment of executive problems (Dong et al 2010) and copyright limits its use. MoCA is recommended for vascular cognitive impairment (Hachinski et al 2006), however MoCA thresholds were derived to assess for mild cognitive impairment in community dwelling older adults and may need to be revised in stroke settings (Davis et al 2015). The current, third, revision of ACE (ACE-III) provides comprehensive assessment but experience is limited particularly in stroke (Hsieh et al 2013). None of these tests were specifically designed for use with a stroke population

Systematic review describing cognitive assessment tools in stroke suggests that accuracy of most multi-domain screening assessments is similar and so choice of test should be guided by other factors such as feasibility and test burden (Lees *et al* 2014a). Feasibility is a particular concern in stroke, as standard "pencil and paper" type assessments may be compromised by clinical issues such as: aphasia; concomitant medical illness and physical or sensory impairments.

There is no consensus on how to interpret results when clinical impairments preclude test completion (Pendlebury *et al* 2015). In some studies, patients unable to complete full cognitive testing have been excluded, or test scores have been adapted. The methods used to handle such missing data may impact on the validity of results. There is an emerging literature in diagnostics around incorporating non-completed results into test accuracy, but the use of "intention to diagnose" has not hitherto been described in the context of cognitive assessment in stroke (Scheutz *et al* 2012)

Methods

Our aims were to describe the feasibility of three cognitive screening tools, ACE-III, MMSE and MoCA, in a stroke rehabilitation setting and to explore the effects of failed test completion on the interpretation of their results. Specifically we tested the effect of four different approaches to scoring test data when some or all items were not completed.

We followed conduct and reporting standards for cognitive test accuracy studies (STARDdem) (Noel-Storr *et al* 2014). The study had approvals from National Research Ethics Scotland (14/SS/0042).

Setting: We recruited from two University Hospital stroke rehabilitation units. Both sites operate similar care pathways, with patients first admitted to the acute stroke unit and subsequent transfer to the rehabilitation site if patients have persisting impairments but are otherwise medically stable.

Population: We included consenting adult patients with confirmed diagnosis of stroke. Where capacity to consent was impaired we approached a relative or carer. We recruited participants at a minimum of two weeks post stroke event. We operated few exclusion criteria but did not approach those patients where the clinical team felt that any attempt at cognitive assessment was inappropriate. We assessed for concomitant issues of depression and delirium but did not exclude patients based on results of these tests.

Screening assessments: Core assessments were ACE-III, MMSE, and MoCA, performed by two psychology graduates (RAL, KH) fully trained in use of the scales. We used standard cut-points to define "screen positivity" (ACE-III<88/100; MMSE<27/30; MoCA<26/30). We also used alternative cut-offs that may be more suited to stroke populations (ACE-III<82; MMSE<24/30; MoCA<22/30) (Lees *et al* 2014a). Tests were administered using pencil and paper and standard assessment

paperwork with researchers offering verbal instruction in the first instance and further assistance as required. If participants were unable to complete any part of the test on first assessment they were approached a second time at least one week later. We assessed for delirium using the Confusion Assessment Method (CAM) (Inouye *et al* 1990), and depression using the Patient Health Questionnaire (PHQ) (Spitzer *et al* 1999).

Clinical assessment: Our reference standard was multidisciplinary team assessment of cognition. The final formulation was made by an experienced consultant in Geriatric Medicine informed by clinical psychology and occupational therapy assessments. The classification of post stroke cognitive impairment was based on current recommendations and required multi-domain cognitive problems that impact on function (Brainin *et al* 2015). Recognising that assessing the functional impact of cognition can be difficult while still inpatient, we operationalised "clinically significant" impairments as interfering with rehabilitation or discharge. Results of research study test scores were not shared with the clinical team as standard, although could be disclosed on request. The researchers performing screening assessments and analyses did not have access to the clinical team's diagnostic formulations.

Process: We kept a log of all admissions. We extracted basic demographic and clinical details from patient case notes and recorded details on a standardised proforma. We included details on previous diagnosis of dementia or mood disorder, and presence of visual or hearing impairments (which are assessed by the clinical

team at time of admission). We described initial (admission to acute stroke unit) stroke severity using National Institutes of Health Stroke Scale (NIHSS) (Brott *et al* 1989).

Order of test administration and researcher administering the tests alternated between patients. With three tests, there were six different potential orderings of test administration; these were changed from patient to patient according to a pre-specified schedule. Choice of first test administrator was based on simple coin toss and then alternated for sequential patients. We split the assessments across a minimum of two sessions on separate days to reduce patient burden and fatigue.

Outcomes: We recorded numbers of patients admitted to each stroke rehabilitation unit, numbers eligible for the study, and numbers that completed each test (total test and individual components). Time taken for test administration was recorded using a stopwatch. We recorded impairments that complicated test completion and whether the researcher had to provide direct assistance. Where a patient required some assistance but was still able to complete the test this was recorded as test completed.

Analyses: We compared proportions completing each test, proportions "screen positive" on each test at the various cut-offs, and time taken to administer tests using chi-square and ANOVA tests.

We described test accuracy of each test against the multidisciplinary teams' clinical reference standard diagnosis using four differing approaches that account for partially or entirely incomplete tests.(Table 1)

Results

From August 2014 to February 2015 inclusive, 86 patients were admitted to the stroke rehabilitation units, 75 (87%) were eligible for our study and we recruited n=51 (68% of eligible).(Figure 1). Median age of included patients was 74 years (IQR:67-84); 28 (55%) were female and median NIHSS was 9 (IQR:6-13). Eighteen patients (35%) were classified as total anterior circulation strokes (TACS) and 39 (76%) were ischaemic. Median time since stroke was 36 days (IQR:20-55). Eight (16%) patients had delirium by CAM criteria at time of testing; four (8%) had a recorded diagnosis of dementia prior to their stroke. Six (12%) had pre-stroke depression, and median score on PHQ was 5 (IQR:3-10, range:0-24). Ten patients (20%) had pre-stroke hearing or visual impairments.

There was a difference in time to complete individual cognitive tests ($p<0.001$), with median time to complete ACE-III:18 minutes (IQR:15-22, range:10-35); MMSE:5 minutes (IQR:5-6, range:3-20); and MoCA:9.5 minutes (IQR:7-11, range:6-20) (Table 2). Of included patients, 33 (65%) had impairments that complicated assessments and required direct assistance from researchers. We recorded a variety of impairments, the most common were motor weakness (for example patient unable to write for "pen and paper" type assessments) and communication problems (usually due to aphasia).(Figure 1).

Partial completion of cognitive tests was common (ACE-III:14/51, MMSE:22/51; MoCA:20/51 fully complete). Examining specific cognitive test domains, in those tests where at least one item was completed, the greatest non completion rate was for test items that required copying or drawing (intersecting pentagons from MMSE not completed in 9 tests; visuospatial/executive items from MoCA not completed in 11 tests; and visuospatial items from ACE-III not completed in 11 tests).

We described the comparative accuracy of the various tests. We compared against a gold standard of multidisciplinary team assessment, but would emphasise that the test used are not suitable for making a diagnosis of dementia on their own. Using "traditional" cut-offs and analyses, the majority of patients screened with ACE-III, MMSE and MoCA had results consistent with cognitive impairment ("screen positive" in 98%,81% and 98% respectively). Altering the cut-offs to those suggested as more appropriate for stroke (Lees *et al* 2014a) resulted in fewer "screen positives".(Table 2)

Final MDT criterion diagnostic formulation identified post stroke cognitive impairment in 27 patients (53%). Assessing screening tests against the MDT diagnostic formulation, ACE-III and MoCA were sensitive but not specific. Test accuracy values varied depending on the approach used for handling missing data.(Table 2)

Discussion

In this study we examined the feasibility of using short cognitive screening tests in a stroke rehabilitation population. Even with dedicated researchers and approvals to allow proxy consent we were still only able to recruit around two thirds of eligible stroke patients into this study, and of those recruited another two thirds had impairments that impacted on completion of cognitive screening tests. These impairments were a mix of stroke related issues and pre-existing problems. Time taken to complete the cognitive tests was similar to that quoted for non-stroke settings, but many subjects needed assistance to complete the tests (Woodford and George 2007). In this study we had dedicated and trained research staff, and we recognise that feasibility of using these tests may be less still if administered by busy clinical staff.

We used our dataset to investigate the implications of four different approaches to handling missing cognitive test data. Depending on the approach, the prevalence of "screen positives" and the properties of the tests could vary substantially. This was particularly evident for MMSE as the other tools had extreme values for sensitivity/specificity.

There are many multi-domain cognitive screening tools available (Lees *et al* 2012). We choose those tests that are most popular in stroke care in the UK. The ideal would have been to compare more than three tests, but we were mindful of patient test burden, particularly in a study designed to assess feasibility. Shorter cognitive

screens, such as the four question abbreviated mental test are available (Schofield *et al* 2010) and are popular in time limited situations such as acute stroke (Lees *et al* 2013). The purpose of these very brief screens is more around early triage than informing an assessment of cognitive impairments.

We chose a reference standard that we felt was best suited to the rehabilitation setting and which recognises the difficulties of making a clinical dementia diagnosis in the early to medium term following stroke. Our reference standard was multidisciplinary assessment by an experienced team. This remains the ideal assessment modality and was possible in this rehabilitation unit based study. Unfortunately the increasingly fast pace of acute stroke care with a focus on early discharge from secondary care precludes this form of multidisciplinary assessment for many people affected by stroke. This is particularly true for those with minor physical impairments, who tend to be managed as outpatients or with short hospital stays, but who often have persisting cognitive issues (Pendlebury *et al* 2011).

The strengths of our study include a “real world” approach, attempting to include all patients where the clinical team felt an attempt at assessment was indicated. By gaining approvals to include patients lacking capacity to consent, we had access to a population that is not biased by exclusion of those with potential major cognitive issues.

There are limitations in our approach. We chose to assess a patient population of stroke survivors requiring inpatient rehabilitation. Although this limits external generalisability to other stroke groups, this group is suited to a study of feasibility. If cognitive testing strategies are feasible in a population with substantial impairments, they should be feasible in any group of stroke survivors. We required patients or their proxy to provide consent to testing and this may have biased the sample, particularly around feasibility. The sample size was modest. We did not pre-specify a sample size since one of the metrics of interest was feasibility of recruitment to a cognitive study over a fixed time period. To limit test burden we spread assessment over at least two sessions. This may have impacted on the between study variability, particularly in the context of delirium (16% in this study).

Our study adds to the limited, but growing, literature on feasibility of cognitive testing in stroke (Lees *et al* 2014b). Completion rates of 68%-80% (Cumming *et al* 2011) for MoCA have been reported in acute stroke (Horstmann *et al* 2014). The differences may relate to differing case-mix. Where MoCA completion rates were assessed as part of an acute rehabilitation study programme, overall completion rates were reasonable (75%) but rates were low in those with more severe stroke at baseline (67%) (Pasi *et al* 2013). When testing is either partially or entirely incomplete, it is common to exclude these data. This approach can lead to biased results (Wall *et al* 2015)

Our study highlights a number of important evidence gaps in the application and interpretation of cognitive screening tests in stroke. Examples of fundamental issues

that need further research include, how early after stroke should cognitive screening be performed; which tests should be used, and is a universal screening policy preferable to modifying the screening test used in relation to patient impairments.

There is no ideal cognitive screening tool, and choice of assessment instrument should be guided by the purpose of the test, feasibility and acceptability. It is interesting that the MMSE, a tool which is becoming less popular in stroke due to perceived lack of utility (ceiling effects, focus on memory), was quickest to complete; had highest Youden index and had the most balanced trade-off between sensitivity and specificity at chosen scoring threshold. MoCA and ACE-III, tests developed primarily for assessment of mild cognitive impairment, were sensitive but had poor specificity (Table 2).

Conclusions (Recommendations for clinical practice and research)

Contemporary practice in stroke medicine pharmacotherapy is based on a robust evidence of randomised controlled trials and meta-analyses (McArthur *et al* 2011,Brainin *et al* 2015). We have highlighted potential limitations in contemporary guidance around neuropsychological assessment. Our findings of potential poor feasibility and differential results dependant on analysis method, have implications for practice, policy and research.

Our results need to be considered in the context of health-care policy that suggests "universal" cognitive screening. There are problems with using cognitive screening tools developed for use with community dwelling older adults in a stroke population with high prevalence of physical, mood and cognitive problems. In choosing a cognitive assessment, feasibility needs to be considered along with classical test properties such as accuracy.

In our cohort, most patients required assistance to complete the screening tests and even with these relatively short screening instruments there was still substantial non completion.

Screening stroke inpatients with MoCA or ACE-III at traditional diagnostic cut-offs may not have particular clinical utility as almost all patients will screen positive. If the purpose of testing is to define a level of impairment that impacts on rehabilitation then thresholds should be adjusted.

We would not propose abandoning brief cognitive screens in stroke settings, but it is important that users of these tests appreciate the clinical “meaning” of the test results. We propose a stepped approach that uses very brief tests and clinical assessment to triage into categories of: unlikely to have important cognitive impairments but keep under review; may have important cognitive issues and needs further assessment; severe stroke, likely to have cognitive issues and unlikely to be able to complete testing therefore modify approach accordingly. The multi-domain screening tools assessed in this paper could be reserved for those in the middle category.

As cognitive testing becomes a standard part of acute stroke care and assessment, as recommended in various guidelines and in keeping with a general move in secondary care to improve early diagnosis of cognitive issues, we would encourage further research around feasibility and acceptability metrics as well as traditional test accuracy measures. Feasibility of testing cognitive impairment in different patient groups should also be encouraged.

In clinical practice, audit, and in research studies that use cognitive assessments there needs to be a priori planning for how missing cognitive data are handled. Whatever approach is chosen, this needs to be made explicit in protocols and study related publications. To allow comparisons between studies it is important that the research community is consistent in the approach used.

Our data do not suggest that any of the proposed approaches to handling missing cognitive test data is superior in terms of correct classification. We would recommend the approach to cognitive test scoring that makes greatest use of available data (i.e. where all incomplete test items are scored as “zero”, described as approach four in this paper, the most inclusive approach). Further work exploring the implications of various approaches to missing data is warranted and data from existing trial registries could be used in this regard.

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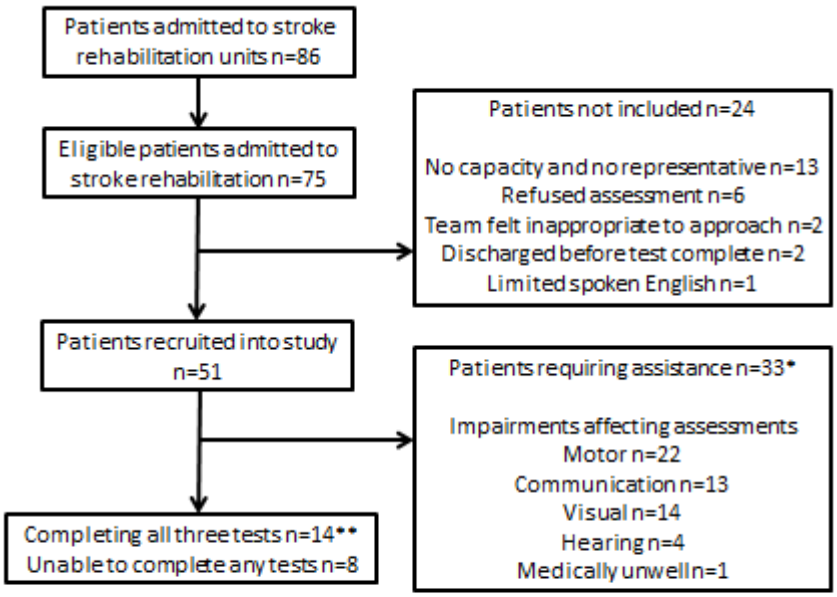
Figure 1 Recruitment Flow Chart



Flow chart detailing numbers of patients admitted to two stroke rehabilitation and numbers completing cognitive tests.

* Some participants had more than one impairment affecting assessment

** Some patients who required assistance were able to complete tests; some patients not completing tests did not require direct assessor assistance

Table 1. Four Approaches To Scoring Tests When Data Are Incomplete

The figure gives a theoretical example of how differing approaches to handling missing data can impact on results. We use the Montreal Cognitive Assessment (MoCA) and present test score for each of the individual test domains. Assuming five patients with differing impairments were administered the MoCA, scores for individual items are presented (white boxes) in the columns labelled “Patient 1-4”.

In the grey fill boxes we present the total MoCA score, sum of individual item scores, modified by the approach to missing data. We include examples of entirely incomplete (Patient 3) and partially incomplete (Patients 4 and 5) test data. These scores are chosen to illustrate the potential effect of differing approaches to scoring missing test data on proportion of patients tested who are “screening test positive”.

MoCA domain	Patient 1	Patient 2	Patient 3	Patient 4	Patient 5	
Visuospatial/executive (maximum score 5)	4	2	unable to complete	unable to complete	2	
Naming (maximum score 3)	3	3	unable to complete	3	unable to complete	
Attention (maximum score 6)	6	4	unable to complete	4	4	
Language (maximum score 3)	2	2	unable to complete	2	unable to complete	
Abstraction (maximum score 2)	2	2	unable to complete	2	2	
Recall (maximum score 5)	4	3	unable to complete	5	3	
Orientation (maximum score 6)	6	3	unable to complete	5	3	
						Proportion “test positive”
Total score (Approach 1)	27/30	19/30	not included	22/30	14/30	3/4 (75%)
Total score (Approach 2)	27/30	19/30	not included	22/25	14/22	2/4 (50%)
Total score (Approach 3)	27/30	19/30	not included	not included	not included	1/2 (50%)
Total score (Approach 4)	27/30	19/30	00/30	22/30	14/30	4/5 (80%)

Approach 1: Excluding those patients whose testing was entirely incomplete, and assigning a score of zero to partially completed items.

Approach 2: Excluding those patients whose testing was entirely incomplete, and for patients whose testing was partially incomplete adapting the total test score and threshold by excluding non-completed items from the total score.

Approach 3: Excluding all patients with either entirely or partially incomplete testing, i.e. only including those patients with fully completed tests (the most restrictive approach).

Approach 4: Including all patients but assigning a minimum value (usually zero) to any incomplete items, hence giving a total score of 0 where testing was entirely incomplete (the most inclusive approach).

Table 2. Accuracy of Cognitive Screening Tools

Measures of discrimination (with 95% confidence intervals) of cognitive screening tools, using adapted thresholds suggested for stroke, against a clinical reference of cognitive impairment, using four differing approaches to account for entirely or partially incomplete cognitive test data.

		Approach 1	Approach 2	Approach 3	Approach 4
ACE-III < 82/100	**CCR**	0.49	0.47	0.67	0.54
	Youden index	-0.08	-0.09	0.04	-0.05
	Sens	0.87 (0.66-0.97)	0.81 (0.59-0.95)	0.93 (0.66-1.00)	0.90 (0.73-0.98)
	Spec	0.05 (0.01-0.25)	0.10 (0.01-0.31)	0.11 (0.01-0.35)	0.05 (0.01-0.22)
	PPV	0.52 (0.35-0.68)	0.48 (0.32-0.66)	0.45 (0.26-0.64)	0.56 (0.41-0.71)
	NPV	0.25 (0.01-0.81)	0.33 (0.04-0.78)	0.67 (0.09-0.99)	0.25 (0.01-0.81)
MMSE < 24/30	**CCR**	0.64	0.69	0.67	0.64
	Youden index	0.30	0.37	0.34	0.29
	Sens	0.78 (0.52-0.94)	0.66 (0.40-0.86)	0.71 (0.42-0.92)	0.85 (0.65-0.96)
	Spec	0.52 (0.30-0.74)	0.71 (0.48-0.89)	0.63 (0.35-0.85)	0.44 (0.24-0.65)
	PPV	0.58 (0.37-0.78)	0.67 (0.41-0.87)	0.63 (0.35-0.85)	0.61 (0.43-0.77)
	NPV	0.73 (0.45-0.92)	0.71 (0.48-0.89)	0.71 (0.42-0.92)	0.73 (0.45-0.92)
MoCA < 22/30	**CCR**	0.47	0.51	0.55	0.53
	Youden index	0.05	0.15	0.14	0.04
	Sens	1.00 (0.80-1.00)	1.00 (0.80-1.00)	1.00 (0.75-1.00)	1.00 (0.87-1.00)
	Spec	0.05 (0.01-0.24)	0.15 (0.03-0.37)	0.14 (0.01-0.43)	0.04 (0.01-0.20)
	PPV	0.46 (0.29-0.63)	0.47 (0.27-0.67)	0.52 (0.31-0.72)	0.52 (0.37-0.66)
	NPV	1.00 (0.03-1.00)	1.00 (0.29-1.00)	1.00 (0.15-1.00)	1.00 (0.03-1.00)

See Table 1 for further details on definition of each approach

CCR=Correct Classification Rate

PPV/NPV=positive / negative predictive values