Assessment with Cognitive Screening Instruments

4

Contents

Abstract

This chapter examines the screening utility of selected cognitive screening instruments, including both multidomain and specific/single domain instruments, which have been examined in the author's clinic for the assessment of cognitive complaints.

Keywords

Dementia · Diagnosis · Cognitive screening instruments

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In addition to the standard clinical methods of history taking, including use of single item cognitive screening questions, and neurological examination (see Chap. 3), a large number of cognitive screening instruments (CSIs) or assessment tools has become available to assist in the diagnosis of patients with cognitive complaints (for compendia, see for example Burns et al. 2004; Tate 2010; Larner 2013a, 2017a; Carnero Pardo 2015). These have superseded the qualitative methods of earlier times, for example fixing the year at a much earlier date than it actually is being taken as evidence for disorientation in time (Allison 1962:175). However, it is the history and examination which set the context for the use of cognitive screening instruments and in light of which the results of the latter should be interpreted.

The available screening instruments encompass not only cognitive but also behavioural, psychiatric, and functional scales (see Chap. 5). Neuroimaging and other investigation techniques may also be required for adequate patient assessment and diagnosis (see Chap. 7). Application of consensus diagnostic criteria for dementia or dementia subtype (see Chap. 2, Box 2.1) usually presupposes the use of at least some of these investigations, and although the diagnostic utility of such criteria is generally found to be good, they may sometimes mislead if there are atypical clinical features which fall outwith the criteria or are deemed exclusionary, for example an apparently acute onset of neurodegenerative disease (Larner 2005a), or epileptic seizures early in the course of Alzheimer's disease (Lozsadi and Larner 2006; see Sect. 8.2.3).

The assessment of cognitive function may be undertaken in various ways (Larner 2018a). Formal neuropsychological assessment by a neuropsychologist may be the "gold standard" but these resources are not universally available and such assessment, usually encompassing tests of intelligence such as the Wechsler Intelligence Scale and potentially many other tests (Mitrushina et al. 2005; Strauss et al. 2006; Lezak et al. 2012), is often time-consuming and fatiguing for patients, sometimes requiring multiple outpatient visits. Hence, although these are either necessary or desirable in some cases of cognitive disorder, tests which are applicable by clinicians within the clinic room are more often indicated. These so called "bedside" neuropsychological tests or "near patient testing" (i.e. results available without reference to a laboratory and rapidly enough to affect immediate patient management; Delaney et al. 1999:824), are quick and easy to administer, score, and interpret.

Many such cognitive screening instruments (CSIs) are available (Burns et al. 2004; Hatfield et al. 2009; Tate 2010; Larner 2013a, 2017a; Carnero Pardo 2015; Olazaran et al. 2016). No particular consensus on their use has emerged (Maruta et al. 2011), and clinician preferences differ (e.g. Ismail et al. 2013). CSIs may be evaluated on theoretical (Cullen et al. 2007) or pragmatic (Woodford and George 2007) grounds, but the proof of the pudding is in the eating, meaning that empirical evaluation of these instruments in the clinical setting (i.e. pragmatic diagnostic test accuracy studies; see Sect. 2.4) must be undertaken. Clearly, only a small selection of the many CSIs potentially available can be sampled in any one clinic. A number of desiderata for CSI have been formulated (Malloy et al. 1997; Larner 2017b; see Box 4.1).

Box 4.1 Desiderata for Cognitive Screening Instruments (After Malloy et al. 1997; Larner 2017b)

- Ideally should take <15 min to administer by a clinician at any level of training.
- Ideally should sample all major cognitive domains, including memory, attention/concentration, executive function, visual-spatial perceptual skills, language, and orientation.
- Should be reliable, with adequate test-retest and inter-rater validity.
- Should be able to detect commonly encountered cognitive disorders.
- Should be easy to administer, i.e. not much equipment required beyond pencil and paper, or laptop computer.
- Should be easy to interpret, i.e. clear test cut-offs, perhaps operationalised, e.g. a particular score on the test should lead to particular actions, such as patient reassurance, continued monitoring of cognitive function over specified time periods, or immediate initiation of further investigations and/or treatment.
- Possibility for repeated, longitudinal use (e.g. variant forms, availability of reliable change indices).

As previously discussed (see Sect. 2.3.2), CSIs with high sensitivity may be particularly desirable, at the risk of false positives, in order to identify as many mild cases as possible (i.e. those with mild cognitive impairment [MCI] or prodromal Alzheimer's disease [AD]) in order to initiate treatment and management strategies early in the disease course.

CSIs may be broadly classified according to whether they test general (multidomain) or specific cognitive functions (Mitchell and Malladi 2010a, b; Tate 2010). CSIs which attempt broad, multidomain, sampling (see Sect. 4.1) include the Mini-Mental State Examination (MMSE), Mini-Mental Parkinson, the Addenbrooke's Cognitive Examination (ACE) and its iterations, DemTect, the Montreal Cognitive Assessment (MoCA), and the Test Your Memory (TYM) test (see Sects. 4.1.1, 4.1.2, 4.1.5, 4.1.7, 4.1.8, and 4.1.9 respectively). Brown (2015) has suggested short cognitive screening instruments be classified as short questionnaires (e.g. Six-item Cognitive Impairment Test; see Sect. 4.1.6), highly selective tests (e.g. Clock Drawing Test [see Sect. 4.1.3], General Practitioner Assessment of Cognition), and multidomain tests (e.g. MMSE, MoCA, ACE, TYM). Generally, the more comprehensive the neuropsychological coverage of a test, the longer it takes to administer, although the Clock Drawing Test (see Sect. 4.3) may be an exception.

Although falling outwith some desiderata for CSIs (Box 4.1), tests which are restricted to the examination of specific cognitive functions may nonetheless have a place in patient assessment (Mitchell and Malladi 2010b). For example, since episodic memory impairment is typically the earliest deficit manifest in AD patients, tests for anterograde amnesia may be appropriate if this diagnosis is suspected clinically, such as the Memory Impairment Screen (Buschke et al. 1999), the Free and

Cued Selective Reminding Test (Grober and Buschke 1987), the Five Words Test (Dubois et al. 2002), and the Visual Association Test (Lindeboom et al. 2002). Similarly, there are tests specifically sensitive to executive function, such as the Frontal Assessment Battery (see Sect. 4.2.1), and to visuoperceptual function, such as the Poppelreuter (overlapping) figure (see Sect. 4.2.3).

It is important to emphasize that CSIs are not stand-alone diagnostic measures. In patients whose performance falls below designated cut-offs consideration needs to be given as to whether further investigations are required to ascertain a cause for the apparent cognitive impairment. Impaired performance on CSIs may result from a number of variables beside disease state, including affective disorder (depression; anxiety, e.g. Larner and Doran 2002), sleep disturbance, low premorbid abilities, medication use, and economy of effort (be that disease-related, subconscious, or wilful as in malingering). Some of these non-cognitive factors may also need to be assessed, formally or informally, during the clinical encounter (see Chap. 5 for screening instruments for depression and sleep disturbance). It is also important to emphasize that qualitative clinician-patient interaction during the administration of CSIs may inform clinical judgements over and above any raw test scores, and it is for this reason that collaborative multi-agency judgements ("diagnosis by committee"), though advocated in some models of service (Banerjee et al. 2007), does, in this author's opinion, present possible risks.

4.1 Multidomain Cognitive Screening Instruments

4.1.1 Mini-Mental State Examination (MMSE)

The Mini-Mental State Examination (MMSE; Folstein et al. 1975) has been the most commonly used bedside test of cognition, with more than 40 years of cumulative experience of its use, as a consequence of which it is often regarded as a benchmark against which newer CSIs are measured (Mitchell 2017).

The MMSE was originally designed to differentiate organic from functional disorders in psychiatric practice, and as a quantitative measure of cognitive impairment useful in monitoring change, but not primarily as a diagnostic tool. However, it has proved acceptable and useful in the assessment of cognitive status in general medical and neurological patients (e.g. Dick et al. 1984; Tangalos et al. 1996; Ridha and Rossor 2005) and has become the most widely used brief cognitive assessment. Surely no other medical investigation can claim to have been memorialised in a sonnet (by Rafael Campo; see Levin, 2001:334), as well as appearing in other literary works (e.g. Healey 2015:154–6). The enforcement of copyright restrictions on the use of the MMSE in recent years may adversely impact on its future use (Newman and Feldman 2011; Seshadri and Mazi-Kotwal 2012; Carnero-Pardo 2014).

MMSE has good intra- and inter-rater reliability and internal consistency, although debate continues about interpretation and appropriate cut-off scores (Tombaugh and McIntyre 1992; Nieuwenhuis-Mark 2010). Patient age and years of education influence MMSE scores, norms for which may be factored into the cut-offs (Crum et al. 1993) although this is seldom done in practice. Meta-analysis of MMSE diagnostic validity studies in dementia indicates that it performs best in a

rule-out (screening) capacity (see Sect. 2.3.2), consistent with its high specificity, but is of more limited value for identification of MCI (Mitchell 2017).

MMSE may also be useful in tracking cognitive decline in AD (Han et al. 2000), falling on average by three points per year, although there is variability, with some untreated patients remaining stable or even improving (Holmes and Lovestone 2003). In the UK, the MMSE has been the required instrument for monitoring the efficacy of treatment with cholinesterase inhibitors for AD (National Institute for Clinical Excellence 2001), even though there is evidence to suggest that it is unsuitable for this purpose (Bowie et al. 1999; Holmes and Lovestone 2003; Davey and Jamieson 2004; see Sect. 10.2.1).

As the item content shows (Box 4.2), MMSE is dominated by language based tests and is perfunctory in its testing of memory, visuoperceptual and executive functions.

Analyses have shown that certain MMSE items are statistically significant predictors of the diagnosis of AD (especially recall memory and orientation to place, with, in decreasing order of significance, copying pentagons, failed serial 7s, and orientation to time) whilst other items (registration, naming, repetition, three-step verbal command, written command, writing a sentence) are only weak predictors (Galasko et al. 1990). An examination of the factorial structure of the MMSE found most of the variance to be accounted for by the orientation in time, delayed recall, attention/concentration, and copying pentagons tasks, with measures of comprehension (three-step command, written command) showing low sensitivity with performance often at ceiling (Brugnolo et al. 2009). The attention/concentration items (serial 7s or spelling WORLD backwards) differ in item difficulty (serial sevens more difficult) and scores are weakly correlated (Ganguli et al. 1990). The language repetition item is often failed by healthy adults, possibly related to poor hearing or attention (Valcour et al. 2002), and it is difficult to translate into other languages (Werner et al. 1999). A number of short MMSE variants have been developed which attempt to exploit these various observations by using only those MMSE elements with high predictive value (Larner 2017c).

Box 4.2 Item Content of Mini-Mental State Examination (MMSE)

Orientation	10
Registration	3
Attention/Concentration (serial 7s or DLROW)	5
Memory recall	3
Language naming	2
Language comprehension:	
“Close your eyes”	1
3 stage command	3
Language writing	1
Language repetition	1
Visuospatial abilities (intersecting pentagons)	1
Total score	**30**

The diagnostic utility of MMSE for the diagnosis of dementia and cognitive impairment in day-to-day clinical practice has been examined in several separate studies in the Cognitive Function Clinic (CFC) at the Walton Centre for Neurology and Neurosurgery (WCNN) in Liverpool (Abdel-Aziz and Larner 2015; Hancock and Larner 2009, 2011; Larner 2005b, 2009a, b, 2012a, b, 2013b, 2015a, b, c). Data from some of these studies are presented here. Most examined MMSE for diagnosis of dementia, but some also looked specifically at MCI (Larner 2016a).

In a study of the Addenbrooke's Cognitive Examination (Mathuranath et al. 2000; see Sect. 4.1.5.1), which incorporates the MMSE (Larner 2005b), MMSE diagnostic utility was investigated at cut-offs of ≥27/30 and ≥24/30 (Table 4.1), with results comparable to those found for the MMSE in other studies of the ACE (Mathuranath et al. 2000; Bier et al. 2004).

In a study of the Addenbrooke's Cognitive Examination-Revised (ACE-R) which also incorporates the MMSE (Mioshi et al. 2006; see Sect. 4.1.5.3), the sensitivity and specificity of the MMSE for cross-sectional use was examined at all cut-off values, with the optimal cut-off being defined by maximal test accuracy for the differential diagnosis of dementia/not dementia. The optimal accuracy of MMSE was

Table 4.1 Demographic and diagnostic parameters for MMSE for diagnosis of dementia (adapted from Larner 2005b)

	MMSE	
N	154	
F:M (% female)	67:87 (43.5)	
Age range (years)	25–84	
Prevalence of dementia (= pre-test probability)	0.51	
Pre-test odds = prevalence/(1 – prevalence)	1.04	
Cut-off	**≥27/30**	**≥24/30**
Accuracy	0.81 (0.74–0.87)	0.79 (0.73–0.86)
Net Reclassification Improvement (NRI)	0.30	0.28
Sensitivity (Se)	0.91 (0.84–0.97)	0.73 (0.63–0.83)
Specificity (Sp)	0.70 (0.60–0.80)	0.86 (0.78–0.94)
Y	0.61	0.59
PPV (= post-test probability)	0.75 (0.66–0.84)	0.84 (0.75–0.92)
NPV	0.88 (0.81–0.97)	0.76 (0.67–0.85)
PSI	0.63	0.60
LR+	3.04 (2.14–4.31) = small	5.09 (2.90–8.95) = moderate
LR−	0.13 (0.09–0.18) = moderate	0.32 (0.18–0.56) = small
DOR	23.5 (16.6–33.3)	16.0 (9.10–28.1)
Post-test odds (= pre-test odds × LR+)	3.16	5.30
CUI+	0.68 (good)	0.61 (adequate)
CUI−	0.62 (adequate)	0.65 (good)
AUC ROC curve	0.88 (0.83–0.94)	

Table 4.2 Demographic and diagnostic parameters for MMSE for diagnosis of dementia (adapted from Larner 2009a, b, 2013b)

	MMSE
N	242
F:M (% female)	108:134 (44.6)
Age range (years)	24–85 (mean 59.8 ± 10.9)
Prevalence of dementia (= pre-test probability)	0.35
Pre-test odds = prevalence/(1 – prevalence)	0.54
Cut-off	**≥24/30**
Accuracy	0.82 (0.77–0.87)
Net Reclassification Improvement (NRI)	0.47
Sensitivity (Se)	0.70 (0.60–0.80)
Specificity (Sp)	0.89 (0.84–0.94)
Y	0.59
PPV (= post-test probability)	0.77 (0.67–0.86)
NPV	0.85 (0.79–0.90)
PSI	0.62
LR+	6.17 (3.91–9.73) = moderate
LR−	0.34 (0.21–0.53) = small
DOR	18.4 (11.6–29.0)
Post-test odds (= pre-test odds × LR+)	3.32
CUI+	0.54 (adequate)
CUI−	0.76 (good)
AUC ROC curve	0.91 (0.88–0.95)

found to be 0.82 at a cut-off of ≥24/100 (this optimized cut-off was similar to that reported in other studies of MMSE, e.g. Feher et al. 1992, and as originally recommended by Folstein et al. 1975). The various parameters of diagnostic accuracy were then calculated at this cut-off (Table 4.2; Larner 2009a, b, 2013b), and proved to be similar to those found at the same cut-off in the ACE study (Larner 2005b), namely sensitivities and specificities around 0.7–0.9, PPV around 0.7–0.8, with LRs moderate to small, and CUIs good to adequate.

In a study of the Test Your Memory (TYM) test (Brown et al. 2009; see Sect. 4.1.9) the results for concurrently administered MMSE ($n = 210$) showed sensitivity and specificity that were somewhat better than found in previous studies (Hancock and Larner 2011; Table 4.3), perhaps related to the casemix which was drawn from both CFC and an old age psychiatry memory clinic (the mean age for the whole study, $n = 224$, was 63.3 ± 12.6 years, a little higher than typically seen in CFC cohorts; see Sect. 1.3.1). For the group with dementia tested with the MMSE ($n = 71$), the mode, median, and mean scores were 19, 20, and 19.7 ± 4.8, respectively; for the non-demented group ($n = 139$) the mode, median, and mean MMSE scores were 30, 29, and 27.6 ± 2.8 (Fig. 4.1). The mean MMSE scores differed significantly between the two groups ($t = 15.0$, df = 208, $p < 0.001$). At the MMSE cut-off of ≤23/30, 81% of the AD/mixed dementia cases ($n = 52$ tested with MMSE) were detected, as compared to 52% in the index TYM paper (Brown et al. 2009).

Table 4.3 Demographic and diagnostic parameters for MMSE for diagnosis of dementia (adapted from Hancock and Larner 2011)

	MMSE
N	210
Prevalence of dementia (= pre-test probability)	0.34
Pre-test odds = prevalence/(1 – prevalence)	0.51
Cut-off	**≤23/30**
Accuracy	0.90 (0.85–0.94)
Net Reclassification Improvement (NRI)	0.56
Sensitivity (Se)	0.79 (0.69–0.88)
Specificity (Sp)	0.95 (0.91–0.99)
Y	0.74
PPV (= post-test probability)	0.89 (0.81–0.97)
NPV	0.90 (0.85–0.95)
PSI	0.79
LR+	15.7 (7.53–32.6) = large
LR−	0.22 (0.11–0.46) = small
DOR	70.4 (33.9–146.4)
Post-test odds (= pre-test odds × LR+)	8.09
CUI+	0.70 (good)
CUI−	0.85 (excellent)
AUC ROC curve	0.94 (0.91–0.97)

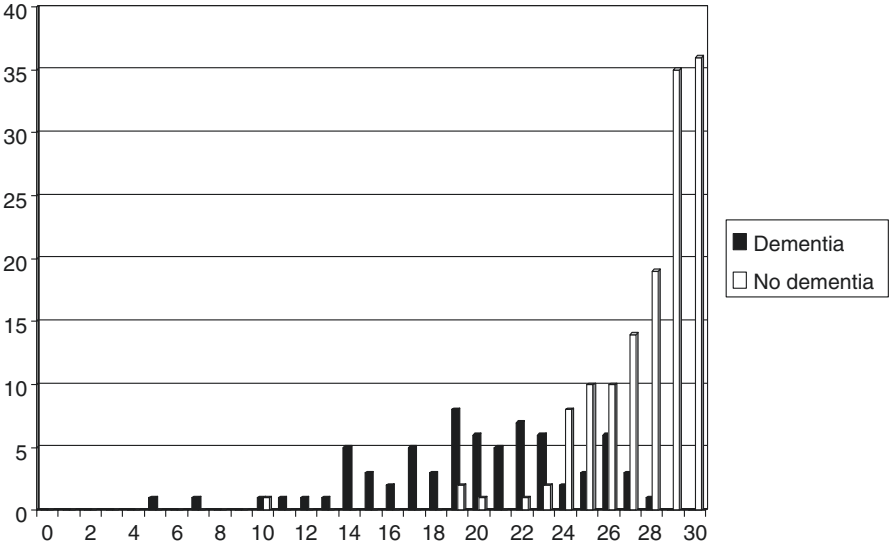

Fig. 4.1 MMSE scores vs. diagnosis (dementia/no dementia) in TYM study (adapted from Hancock and Larner 2011) reprinted with permission

Table 4.4 Demographic and diagnostic parameters for MMSE for diagnosis of any cognitive impairment (= both dementia and MCI) (adapted from Larner 2012a)

	MMSE
N	150
F:M (% female)	57:93 (38)
Age range (years)	20–87 (median 61)
Prevalence of cognitive impairment (dementia + MCI) (= pre-test probability)	0.43 (0.24 + 0.19)
Pre-test odds = prevalence/(1 – prevalence)	0.75
Cut-off	**≥26/30**
Accuracy	0.79 (0.72–0.86)
Net Reclassification Improvement (NRI)	0.36
Sensitivity (Se)	0.65 (0.53–0.77)
Specificity (Sp)	0.89 (0.83–0.96)
Y	0.54
PPV (= post-test probability)	0.82 (0.71–0.93)
NPV	0.78 (0.69–0.86)
PSI	0.60
LR+	6.15 (3.23–11.7) = moderate
LR−	0.39 (0.21–0.74) = small
DOR	15.7 (8.3–30.0)
Post-test odds (= pre-test odds × LR+)	4.64
CUI+	0.53 (adequate)
CUI−	0.69 (good)
AUC ROC curve	0.83 (0.77–0.90)

In a study of the Montreal Cognitive Assessment (MoCA) undertaken at CFC (Nasreddine et al. 2005; see Sect. 4.1.8), MMSE performance was examined for diagnosis of cognitive impairment, i.e. both dementia and MCI combined (Larner 2012a; Table 4.4). In the cognitively impaired group the mean MMSE score was 23.6 ± 3.8, and in the non-impaired group 27.7 ± 2.1. The mean MMSE scores differed significantly between the two groups ($t = 6.62$, df = 148, $p < 0.001$; Fig. 4.2). Mean MMSE scores in the demented and MCI groups were 22.2 ± 3.9 and 25.3 ± 3.1 respectively and differed significantly between the two groups ($t = 2.02$, df = 63, $p < 0.05$). Measures of discrimination for MMSE were examined at a cut-off of ≥26/30 as in the index MoCA study (Nasreddine et al. 2005). Sensitivity and specificity were more akin to those seen in earlier studies from CFC (Tables 4.1 and 4.2) than in the TYM study (Table 4.3), but this may relate to the use of a more stringent MMSE cut-off (more false negatives).

In a study of the Six-Item Cognitive Impairment Test (6CIT; Brooke and Bullock 1999; see Sect. 4.1.6) undertaken at CFC, the performance of MMSE for diagnosis of dementia versus no dementia at the cut-off of ≤22/30 showed a sensitivity of 0.59 and a specificity of 0.85 (Abdel-Aziz and Larner 2015; Table 4.5).

In a study of the AD8 (Galvin et al. 2005; see Sect. 5.4.2) undertaken at CFC (Larner 2015a), the performance of MMSE for diagnosis of dementia versus no

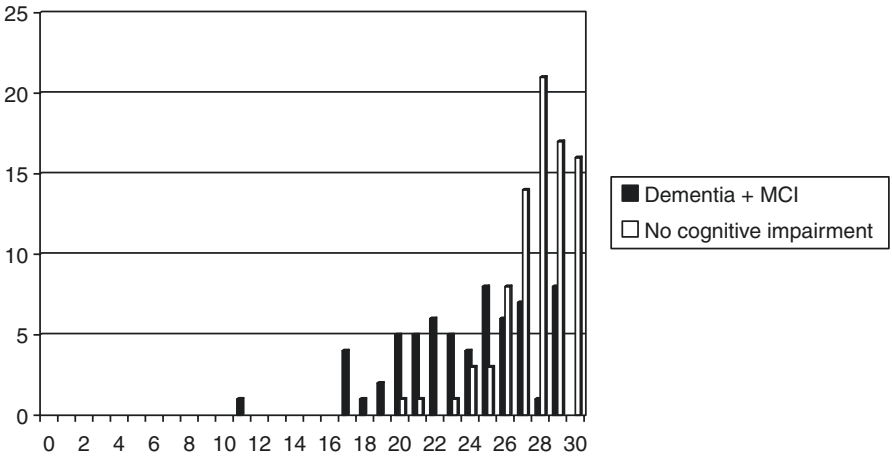

Fig. 4.2 MMSE scores vs. diagnosis (any cognitive impairment/no cognitive impairment) in MoCA study (adapted from Larner 2012a) reprinted with permission

dementia at a cut-off of ≤24/30 showed reasonable sensitivity (0.75) and specificity (0.69).

In a study of the Mini-Addenbrooke's Cognitive Examination (MACE; Hsieh et al. 2015; see Sect. 4.1.5.5), undertaken at CFC (Larner 2015b, c; data summed in Larner 2016b), MMSE (cut-off ≥26/30) had high sensitivity (0.86) and low specificity (0.64) for the diagnosis of dementia (Table 4.6), a result contrary to most of the other studies of MMSE in this clinic (and generally; Mitchell 2017) which have shown that MMSE has better specificity than sensitivity for dementia diagnosis.

The diagnostic utility of MMSE for the diagnosis of MCI in day-to-day clinical practice has also been examined in some of the aforementioned studies.

In the study of the Mini-Mental Parkinson (Mahieux et al. 1995; see Sect. 4.1.2; Larner 2012b), MMSE sensitivity for MCI was inadequate (0.32) although specificity was good (0.90) (Table 4.7). Mean MMSE scores of the MCI (24.9 ± 3.2) and non-demented non MCI groups (27.1 ± 3.2) differed significantly ($t = 3.3$, df = 152, $p < 0.01$).

In the study of the 6CIT undertaken at CFC (see Sect. 4.1.6; Abdel-Aziz and Larner 2015), the performance of MMSE for the diagnosis of MCI versus no cognitive impairment at the MMSE cut-off of ≤25/30 showed a sensitivity of 0.51 and a specificity of 0.75 (Table 4.5).

In the study of the AD8 (see Sect. 5.4.2; Larner 2015a), the performance of MMSE for diagnosis of MCI versus no cognitive impairment at a cut-off of ≤24/30 showed poor sensitivity (0.39) but reasonable specificity (0.75).

MMSE has also proved useful in individual cases seen in CFC to detect longitudinal change in cognitive performance, for example due to recurrent episodes of severe hypoglycaemia (e.g. Cox and Larner 2016; Larner et al. 2003a) and in variant forms of AD (Wojtowicz et al. 2017).

Table 4.5 Demographic and diagnostic parameters for MMSE for diagnosis of dementia and of MCI (adapted from Abdel-Aziz and Larner 2015)

	MMSE		
N	150		
F:M (% female)	69:81 (46)		
Age range (years)	23–94 (median 60.5)		
Prevalence of cognitive impairment (dementia + MCI) (= pre-test probability)	0.43 (0.15 and 0.28)		
Pre-test odds = prevalence/(1 – prevalence)	0.75		
	Diagnosis of dementia vs. no dementia	**Diagnosis of dementia vs. MCI**	**Diagnosis of MCI vs. no cognitive impairment**
N	150	65	128
MMSE cut-off	≤22/30	≤22/30	≤25/30
Accuracy	0.81 (0.75–0.88)	0.69 (0.58–0.80)	0.67 (0.59–0.75)
Net Reclassification Improvement (NRI)	0.66	N/A	N/A
Sensitivity (Se)	0.59 (0.39–0.80)	0.59 (0.39–0.80)	0.51 (0.36–0.66)
Specificity (Sp)	0.85 (0.79–0.91)	0.74 (0.61–0.87)	0.75 (0.66–0.84)
Y	0.44	0.33	0.26
PPV (= post-test probability)	0.41 (0.24–0.58)	0.54 (0.34–0.74)	0.51 (0.36–0.66)
NPV	0.92 (0.88–0.97)	0.78 (0.65–0.91)	0.75 (0.66–0.84)
PSI	0.33	0.32	0.26
LR+	3.98 (2.33–6.81) = small	2.31 (1.25–4.28) = small	2.07 (1.29–3.32) = small
LR−	0.48 (0.28–0.82) = small	0.55 (0.30–1.02) = unimportant	0.65 (0.40–1.00) = unimportant
DOR	8.29 (4.85–14.2)	4.20 (2.27–7.79)	3.19 (1.99–5.12)
Post-test odds (= pre-test odds × LR+)	3.00	N/A	N/A
CUI+	0.24 (very poor)	0.32 (very poor)	0.26 (very poor)
CUI−	0.79 (good)	0.58 (adequate)	0.57 (adequate)
AUC ROC curve	0.83 (0.74–0.92)	0.74 (0.61–0.87)	0.69 (0.60–0.79)

4.1.1.1 MMSE Ala Subscore

A number of variants and subscores derived from elements of the MMSE have been described (Larner 2017c). MMSE subscores have been suggested to help in the differential diagnosis of AD from multi-infarct dementia (Magni et al. 1996) and of AD from dementia with Lewy bodies (DLB) (Ala et al. 2002). The latter, the Ala subscore, is given by the formula:

$$\text{Ala subscore} = \text{Attention} - 5/3\left(\text{Memory}\right) + 5\left(\text{Construction}\right)$$

Table 4.6 Demographic and diagnostic parameters for MMSE for diagnosis of dementia (adapted and corrected from Larner 2015b, c, 2016b)

	MMSE
N	244
F:M (% female)	117:128 (48)
Age range (years)	18–94 (median 60)
Prevalence of dementia (= pre-test probability)	0.18
Pre-test odds = prevalence/(1 – prevalence)	0.21
Cut-off	**≥26/30**
Accuracy	0.68 (0.62–0.73)
Net Reclassification Improvement (NRI)	0.50
Sensitivity (Se)	0.86 (0.76–0.96)
Specificity (Sp)	0.64 (0.57–0.70)
Y	0.50
PPV (= post-test probability)	0.34 (0.25–0.42)
NPV	0.96 (0.92–0.99)
PSI	0.30
LR+	2.37 (1.95–2.87) = small
LR−	0.22 (0.18–0.27) = small
DOR	10.8 (8.92–13.1)
Post-test odds (= pre-test odds × LR+)	0.50
CUI+	0.29 (very poor)
CUI−	0.61 (adequate)

Table 4.7 Demographic and diagnostic parameters for MMSE for diagnosis of MCI (adapted and corrected from Larner 2012b)

	MMSE
N	154
F:M (% female)	81:93 (39.6)
Age range (years)	20–85 (median 60)
Prevalence of MCI (= pre-test probability)	0.18
Pre-test odds = prevalence/(1 – prevalence)	0.22
Cut-off	**≤22/30**
Accuracy	0.80 (0.74–0.86)
Net Reclassification Improvement (NRI)	0.62
Sensitivity (Se)	0.32 (0.15–0.49)
Specificity (Sp)	0.90 (0.85–0.96)
Y	0.22
PPV (= post-test probability)	0.43 (0.22–0.64)
NPV	0.86 (0.80–0.92)
PSI	0.29
LR+	3.37 (1.58–7.22) = small
LR−	0.75 (0.35–1.61) = unimportant
DOR	4.50 (2.10–9.63)
Post-test odds (= pre-test odds × LR+)	0.74
CUI+	0.14 (very poor)
CUI−	0.78 (good)
AUC ROC curve	0.72 (0.62–0.82)

Hence the Ala subscore may range from −5 to +10. In a small cohort of patients, an Ala subscore of <5 was associated with a pathologically confirmed diagnosis of DLB with sensitivity of 0.82 and specificity 0.81 in patients with an MMSE ≥13/30 (Ala et al. 2002).

The Ala subscore was evaluated in a prospective study of clinically diagnosed patients seen in CFC (Larner 2003, 2004). Very few patients with DLB were seen (3/271), in keeping with prior experience in this clinic (Ferran et al. 1996), local epidemiological studies (Copeland et al. 1992, 1999), and within the range of population prevalence estimates of DLB (Zaccai et al. 2005). Hence, no meaningful statement about Ala subscore sensitivity, PPV, or NPV could be made since this might involve a type II statistical error (failure to detect an effect that does exist). However, specificity and false positive rates of the Ala subscore could be calculated, 0.51 (95% CI = 0.45–0.57) and 0.49 (95% CI = 0.43–0.55) respectively, with a diagnostic odds ratio of 0.52. These figures did not encourage the view that the Ala subscore might be useful prospectively for the clinical diagnosis of DLB, although individual pathologically confirmed cases of DLB with Ala subscore <5 have been encountered in CFC (Doran and Larner 2004, case 1).

4.1.2 Mini-Mental Parkinson (MMP)

The Mini-Mental Parkinson (MMP) test is a derivative of the MMSE which was specifically devised to detect cognitive impairments in Parkinson's disease (PD; Mahieux et al. 1995). A review of studies of its use (Larner 2017c:58) identified few published to date, but these indicated the utility of MMP in detecting cognitive impairment comparing PD to PD with dementia or cognitive impairment short of dementia or in comparison with normal controls (Caslake et al. 2013). As the item content shows (Box 4.3), MMP addresses many of the shortcomings of the MMSE (in a manner similar to the ACE and ACE-R; see Sects. 4.1.5.1 and 4.1.5.3 respectively).

Box 4.3 Item Content of Mini-Mental Parkinson (MMP)

Orientation	10 (as for MMSE)
Visual registration	3
Attention	5 (as for MMSE)
Two set fluency	3
Visual recall	4
Shifting	4
Concept processing	3
Total score	**32**

In a study of MMP in newly referred patients to CFC and in patients with established PD seen in general neurology clinics (Larner 2010, 2012b), MMP scores did not correlate with patient age ($r = -0.26$). For the PD patients, there was a moderate correlation between disease duration and the modified Hoehn and Yahr (MHY) score (Hoehn and Yahr 1967; $r = 0.58$; $t = 3.39$, df = 23, $p < 0.01$), but no correlation between MMP score and disease duration ($r = 0.16$; $t = 0.80$, $p > 0.1$), or between MMP score and MHY score ($r = 0.02$; $t = 0.11$, $p > 0.5$).

In a cohort of 201 patients seen in CFC over a 12-month period (August 2009 to August 2010) and prospectively administered the MMP (Larner 2012b), the most accurate cut-off for the differentiation of dementia from no dementia was ≤17/32, at which cut-off MMP had excellent specificity, positive and negative predictive values but poor sensitivity (Table 4.8). The various parameters of diagnostic utility were comparable to the MMSE. The very high correlation between MMP and MMSE scores ($r = 0.93$; $t = 35.7$, df = 199, $p < 0.001$) suggested concurrent validity. Diagnostic agreement between tests was also high ($\kappa = 0.85$, 95% CI 0.74–0.96).

For patients with dementia ($n = 47$), median and mean MMP scores were 17 and 17.1 ± 6.4, respectively; for the non-demented group ($n = 154$) the median and mean MMP scores were 27 and 26.5 ± 4.3. For single group comparisons, the mean MMP scores differed significantly between the demented and non-demented groups ($t = 11.7$, df = 199, $p < 0.001$).

Table 4.8 Demographic and diagnostic parameters for MMP for diagnosis of dementia (adapted from Larner 2010, 2012b)

	MMP
N	201
F:M (% female)	86:115 (42.7)
Age range (years)	20–86 (median 62)
Prevalence of dementia (= pre-test probability)	0.23
Pre-test odds = prevalence/(1 – prevalence)	0.30
Cut-off	**≤17/32**
Accuracy	0.86 (0.81–0.91)
Net Reclassification Improvement (NRI)	0.63
Sensitivity (Se)	0.51 (0.37–0.65)
Specificity (Sp)	0.97 (0.94–0.99)
Y	0.48
PPV (= post-test probability)	0.83 (0.69–0.97)
NPV	0.87 (0.82–0.92)
PSI	0.70
LR+	15.7 (6.35–38.9) = large
LR−	0.51 (0.20–1.25) = unimportant
DOR	31.1 (12.6–77.0)
Post-test odds (= pre-test odds × LR+)	4.70
CUI+	0.42 (poor)
CUI−	0.84 (excellent)
AUC ROC curve	0.89 (0.84–0.94)

Table 4.9 Diagnostic parameters for MMP for diagnosis of MCI (adapted from Larner 2012b)

	MMP
N	154
F:M (% female)	61:93 (39.6)
Age range (years)	20–85 (median 60)
Prevalence of MCI (= pre-test probability)	0.18
Pre-test odds = prevalence/(1 – prevalence)	0.22
Cut-off	**≤20/32**
Accuracy	0.81 (0.74–0.87)
Net Reclassification Improvement (NRI)	0.63
Sensitivity (Se)	0.29 (0.12–0.45)
Specificity (Sp)	0.92 (0.87–0.97)
Y	0.21
PPV (= post-test probability)	0.44 (0.21–0.67)
NPV	0.85 (0.79–0.91)
PSI	0.29
LR+	3.59 (1.56–8.29) = small
LR−	0.78 (0.34–1.79) = unimportant
DOR	4.64 (2.01–10.7)
Post-test odds (= pre-test odds × LR+)	0.79
CUI+	0.13 (very poor)
CUI−	0.79 (good)
AUC ROC curve	0.74 (0.65–0.83)

The diagnostic utility of MMP for the diagnosis of MCI was also examined (Larner 2012b). Of the 154 non-demented patients in the cohort, 28 fulfilled modified diagnostic criteria for MCI (as used in Petersen et al. 2005). In the non-demented group, the median and mean scores for the MCI patients were 24.5 and 24.0 ± 3.7. The mean MMP scores differed significantly between the demented and MCI groups (t = 5.2, df = 73, $p < 0.001$). For the non-demented and non MCI group (n = 126), median and mean MMP scores were 28 and 27.1 ± 4.2. For the intra-group comparison, the mean MMP scores differed significantly between MCI and the non-demented non MCI groups (t = 3.6, df = 152, $p < 0.001$).

Examining all test cut-off scores for MMP, optimal test accuracy for a diagnosis of MCI versus no dementia (0.81) was at the cut-off of ≤20/32, at which cut-off MMP had excellent specificity and negative predictive value but poor sensitivity and positive predictive value (Table 4.9). The various parameters of diagnostic utility were again comparable to the MMSE (compare Tables 4.7 and 4.9; Larner 2012b).

MMP has also proved useful in individual cases to detect cognitive impairment not identified using the MMSE, for example due to non-dominant hemisphere pathology of traumatic (Aji et al. 2012) or neoplastic (Smithson and Larner 2013) origin (Case Study 4.1), and in a case of Perry syndrome (Aji et al. 2013; Case Study 7.8).

Case Study 4.1 Clinical Utility of Cognitive Screening Instruments in Diagnosis of Cognitive Impairment: MMP

Two months after an episode of presumed herpes simplex encephalitis with oedematous change confined to the right (non-dominant) anterior and medial temporal lobes on MR imaging, and treated with aciclovir, a 48 year-old man declared himself back to normal, although his partner thought he was occasionally confused. Cognitive testing with the MMSE was unremarkable (29/30) but using the MMP he scored 27/32 with impairment on a test of visual recall. Subsequent re-imaging showed an intrinsic right temporal lobe mass lesion, not evident on review of the original MR images. Stereotactic biopsy of the lesion showed histological evidence of glioblastoma multiforme.

4.1.3 Clock Drawing Test (CDT)

The Clock Drawing Test (CDT) is a quick and simple CSI which has been used for many years, with a large literature on its scoring and utility. It is thought to assess attentional mechanisms, auditory comprehension, verbal working memory, numerical knowledge, visuospatial skills, praxis, and executive function, hence a multidomain test. Many variants and scoring systems have been developed, and it has been used in a wide variety of cognitive disorders, partly due to its high acceptability to both patients and clinicians (Freedman et al. 1994; Mainland and Shulman 2017).

No specific examination of the CDT per se has been undertaken in CFC. However, some form of clock drawing test has been incorporated into other CSIs which have been examined in CFC such as the various Addenbrooke's Cognitive Examinations, the Montreal Cognitive Assessment, the Test Your Memory test, and Free-Cog (see Sects. 4.1.5, 4.1.8, 4.1.9, and 4.1.10 respectively) as well as the Codex decision tree (see Sect. 4.1.4).

Can et al. (2012) suggested that the CDT was a valid and reliable screening tool for cognitive impairment in fibromyalgia patients, but this has not been our experience in CFC using the CDT from the mini-Addenbrooke's Cognitive Examination (see Sect. 4.1.5.5), wherein it was the subtest most often at ceiling (13/17) in fibromyalgia patients seen over a 2-year period (Williamson and Larner 2016, and unpublished observations).

4.1.3.1 Backward Clock Test

A variant on the theme of the CDT has been developed using a "Backward Clock" (Accoutrements, Seattle, USA), the mirror image of normal analogue clock (Larner 2007a). In a convenience cohort (n = 17) recruited from CFC, patients were asked to read matched strings of times shown either backward (=Backward Clock, or normal analogue clock viewed in a mirror) or forward (=normal analogue clock, or Backward clock viewed in a mirror). Patients with dementia (6 AD, 1 FTLD) failed

to read backward times correctly, with most errors resulting from reading the long hand according to its position rather than the number to which it pointed. Patients with posterior cortical atrophy (4) could read neither forward nor backward times, indeed could not discriminate any difference between the two clocks. Patients with focal lesions, namely isolated amnesia (3; amnestic MCI, post severe hypoglycaemia; Larner et al. 2003a) and agnosia (1; developmental prosopagnosia; Larner et al. 2003b), made only occasional errors on backward times, like a normal aged control (1). One patient with amnesia due to a fornix lesion with additional evidence of executive dysfunction (Ibrahim et al. 2009) performed at the level of the demented patients. The Backward Clock Test may therefore be useful in differentiating focal from global cognitive deficits, and hence in the diagnosis of dementia.

4.1.4 Cognitive Disorders Examination (Codex)

Belmin et al. (2007) developed a two-step decision tree incorporating the three-word recall and spatial orientation components from the MMSE along with a simplified clock drawing test (sCDT) which took around 3 min to perform. This cognitive disorders examination or Codex produced four diagnostic categories (hence unlike all the other CSIs considered in this chapter, Codex produces categorical as opposed to quantitative data) with differing probabilities of dementia (A = very low, B = low, C = high, D = very high). In a validation study in elderly people, taking categories C and D as indicators of dementia, Codex was found to have high sensitivity and specificity for the diagnosis of dementia (0.92 and 0.85 respectively), a better sensitivity than the MMSE (Belmin et al. 2007).

The diagnostic utility of Codex has been examined in CFC (Larner 2013c; Ziso and Larner 2013). In a cohort of 162 patients seen over a 9-month period (February to November 2012), all patients completed the MMSE and sCDT and could therefore be categorized according to the Codex decision tree (A = 42, B = 63, C = 5, D = 52). The probability of dementia in each Codex category was A = 0.05, B = 0.08, C = 0.2 and D = 0.67 (Fig. 4.3); the probability of any cognitive impairment in each Codex category was A = 0.07, B = 0.32, C = 0.6 and D = 0.88. The correlation coefficient between Codex diagnostic categories (A–D translated to 1–4 respectively) and MMSE scores in a subgroup of patients ($n = 57$) showed a moderate negative correlation ($r = -0.68$; $t = 6.83$, df = 55, $p < 0.001$). Taking Codex categories C and D as indicators of dementia, as in Belmin et al. (2007), Codex was found to have good sensitivity and specificity for the diagnosis of dementia (0.84 and 0.82 respectively) (Table 4.10, left hand column).

Taking Codex categories C and D as indicators of any cognitive impairment (cases of both dementia and MCI), Codex sensitivity declined (0.68; more false negatives) whilst specificity improved (0.91; fewer false positives) (Table 4.10, right hand column). It appeared from this study that Codex may not be equivalent to other instruments designed specifically to identify MCI, such as the Montreal Cognitive Assessment (see Sect. 4.1.8).

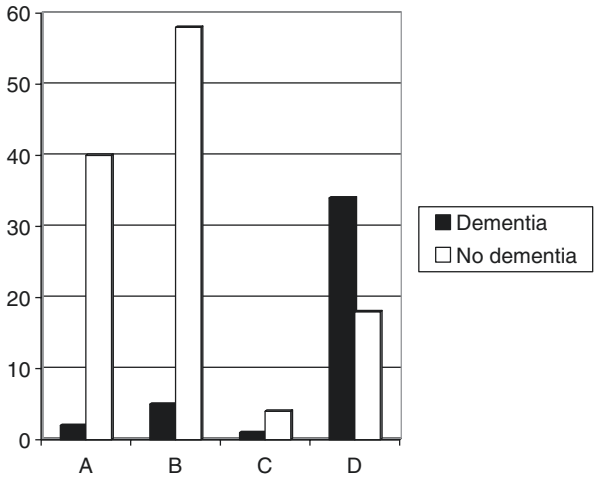

Fig. 4.3 Codex category vs. diagnosis (dementia/no dementia) (adapted from Ziso and Larner 2013) reprinted with permission

Table 4.10 Demographic and diagnostic parameters for Codex for diagnosis of dementia and any cognitive impairment (adapted from Ziso and Larner 2013)

	CODEX	
N	162	
F:M (% female)	79:83 (48.8)	
Age range (years)	20–89 (median 61)	
Prevalence of cognitive impairment (dementia + MCI) (= pre-test probability)	0.44 (0.26 + 0.18)	
Pre-test odds = prevalence/(1 – prevalence)	0.79 (0.35 and 0.22)	
	Diagnosis of dementia	**Diagnosis of any cognitive impairment**
Accuracy	0.83 (0.77–0.89)	0.81 (0.75–0.87)
Net Reclassification Improvement (NRI)	0.57	0.37
Sensitivity (Se)	0.84 (0.73–0.95)	0.68 (0.57–0.79)
Specificity (Sp)	0.82 (0.76–0.89)	0.91 (0.85–0.97)
Y	0.66	0.59
PPV (= post-test probability)	0.63 (0.51–0.77)	0.86 (0.77–0.95)
NPV	0.93 (0.89–0.98)	0.78 (0.70–0.86)
PSI	0.56	0.64
LR+	4.74 (3.15–7.15) = small	7.66 (3.88–15.1) = moderate
LR−	0.20 (0.13–0.30) = small	0.35 (0.18–0.69) = small
DOR	24.0 (15.9–36.2)	21.8 (11.1–43.1)
Post-test odds (= pre-test odds × LR+)	1.66	6.05
CUI+	0.53 (adequate)	0.59 (adequate)
CUI−	0.77 (good)	0.71 (good)
AUC ROC curve	0.85 (0.78–0.92)	0.85 (0.80–0.91)

4.1.5 Addenbrooke's Cognitive Examinations

A number of iterations of the Addenbrooke's Cognitive Examination have been published over the past 20 years by Professor John Hodges and his colleagues (reviewed in Hodges and Larner 2017).

4.1.5.1 Addenbrooke's Cognitive Examination (ACE)

The Addenbrooke's Cognitive Examination (ACE; Mathuranath et al. 2000) was a theoretically motivated cognitive screening test which attempted to address the neuropsychological omissions of the MMSE (which it incorporated) and to bridge the gap between very brief screening instruments and a full neuropsychological assessment for use in memory clinics.

ACE may be used as a brief "bedside" cognitive screen, encompassing tests of attention/orientation, memory, language, visual perceptual and visuospatial skills, and executive function, with a total score out of 100 (Box 4.4). It attempted to address some of the recognised shortcomings of the MMSE (i.e. perfunctory memory and visuospatial testing, absence of executive function tests). ACE was initially reported to have good sensitivity and specificity for identifying dementia, was relatively quick to administer (ca. 15 min), and had good patient acceptability (Mathuranath et al. 2000). The ACE has been widely adopted and translated into various languages (Hodges and Larner 2017).

Box 4.4 Item Content of Addenbrooke's Cognitive Examination (ACE)

Orientation	10
Registration	3
Attention/Concentration (serial 7s, DLROW)	5 (best performed task)
Recall	3
Memory:	
Anterograde	28
Retrograde	4
Verbal fluency:	
Letters (P)	7
Animals	7
Language:	
Naming	12
Comprehension	8
Repetition	5
Reading	2
Writing	1
Visuospatial abilities:	
Intersecting pentagons	1
Wire (Necker) cube	1
Clock drawing	3
Total score	**100**

Table 4.11 Demographic and diagnostic parameters for ACE (adapted from Larner 2007b)

	ACE	
N	285	
F:M (% female)	138:147 (48.4)	
Prevalence of dementia (= pre-test probability)	0.49	
Pre-test odds = prevalence/(1 – prevalence)	0.96	
Cut-off	**≥88/100**	**≥75/100**
Accuracy	0.71 (0.66–0.76)	0.84 (0.80–0.88)
Net Reclassification Improvement (NRI)	0.22	0.35
Sensitivity (Se)	1.00	0.85 (0.79–0.91)
Specificity (Sp)	0.43 (0.35–0.42)	0.83 (0.77–0.89)
Y	0.43	0.68
PPV (= post-test probability)	0.63 (0.57–0.69)	0.83 (0.77–0.89)
NPV	1.00	0.85 (0.79–0.91)
PSI	0.63	0.65
LR+	1.77 (1.53–2.04) = unimportant	5.14 (3.54–7.45) = moderate
LR−	0 = large	0.18 (0.12–0.26) = moderate
DOR	∞	28.6 (19.7–41.4)
Post-test odds (= pre-test odds × LR+)	1.70	4.93
CUI+	0.63 (adequate)	0.71 (good)
CUI−	0.43 (poor)	0.71 (good)
AUC ROC curve	0.93 (0.90–0.96)	

The diagnostic utility of the ACE in screening for dementia in day-to-day clinical practice was assessed prospectively in new referrals to CFC over a 3½-year period (February 2002 to August 2005; Larner 2005b, 2006, 2007b). ACE was used in 285 patients, a cohort in which dementia prevalence was 49% (Table 4.11). ACE was easy to use but a few patients failed to complete the test, including three patients with frontotemporal lobar degeneration who had features of either profound apathy or marked motor restlessness. The correlation coefficient between ACE scores and MMSE scores ($n = 154$) was $r = 0.92$ ($t = 28.9$, df = 152, $p < 0.001$) (Larner 2005b).

Using the ACE cut-offs of ≥88/100 and ≥83/100 as defined in the index paper (Mathuranath et al. 2000), test sensitivity was high but specificity less good (Table 4.11; Larner 2007b). Using a lower cut-off of ≥75/100 (Larner 2006), arbitrarily chosen but justified on the basis that, unlike the index study, this pragmatic study did not include a normal control group, and hence was more representative of day-to-day clinical practice, sensitivity and specificity and PPV were all greater than 0.8 (Table 4.11, right hand column).

Longitudinal use of the ACE has proven useful in individual cases (e.g. Larner et al. 2003a; Wilson et al. 2010; Wong et al. 2008, 2010), and has also been examined more systematically (Larner 2006). Over the 3½ year period that the ACE was

Table 4.12 Diagnostic parameters for longitudinal use of ACE (at last assessment) (adapted from Larner 2006)

	ACE	
N	23	
Cut-off	**≥88/100**	**≥75/100**
Accuracy	0.74 (0.56–0.92)	0.74 (0.56–0.92)
Sensitivity (Se)	1.00	0.88 (0.71–1.04)
Specificity (Sp)	0.14 (−0.12–0.40)	0.43 (0.06–0.80)
Y	0.14	0.31
PPV	0.73 (0.54–0.91)	0.78 (0.59–0.97)
NPV	1.00	0.60 (0.17–1.03)
PSI	0.73	0.38
LR+	1.16 (0.86–1.57) = unimportant	1.53 (0.78–2.98) = unimportant
LR−	0 = large	0.29 (0.15–0.57) = small
DOR	∞	5.25 (2.69–10.2)
CUI+	0.73 (good)	0.69 (good)
CUI−	0.14 (very poor)	0.26 (very poor)

in use in CFC, 23 of the 285 patients tested had more than one assessment with the ACE over periods of follow-up ranging from 7 to 36 months. At first assessment, six patients were suspected to have dementia and 17 were not demented. Based on patient and caregiver report and clinical judgement, 16 patients declined over follow-up, six remained static and one improved, with final clinical diagnoses of dementia in 16 and no dementia in seven. On the ACE, 17 patients had declined, 4 remained static (≤2 point change in ACE scores) and two improved. The diagnostic utility of longitudinal use of the ACE is summarised in Table 4.12.

Studies of the ACE undertaken in CFC have also been included in systematic reviews (Crawford et al. 2012) and meta-analysis of ACE (see Sect. 6.1.4; Larner and Mitchell 2014).

4.1.5.2 ACE Subscores: VLOM Ratio; Standardized Verbal Fluency; Semantic Index; and Modified Ala Subscore

A number of subscores derived from the ACE have been described (Hodges and Larner 2017).

Mathuranath et al. (2000) defined the VLOM ratio, given by the formula:

$$\text{VLOM ratio} = (\text{verbal fluency} + \text{language}) / (\text{orientation} + \text{delayed recall})$$

with possible maxima of (verbal fluency + language) = 42 and (orientation + delayed recall) = 17. VLOM ratio was reported to differentiate AD and frontotemporal lobar degenerations (FTLD): a VLOM ratio >3.2 showed sensitivity of 0.75 and specificity of 0.84 for the diagnosis of AD (Mathuranath et al. 2000), a finding later confirmed in an independent cohort (Bier et al. 2004). A VLOM ratio <2.2 showed sensitivity of 0.58 and specificity of 0.97 for the diagnosis of FTLD (Mathuranath et al. 2000). A later independent study confirmed the specificity figure, but reported a much lower sensitivity of VLOM ratio <2.2 for the diagnosis of FTLD (Bier et al. 2004).

In the cohort of patients from CFC tested with the ACE, the diagnostic utility of the VLOM ratio >3.2 for the diagnosis of AD was confirmed, whereas the diagnostic utility of the VLOM ratio <2.2 for the diagnosis of FTLD showed poor sensitivity but good specificity, with accordingly very poor and excellent positive and negative utility indices respectively (Table 4.13; Larner 2007b). Others have also questioned the utility of the VLOM ratio in identifying FTLD, particularly behavioural variant FTD (Bier et al. 2004).

ACE includes verbal fluency (VF) tests for both letter (P) and category (animals) (Box 4.4). Scaled scoring systems for letter fluency (LF) and category fluency (CF) derived using a Gaussian distribution of raw scores from normal controls ($n = 127$) took account of the finding that CF is easier than LF for normals. This component of the ACE had good concordance with standard neuropsychological tests ($\kappa = 0.60$ against FAS test), indicating good construct validity (Mathuranath et al. 2000).

Verbal fluency has been described as the "ESR of cognition", impairment being a nonspecific indicator of cognitive ill-health. VF tasks have been reported to have very high sensitivity in detecting dementia (e.g. Duff Canning et al. 2004), although there may be differential impairments. One study comparing patients with dementia and pure affective disorder suggested that LF < CF was suggestive of affective disorder (Dudas et al. 2005; see Sect. 5.2.3). Since patients with AD generally show greater impairment in CF than LF, reflecting degradation in semantic knowledge stores and/or access to this knowledge (Henry et al. 2004), whilst LF is particularly sensitive to FTLD, especially the behavioural variant of FTD (Hodges et al. 1999), differential impairment of CF and LF might possibly be useful in the differentiation of AD from FTLD.

Examining this in AD ($n = 114$) and FTLD ($n = 16$) patients in the CFC cohort who were administered the ACE, VF parameters showed similar patterns to VLOM ratios, i.e. VLOM ratio >3.2 and LF > CF favoured diagnosis of AD, whereas

Table 4.13 Diagnostic parameters for VLOM ratios from the ACE (adapted from Larner 2007b)

	ACE VLOM ratio	
N	130 (AD 114, FTLD 16)	
Cut-off	**>3.2 (for diagnosis of AD)**	**<2.2 (for diagnosis of FTLD)**
Accuracy	0.76 (0.71–0.81)	0.87 (0.83–0.91)
Sensitivity (Se)	0.76 (0.69–0.84)	0.31 (0.09–0.54)
Specificity (Sp)	0.76 (0.69–0.84)	0.90 (0.87–0.94)
Y	0.52	0.21
PPV	0.69 (0.60–0.77)	0.16 (0.03–0.29)
NPV	0.83 (0.77–0.89)	0.96 (0.93–0.98)
PSI	0.52	0.12
LR+	3.21 (2.40–4.28) = small	3.20 (1.42–7.21) = small
LR−	0.31 (0.23–0.42) = small	0.76 (0.34–1.72) = unimportant
DOR	10.3 (7.72–13.8)	4.19 (2.99–5.88)
CUI+	0.52 (adequate)	0.05 (very poor)
CUI−	0.63 (adequate)	0.86 (excellent)
AUC ROC (AD vs. FTD)	0.80 (0.64–0.96)	

Table 4.14 Diagnostic parameters for Standardized Verbal Fluency scores from the ACE (adapted from Larner 2013d)

	ACE standardized verbal fluency scores	
N	130 (AD 114, FTLD 16)	
	LF > CF (for diagnosis of AD)	**LF < CF (for diagnosis of FTD)**
Accuracy	0.63 (0.55–0.71)	0.91 (0.86–0.96)
Sensitivity (Se)	0.66 (0.57–0.75)	0.25 (0.04–0.46)
Specificity (Sp)	0.44 (0.19–0.68)	0.86 (0.80–0.92)
Y	0.10	0.11
PPV	0.89 (0.83–0.96)	0.20 (0.03–0.38)
NPV	0.15 (0.05–0.26)	0.89 (0.83–0.95)
PSI	0.04	0.09
LR+	1.17 (0.74–1.84) = unimportant	1.78 (0.68–4.66) = unimportant
LR−	0.78 (0.50–1.23) = unimportant	0.87 (0.33–2.28) = unimportant
DOR	1.50 (0.95–2.35)	2.04 (0.78–5.35)
CUI+	0.59 (adequate)	0.05 (very poor)
CUI−	0.07 (very poor)	0.77 (good)
AUC ROC (AD vs. FTD)	0.56 (0.49–0.65)	

VLOM ratio <2.2 and CF > LF favoured diagnosis of FTLD, but overall the standardized verbal fluency offered no diagnostic advantage over the VLOM ratios (Table 4.14, compare with Table 4.13; Larner 2013d).

Another ACE subscore is the Semantic Index (SI) which was reported to differentiate AD from semantic dementia (Davies et al. 2008), and is given by the formula:

$$\text{SI} = (\text{naming} + \text{reading}) - (\text{serial 7s} + \text{orientation in time} + \text{drawing})$$

Hence SI ranges from +14 to −15, with a cut-off of zero said to differentiate AD cases (SI = 3.8 ± 3.6) from semantic dementia cases (SI = −6.7 ± 4.7). Few cases of semantic dementia have been identified in CFC but all those scored by this method ($n = 4$) had SI <0 (range −7 to −15), suggesting that this probably is a useful score for differentiating AD and semantic dementia.

The Ala subscore derived from the MMSE (see Sect. 4.1.1) which was reported to differentiate AD and DLB (Ala et al. 2002), may also be derived, in a modified form, from the ACE (Larner 2003), namely:

$$\text{Modified Ala subscore} = \text{Attention} - ½(\text{Memory}) + (\text{Construction})$$

Like the Ala subscore, this modified subscore may range from −5 to +10.

The modified Ala subscore was evaluated in a prospective study of clinically diagnosed patients seen in CFC (Larner 2003, 2004). Only specificity and false positive rates could be calculated because of the very small number of DLB cases seen, with results similar to those found for the Ala subscore (see Sect. 4.1.1), specificity 0.47 (95% CI = 0.41–0.53) and false positive rate 0.53 (95% CI = 0.47–0.59) and a diagnostic odds ratio of 0. These figures did not encourage the view that the modified Ala subscore might be useful prospectively for the clinical diagnosis of DLB.

4.1.5.3 Addenbrooke's Cognitive Examination-Revised (ACE-R)

The Addenbrooke's Cognitive Examination-Revised (ACE-R) is a brief (15–20 min) cognitive test battery designed for dementia screening (Mioshi et al. 2006), developed from the earlier ACE (see Sect. 4.1.5.1), and also incorporating the MMSE (see Sect. 4.1.1). Because of copyright issues relating to use of the MMSE, ACE-R, like ACE, has now been superseded by ACE-III (Hsieh et al. 2013; available at www.neura.edu.au/frontier/research/test-downloads/).

From the overall ACE-R score (range 0–100), domain subscores for attention and orientation, memory, fluency, language, and visuospatial abilities can be generated (Box 4.5). Like the ACE, the ACE-R has been widely adopted and translated into various languages (Hodges and Larner 2017).

Box 4.5 Item content of Addenbrooke's Cognitive Examination-Revised (ACE-R); cf. Box 4.4

Orientation	10
Registration	3
Attention/Concentration (serial 7s, DLROW)	5 (best performed task)
Recall	3
Memory:	
Anterograde	19
Retrograde	4
Verbal fluency:	
Letters	7
Animals	7
Language:	
Naming	12
Comprehension	8
Repetition	4
Reading	1
Writing	1
Visuospatial abilities:	
Intersecting pentagons	1
Wire (Necker) cube	2
Clock drawing	5
Perceptual abilities: Dot counting	4
Perceptual abilities: Fragmented letters	4
Total score	**100**
ACE-R domain subscores	
Attention and Orientation	18
Memory	26
Fluency	14
Language	26
Visuospatial	16
Total score	**100**

The index study of the ACE-R in a University Hospital Clinic reported sensitivity and specificity of 0.94 and 0.89 at a cut-off of ≥88/100, and 0.84 and 1.00 at a cut-off of ≥82/100 (Mioshi et al. 2006). However, preliminary data from CFC (Larner 2007c) found optimal sensitivity and specificity at a lower cut-off (≥75/100), and a systematic study indicated the optimal accuracy in this clinic was achieved with a cut-off of ≥73/100 (Larner 2009a, b, 2013b), perhaps reflecting the absence of normal controls in clinical practice (observational) studies as compared with index (experimental) studies.

The diagnostic utility of the ACE-R in screening for dementia in day-to-day clinical practice has been assessed prospectively in new referrals to the CFC over a 3-year period (August 2005 to August 2008; Larner 2007c, 2008a, 2009a, b, 2013b). ACE-R was used on 261 occasions in 243 patients. A total of 84 patients were diagnosed with dementia by DSM-IV criteria (=35%; Table 4.15), a dementia prevalence rather lower than that recorded in previous CFC cohorts (ca. 50%; Larner 2007b). This may perhaps have been a consequence of selective rather than consecutive use of ACE-R in the later part of the study period, or may reflect a falling frequency of dementia cases amongst referrals to the clinic (see Sect. 1.4). ACE-R proved easy to administer, with very few patients failing to complete the test, one example being an AD patient with multiple cognitive impairments including profound amnesia and visual agnosia (Larner et al. 2007).

Table 4.15 Demographic and diagnostic parameters for ACE-R (adapted from Larner 2009a, 2013b)

	ACE-R
N	243
F:M (% female)	108:135 (44.4)
Age range (years)	24–85 (mean 59.8 ± 10.9)
Prevalence of dementia (= pre-test probability)	0.35
Pre-test odds = prevalence/(1 – prevalence)	0.54
Cut-off	**≥73/100**
Accuracy	0.89 (0.85–0.93)
Net Reclassification Improvement (NRI)	0.54
Sensitivity (Se)	0.87 (0.80–0.94)
Specificity (Sp)	0.91 (0.86–0.95)
Y	0.78
PPV (= post-test probability)	0.83 (0.75–0.91)
NPV	0.93 (0.89–0.97)
PSI	0.76
LR+	9.21 (5.65–15.0) = moderate
LR−	0.14 (0.09–0.24) = moderate
DOR	63.7 (39.1–103.9)
Post-test odds (= pre-test odds × LR+)	4.97
CUI+	0.72 (good)
CUI−	0.85 (excellent)
AUC ROC curve	0.94 (0.91–0.97)

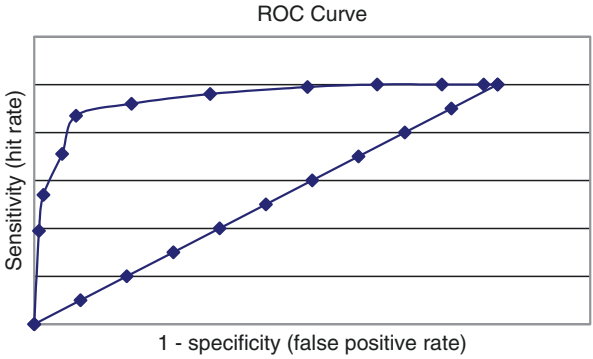

Fig. 4.4 ROC curve for ACE-R (adapted from Larner 2009a) reprinted with permission

The correlation coefficient for ACE-R scores and simultaneously recorded MMSE scores (n = 259) was, as expected, very high (r = 0.90, t = 32.8, df = 257, $p < 0.001$), as previously noted with the ACE and MMSE (Larner 2005b). A high correlation of ACE-R and MMSE scores was also found in data from a national dementia research register in Scotland in patients with established AD (r = 0.92) (Law et al. 2013), and also in a study based in an old age psychiatry clinic (r = 0.77) (Hancock and Larner 2015; see Sect. 5.2.4). Using the test of agreement (Cohen's kappa statistic) for MMSE and ACE-R, κ = 0.72 (0.63–0.81), where 1 is perfect agreement between tests and 0 is agreement due to chance alone.

For cross-sectional use, the sensitivity and specificity of ACE-R were examined at all cut-off values with the optimal cut-off being defined by maximal test accuracy (see Sect. 2.3.2) for the differential diagnosis of dementia/not dementia (Larner 2015d). For ACE-R, the optimal accuracy was 0.89 at a cut-off of ≥73/100 (Table 4.15), which compared favourably to the MMSE (optimal accuracy 0.82 at a cut-off of ≥24/100; see Table 4.2). The various parameters of diagnostic test utility for ACE-R were calculated at this cut-off (Table 4.15) and ROC curve constructed (Fig. 4.4), all results comparing favourably with MMSE (Table 4.2). Although the cohort included individuals with MCI, numbers were insufficient (<20) to report separate results.

ACE-R has also been investigated in a number of other CFC studies undertaken jointly with an old age psychiatry memory clinic (Brooker Centre, Runcorn), specifically those studies evaluating the Instrumental Activities of Daily Living (IADL) Scale (Hancock and Larner 2007; Larner and Hancock 2012; see Sects. 5.1.1 and 6.2.3), the Informant Questionnaire on Cognitive Decline in the Elderly (IQCODE; Hancock and Larner 2009; see Sects. 5.4.1 and 6.2.2.1), and the Test Your Memory (TYM) test (Hancock and Larner 2011; see Sect. 4.1.9). Although ACE-R use in the former two studies overlapped with that in the 3-year study reported above, nonetheless of those completing ACE-R in the IQCODE study (n = 114) more than half (63/114 = 55%) were from the old age psychiatry unit, affording the possibility of evaluating ACE-R diagnostic accuracy in a group with higher dementia prevalence and median age than typically seen in CFC. Although the optimal accuracy cut-off was ≥70/100, the various parameters of diagnostic utility were only marginally

Table 4.16 Demographic and diagnostic parameters for ACE-R (adapted from Hancock and Larner 2009)

	ACE-R
N	114
F:M (% female)	57:57 (50)
Age range (years)	29–94 (median 67)
Prevalence of dementia (= pre-test probability)	0.51
Pre-test odds = prevalence/(1 – prevalence)	1.04
Cut-off	**≥73/100**
Accuracy	0.81 (0.73–0.88)
Net Reclassification Improvement (NRI)	0.30
Sensitivity (Se)	0.78 (0.69–0.88)
Specificity (Sp)	0.84 (0.74–0.93)
Y	0.62
PPV (= post-test probability)	0.83 (0.73–0.93)
NPV	0.78 (0.68–0.89)
PSI	0.62
LR+	4.83 (2.61–8.92) = small
LR−	0.27 (0.14–0.49) = small
DOR	18.1 (9.78–33.4)
Post-test odds (= pre-test odds × LR+)	5.03
CUI+	0.65 (good)
CUI−	0.66 (good)
AUC ROC curve	0.90 (0.85–0.95)

better than at the optimal cut-off (≥73/100) in the main study, so for ease of comparison diagnostic parameters have been calculated for this cut-off (Table 4.16).

In the Test Your Memory (TYM) test study (Hancock and Larner 2011; see Sect. 4.1.9), results for ACE-R (n = 140) sensitivity and specificity (Table 4.17) were comparable to those in previous studies. For the group with dementia (n = 39), the mode, median, and mean ACE-R scores were 71, 61, and 60.5 ± 11.3, respectively: for the non-demented group (n = 101) the mode, median, and mean scores were 94, 90, and 87.6 ± 8.2. The mean ACE-R scores differed significantly between the two groups (t = 15.6, df = 138, $p < 0.001$). At the ACE-R cut-off of ≤73/100, 87% of the AD/mixed dementia cases (n = 31 tested with ACE-R) were detected.

ACE-R has also proved useful in individual cases, including longitudinal use (Ibrahim et al. 2009; Larner and Young 2009; Larner et al. 2007; Case Study 8.1). Longitudinal use has also been examined systematically in 17 patients who were assessed for a second or third time with ACE-R over periods of follow-up ranging from 6 to 36-months (Larner 2009a, b), some in the context of a study of patients with non-paraneoplastic limbic encephalitis with antibodies against voltage-gated potassium channels (Wong et al. 2008, 2010). Of these 17, four were eventually diagnosed with dementia, in whom the ACE-R score declined in two and remained stable (≤5-point change) in two. In the 13 patients eventually diagnosed as not demented, ACE-R score remained stable in 8 and improved in 5 patients.

Table 4.17 Demographic and diagnostic parameters for ACE-R (adapted from Hancock and Larner 2011)

	ACE-R
N	140
Prevalence of dementia (= pre-test probability)	0.28
Pre-test odds = prevalence/(1 – prevalence)	0.39
Cut-off	**≤73/100**
Accuracy	0.92 (0.88–0.97)
Net Reclassification Improvement (NRI)	0.64
Sensitivity (Se)	0.90 (0.80–0.99)
Specificity (Sp)	0.93 (0.88–0.98)
Y	0.83
PPV (= post-test probability)	0.83 (0.72–0.95)
NPV	0.96 (0.92–0.99)
PSI	0.79
LR+	12.9 (6.29–26.7) = large
LR−	0.11 (0.05–0.23) = moderate
DOR	117.5 (57.0–242)
Post-test odds (= pre-test odds × LR+)	5.02
CUI+	0.75 (good)
CUI−	0.89 (excellent)
AUC ROC curve	0.98 (0.97–0.99)

Studies of the ACE-R undertaken in CFC have also been included in systematic reviews (Crawford et al. 2012) and meta-analysis of ACE-R (see Sect. 6.1.4; Larner and Mitchell 2014). Weighted comparison with MMSE has also been performed (Larner and Hancock 2014; see Sect. 6.1.1).

4.1.5.4 ACE-III

Copyright issues concerning the MMSE, acquired by Psychological Assessment Resources in 2001, have prompted the removal of the MMSE elements from ACE-III which officially supersedes ACE and ACE-R (Hsieh et al. 2013; available at www.neura.edu.au/frontier/research/test-downloads/). Some clinicians prefer to continue using ACE-R, precisely because it gives the MMSE score as well as more in depth neuropsychological testing. ACE-III and ACE-R scores were highly correlated ($r = 0.99$) in the index study (Hsieh et al. 2013).

ACE-III has proved useful in individual cases examined in CFC to detect cognitive impairment (e.g. St John and Larner 2015) but no diagnostic test accuracy study has been performed.

ACE-III has also been made available as an i-pad based app, which is available cost-free via iTunes and at acemobileorg@gmail.com. The automated scoring and the clear instructions are designed to reduce errors in administration and scoring (Newman et al. 2017).

4.1.5.5 Mini-Addenbrooke's Cognitive Examination (MACE)

The Mini-Addenbrooke's Cognitive Examination (MACE; Box 4.6), originally described by Hsieh et al. (2015), has been examined in a number of studies undertaken at CFC (Larner 2015b, c, 2016b, c, 2017d, 2018a, b) as well as individual case reports (St John and Larner 2015; Connon and Larner 2017a; Wojtowicz et al. 2017) and small case series (Stagg and Larner 2015; Williamson and Larner 2016; Ziso and Larner 2016).

Box 4.6 ITEM content of Mini-Addenbrooke's Cognitive Examination (MACE)

Orientation (Time)	4
Registration (7-item name and address, scored on third presentation)	7
Verbal fluency	7
Visuospatial abilities (Clock drawing)	5
Memory Recall	7
Total score	**30**

The diagnostic utility of MACE in screening for dementia and MCI in day-to-day clinical practice has been assessed prospectively in new referrals to the CFC over a 3-year period (June 2014 to May 2017). Of 599 patients assessed, 99 were diagnosed with dementia by DSM-IV criteria (prevalence = 17%) and with MCI in 172 (=29%; Fig. 4.5). MACE proved quick and easy to administer. Measures of discrimination (Table 4.18) showed it to be highly sensitive for the diagnosis of both dementia and MCI but with poorer specificity, and poor metrics for distinguishing dementia and MCI (Williamson and Larner 2018).

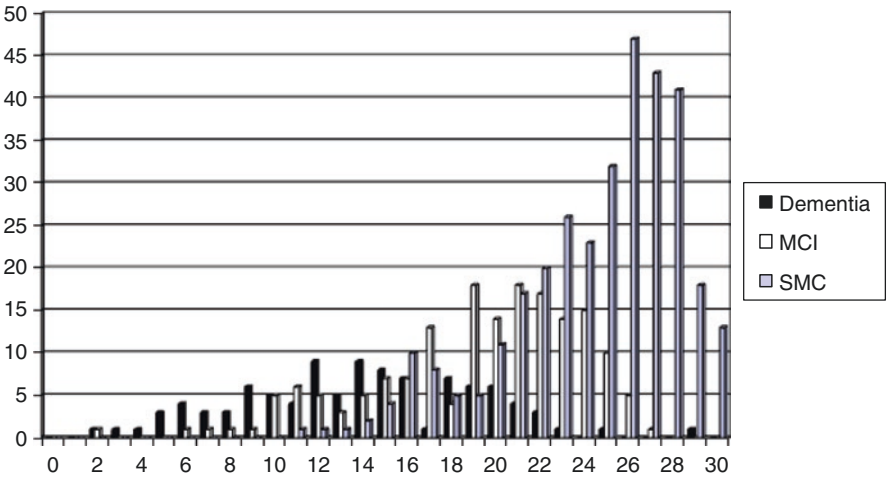

Fig. 4.5 MACE scores vs. patient diagnosis (Williamson and Larner 2018) reprinted with permission

Table 4.18 Demographic and diagnostic parameters for MACE (cut-off ≤25/30) for diagnosis of dementia and of MCI (Williamson and Larner 2018)

	MACE		
N	599		
F:M (% female)	280:319 (47)		
Age range (years)	18–94 (median 60)		
	Diagnosis of dementia vs. no dementia	**Diagnosis of dementia vs. MCI**	**Diagnosis of MCI vs. no cognitive impairment**
N	599 (99 vs 500)	271 (99 vs 172)	500 (172 vs 328)
Prevalence (= pre-test probability)	0.165	0.365	0.344
Pre-test odds = prevalence/ (1 − prevalence)	0.198	0.576	0.524
Accuracy	0.44 (0.40–0.48)	0.38 (0.33–0.44)	0.66 (0.61–0.70)
Net Reclassification Improvement (NRI)	0.278	0.018	0.312
Sensitivity (Se)	0.99 (0.97–1.00)	0.99 (0.97–1.00)	0.97 (0.94–0.99)
Specificity (Sp)	0.37 (0.29–0.38)	0.035 (0.007–0.062)	0.49 (0.44–0.55)
Y	0.36	0.024	0.46
PPV (= post-test probability)	0.23 (0.19–0.27)	0.37 (0.31–0.43)	0.50 (0.45–0.55)
NPV	0.99 (0.98–1.00)	0.86 (0.60–1.00)	0.96 (0.94–0.99)
PSI	0.22	0.23	0.46
LR+	1.49 (1.40–1.59) = unimportant	1.03 (1.00–1.06) = unimportant	1.91 (1.71–2.13) = unimportant
LR−	0.03 (0.028–0.032) = large	0.29 (0.28–0.30) = small	0.07 (0.06–0.08) = large
DOR	49.6 (46.4–52.9)	3.54 (3.43–3.67)	27.0 (24.2–30.2)
Post-test odds (= pre-test odds × LR+)	0.295	0.591	1.00
CUI+	0.23 (very poor)	0.37 (poor)	0.48 (poor)
CUI−	0.33 (very poor)	0.03 (very poor)	0.48 (poor)
AUC ROC curve	0.884 (0.851–0.917) = good	0.776 (0.720–0.833) = fair	0.823 (0.787–0.858) = good
Effect size (Cohen's d)	1.71 =large	1.04 =large	1.23 =large

4.1.6 Six-Item Cognitive Impairment Test (6CIT)

The Six-Item Cognitive Impairment Test (6CIT) is a brief (2–3 min) CSI developed for use in primary care (Brooke and Bullock 1999) which has proved valid for the detection of dementia in a number of studies (Gale and Larner 2017; Box 4.7). Unlike the CSIs discussed hitherto, 6CIT is negatively scored (i.e. higher score = worse performance) which may perhaps be confusing for those more familiar with instruments such as MMSE and ACE, although 6CIT scores are classified to aid test interpretation, as "normal cognition" (0–4), "questionable impairment" (5–9), or "suggesting impairment consistent with dementia and requiring further evaluation" (10 or more). Other sources report different 6CIT score ranges, and hence cut-off, namely 0–7 "normal" and ≥8 "significant" (www.patient.co.uk/doctor/six-item-cognitive-impairment-test-6cit).

Box 4.7 Item Content of Six-Item Cognitive Impairment Test (6CIT)

Orientation (year, month, time)	10
Calculation (20–1, months backwards)	8
Memory recall (5 item name and address)	10
(NB negatively scored, i.e. higher score = worse performance)	
Total score	**28**

The diagnostic utility of 6CIT in screening for dementia and cognitive impairment in day-to-day clinical practice has been assessed prospectively in new referrals to CFC (Abdel-Aziz and Larner 2015; Larner 2015e).

In a cohort of 245 patients seen over a 12-month period (June 2013 to June 2014) and prospectively administered 6CIT, the results (Table 4.19) showed that at the specified cut-off of ≤4 6CIT had good sensitivity and specificity for the diagnosis of dementia vs. no dementia (0.88 and 0.78 respectively), good sensitivity (0.88) but poor specificity (0.61) for the diagnosis of dementia vs. MCI, and parameters for the diagnosis of MCI vs. no cognitive impairment (specified cut-off of ≤9) were suboptimal (sensitivity and specificity 0.66 and 070 respectively). 6CIT appeared to be a viable alternative to MMSE for cognitive screening in the secondary care setting.

Re-interrogating the original study dataset to quantify test metrics at 6CIT 7/8 cut-off (Larner 2015e) showed (Table 4.20) the anticipated greater sensitivity of the higher cut-off for dementia (0.90 vs 0.88) but with lower specificity (0.68 vs 0.78); and lower sensitivity of the lower cut-off for MCI (0.55 vs 0.66) with higher specificity (0.80 vs 0.70).

6CIT was originally designed, and has subsequently been recommended, for use in primary care settings, but few studies of diagnostic accuracy have emerged from this setting (the most notable exception being the study of Hessler et al. 2014). Sequential studies of CSI use as mentioned in referrals to CFC from primary care have shown an increase in 6CIT use (see Table 1.5) although errors in the reporting

Table 4.19 Demographic and diagnostic parameters for 6CIT for diagnosis of dementia and MCI (adapted from Abdel-Aziz and Larner 2015)

		6CIT	
N		245	
F:M (% female)		121:124 (49.4)	
Age range (years)		16–94 (median 59)	
	Diagnosis of dementia vs. no dementia	**Diagnosis of dementia vs. MCI**	**Diagnosis of MCI vs. no cognitive impairment**
N	245 (48 vs 197)	115 (48 vs 67)	197 (67 vs 130)
Prevalence (= pre-test probability)	0.196	0.417	0.340
Pre-test odds = prevalence/ (1 − prevalence)	0.24	0.72	0.52
Accuracy	0.80 (0.75–0.85)	0.72 (0.64–0.80)	0.69 (0.62–0.75)
Net Reclassification Improvement (NRI)	0.60	0.30	0.35
Sensitivity (Se)	0.88 (0.78–0.97)	0.88 (0.78–0.97)	0.66 (0.54–0.77)
Specificity (Sp)	0.78 (0.72–0.84)	0.61 (0.50–0.73)	0.70 (0.62–0.78)
Y	0.66	0.49	0.36
PPV (= post-test probability)	0.49 (0.39–0.60)	0.62 (0.50–0.73)	0.53 (0.42–0.64)
NPV	0.96 (0.93–0.99)	0.87 (0.78–0.97)	0.80 (0.72–0.87)
PSI	0.46	0.49	0.33
LR+	4.00 (3.01–5.33) = small	2.25 (1.64–3.10) = small	2.19 (1.60–3.00) = small
LR−	0.16 (0.12–0.21) = moderate	0.20 (0.15–0.28) = small	0.49 (0.36–0.67) = small
DOR	25.1 (18.9–33.3)	11.0 (8.02–15.2)	4.46 (3.26–6.11)
Post-test odds (= pre-test odds × LR+)	0.97	1.61	1.13
CUI+	0.43 (poor)	0.54 (adequate)	0.35 (very poor)
CUI−	0.75 (good)	0.53 (adequate)	0.56 (adequate)
AUC ROC curve	0.90 (0.85–0.95)	0.85 (0.82–0.87)	0.71 (0.64–0.79)

and scoring of 6CIT are not uncommon (Fisher and Larner 2007; Menon and Larner 2011; Cagliarini et al. 2013; Ghadiri-Sani and Larner 2014; Wojtowicz and Larner 2015, 2016; Cannon and Larner 2016).

Connon and Larner (2017b) reasoned that a primary care diagnostic test accuracy study of 6CIT could be undertaken by using the scores of 6CIT administered by primary care practitioners to patients who were subsequently referred to CFC, and using the secondary care consensus diagnosis as reference standard. Over a 2-year period (2015–2016 inclusive), of 668 consecutive new patients seen, 511 (76.5%) were referrals from primary care, of whom 84 had been assessed with 6CIT according to information contained in the patient referral letter. Of these 84, 6 had

Table 4.20 Demographic and diagnostic parameters for 6CIT for diagnosis of dementia and of MCI at different cut-offs (adapted from Larner 2015e)

			6CIT			
N			245			
F:M (% female)			121:124 (49.4)			
Age range (years)			16–94 (median 59)			
	Diagnosis of dementia vs. no dementia (=MCI + no cognitive impairment)		**Diagnosis of dementia vs. MCI**		**Diagnosis of MCI vs. no cognitive impairment**	
n	245		115		197	
Cut-off	**6CIT ≥ 8**	**6CIT > 4**	**6CIT ≥ 8**	**6CIT > 4**	**6CIT ≥ 8**	**6CIT > 9**
Accuracy	0.72 (0.67–0.78)	0.80 (0.75–0.85)	0.63 (0.55–0.72)	0.72 (0.64–0.80)	0.72 (0.65–0.78)	0.69 (0.62–0.75)
Sensitivity (Se)	0.90 (0.81–0.98)	0.88 (0.78–0.97)	0.90 (0.81–0.98)	0.88 (0.78–0.97)	0.55 (0.43–0.67)	0.66 (0.54–0.77)
Specificity (Sp)	0.68 (0.62–0.75)	0.78 (0.72–0.84)	0.45 (0.33–0.57)	0.61 (0.50–0.73)	0.80 (0.73–0.87)	0.70 (0.62–0.78)
PPV	0.41 (0.31–0.50)	0.49 (0.39–0.60)	0.54 (0.43–0.65)	0.62 (0.50–0.73)	0.59 (0.47–0.71)	0.53 (0.42–0.64)
NPV	0.96 (0.93–0.99)	0.96 (0.93–0.99)	0.86 (0.74–0.97)	0.87 (0.78–0.97)	0.78 (0.71–0.85)	0.80 (0.72–0.87)
LR+	2.80 (2.24–3.51)	4.00 (3.01–5.33)	1.62 (1.28–2.05)	2.25 (1.64–3.10)	2.76 (1.86–4.11)	2.19 (1.60–3.00)
LR−	0.15 (0.12–0.19)	0.16 (0.12–0.21)	0.23 (0.18–0.29)	0.20 (0.15–0.28)	0.56 (0.38–0.83)	0.49 (0.36–0.67)
DOR	18.3 (14.6–22.9)	25.1 (18.9–33.3)	6.97 (5.51–8.83)	11.0 (8.02–15.2)	4.93 (3.32–7.33)	4.46 (3.26–6.11)
AUC ROC curve	0.90 (0.85–0.95)		0.85 (0.82–0.87)		0.71 (0.64–0.79)	

incomplete information on 6CIT, leaving 78 patients available for analysis. 6CIT scores were adjusted where necessary because of incorrect scoring or reporting in primary care (Cannon and Larner 2016). Reference diagnoses were dementia (16), mild cognitive impairment (18), and no cognitive impairment (44). Because of the small number of dementia and mild cognitive impairment cases, these were combined for analysis as "any cognitive impairment". Using either of the specified cut-offs, 6CIT showed only modest sensitivity (>0.70), specificity (>0.55), positive and negative predictive values (>0.55 and >0.70 respectively) for the diagnosis of any cognitive impairment (Table 4.21). Unitary measures of test utility (correct classification accuracy, Youden index, predictive summary index, diagnostic odds ratio)

Table 4.21 Demographic and diagnostic parameters for 6CIT performed in primary care for the diagnosis of any cognitive impairment (dementia or mild cognitive impairment) at cut-offs of ≤4/28 or ≤7/28 (adapted from Connon and Larner 2017b)

	6CIT	
N	78	
F:M (% female)	36:42 (46)	
Age range (years)	37–88 (median 60.5)	
Prevalence of cognitive impairment (= pre-test probability)	0.44	
Pre-test odds = prevalence/(1 – prevalence)	0.77	
Cut-off	**≤4/28**	**≤7/28**
Accuracy	0.67 (0.56–0.77)	0.65 (0.55–0.76)
Net Reclassification Improvement (NRI)	0.23	0.21
Sensitivity (Se)	0.79 (0.66–0.93)	0.71 (0.55–0.86)
Specificity (Sp)	0.57 (0.42–0.71)	0.61 (0.47–0.76)
Y	0.36	0.32
PPV (= post-test probability)	0.59 (0.44–0.73)	0.59 (0.43–0.74)
NPV	0.78 (0.64–0.92)	0.73 (0.59–0.87)
PSI	0.37	0.32
LR+	1.84 (1.26–2.69) = unimportant	1.83 (1.19–2.81) = unimportant
LR−	0.36 (0.25–0.53) = small	0.48 (0.31–0.74) = small
DOR	5.08 (3.47–7.42)	3.81 (2.48–5.87)
Post-test odds (= pre-test odds × LR+)	1.42	1.41
CUI+	0.47 (poor)	0.41 (poor)
CUI−	0.44 (poor)	0.45 (poor)

suggested a slight advantage using the ≤4/28 cut-off. The greater sensitivity of the ≤7/28 cut-off reported in a diagnostic test accuracy study based in secondary care (Larner 2015e) was not found in this study.

6CIT has also proved useful in individual cases to detect cognitive impairment (e.g. Rawle and Larner 2013; Ziso and Larner 2015; Aji et al. 2016; Case Studies 4.2 and 5.2). Because it is entirely verbal, 6CIT may have a particular role in the screening of cognitive function in visually impaired patients (Larner 2015f).

Case Study 4.2 Clinical Utility of Cognitive Screening Instruments in Diagnosis of Dementia: 6CIT

A 53 year-old man presented to his primary care practitioner accompanied by his mother and she complained about her son's poor short term memory. On referral to CFC, the mother's complaint about her son was change in personality: he required prompting for most activities. He responded to all questions on the MMSE with "Not a clue", reflecting an impoverished speech output and

Case Study 4.2 (continued)

economy of effort, thus explaining his maximal score of 28/28 on 6CIT performed in primary care. He was impaired on the Frontal Assessment Battery (see Sect. 4.2.1) with a score of 6/18, with points dropped on tests of similarities, lexical fluency, motor series programming, conflicting instructions, and go-no-go. Structural brain imaging showed asymmetrical brain volume loss worse on the left with an anterior-posterior severity gradient, with sparing of the occipital lobes. A diagnosis of frontotemporal lobar degeneration was made.

4.1.7 DemTect

The DemTect Scale is a brief (8–10 min) screening test for dementia (Kalbe et al. 2004; Kalbe and Kessler 2017). It comprises five short subtests (Box 4.8), two of which (number transcoding, semantic fluency) form the Rapid Dementia Screening Test also published by these authors (Kalbe et al. 2003). Raw scores are transformed to give a final score (maximum 18) which attempts to correct for patient age and education, unlike the raw MMSE score. Transformed scores are classified as "suspected dementia" (score ≤8), "mild cognitive impairment" (9–12), and "appropriate for age" (13–18), a feature which may aid in test interpretation and which is absent from many other CSIs.

Box 4.8 Item Content of DemTect

10 word list (×2)	3
Number transcoding	3
Semantic fluency	4
Reverse digit span	3
Delayed recall of word list	5
(Education ≤11 years +1)	
Total score	**18**

DemTect scores are reported to correlate with MMSE scores above 20/30 in patients with dementia (Kalbe et al. 2004) and also with the Global Clinical Impression (Möller et al. 2009). DemTect is also reported to have the capacity to detect patients with early dementia and MCI (Kalbe et al. 2004). It has been validated using ^{18}FDG-PET imaging (Scheurich et al. 2005) and has been used in some geriatric services as a measure of cognitive abilities (Burkhardt et al. 2006). Use of DemTect has also been reported in CADASIL, a subcortical dementia (Hennerici et al. 2006:137 [Case 31]).

The diagnostic utility of DemTect in screening for dementia in day-to-day clinical practice has been assessed in a prospective study of 111 consecutive new referrals to

CFC seen over a 1-year period (September 2004 to September 2005; Larner 2007d, e). DemTect proved easy to administer, and no patient failed to complete the test. DemTect scores ranged from 0 to 18 (median 7, mode 6 and 7). Sixty-four patients (=58%) scored ≤8 on the DemTect (="suspected dementia") and 47 (=42%) scored >8 (="normal for age" or "MCI"). Using the cut-off of 8/18, DemTect proved to have good sensitivity, specificity, and positive predictive value for the diagnosis of dementia in this clinic population (Table 4.22), with area under the ROC curve of 0.87 (Fig. 4.6).

Table 4.22 Demographic and diagnostic parameters for DemTect (adapted from Larner 2007e)

	DemTect
N	111
F:M (% female)	59:52 (53)
Age range (years)	23–86 (median 63)
Prevalence dementia (= pre-test probability)	0.52
Pre-test odds = prevalence/(1 – prevalence)	1.08
Cut-off	**≤8/18**
Accuracy	0.78 (0.71–0.86)
Net Reclassification Improvement (NRI)	0.26
Sensitivity (Se)	0.85 (0.75–0.94)
Specificity (Sp)	0.72 (0.60–0.84)
Y	0.57
PPV (= post-test probability)	0.78 (0.67–0.88)
NPV	0.81 (0.70–0.92)
PSI	0.59
LR+	2.99 (1.92–4.65) = small
LR–	0.22 (0.14–0.34) = small
DOR	13.8 (7.55–25.2)
Post-test odds (= pre-test odds × LR+)	3.23
CUI+	0.66 (good)
CUI–	0.58 (adequate)
AUC ROC curve	0.87 (0.80–0.93)

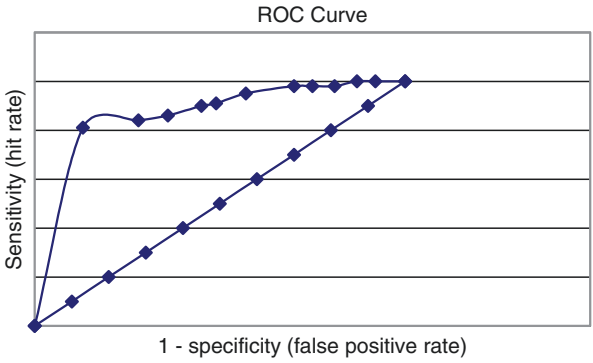

Fig. 4.6 ROC curve for DemTect (Larner 2007e) reprinted with permission

The correlation coefficient for DemTect scores and simultaneously recorded MMSE scores (n = 108) was r = 0.76 (t = 12.0, df = 106, $p < 0.001$); and for DemTect scores and simultaneously recorded ACE scores (n = 96) was r = 0.79 (t = 12.5, df = 94, $p < 0.001$). The correlation of DemTect with MMSE compared favourably with the correlations reported between these tests in control, MCI and AD patients reported in the index paper (Kalbe et al. 2004).

Hence, DemTect proved a useful screening test for dementia, as indicated by the good sensitivity. Its advantages include brevity and ease of use, which may be particularly helpful in the primary care setting, and the use of defined cut-offs ("suspected dementia", "mild cognitive impairment", and "appropriate for age") which may be useful to guide appropriate clinical management (Larner 2007d, e).

4.1.8 Montreal Cognitive Assessment (MoCA)

The Montreal Cognitive Assessment (MoCA; available free, and in multiple languages, at www.mocatest.org) is a brief (10–15 min) cognitive screening test which has been reported to be of particular use in screening for MCI, being more stringent than the MMSE (Box 4.9; Nasreddine et al. 2005). MoCA has been increasingly used worldwide and may detect cognitive impairment in a variety of conditions including vascular cognitive impairment, Parkinson's disease and Huntington's disease as well as Alzheimer's disease and MCI (Julayanont and Nasreddine 2017).

Box 4.9 Item Content of MoCA and s-MoCA

	MoCA	s-MoCA
Reference	Nasreddine et al. 2005	Roalf et al. 2016
Orientation: Time	4	
Orientation: Place	2	1
Attention/Concentration	6 (3 for serial 7s; 2 repeating digits forwards or backwards; 1 tapping to letter A)	3 (3 for serial 7s)
Memory: Recall	5	5
Lexical verbal fluency: in 1 min	1	1
Language: Naming	3	1 (rhinoceros)
Language: Repetition	2	
Visuospatial abilities: Wire (Necker) cube	1	
Visuospatial abilities: Clock drawing	3	3
Visuospatial abilities: Trail making	1	1
Abstraction	2	1 (measurement)
Total Score	**30**	**16**

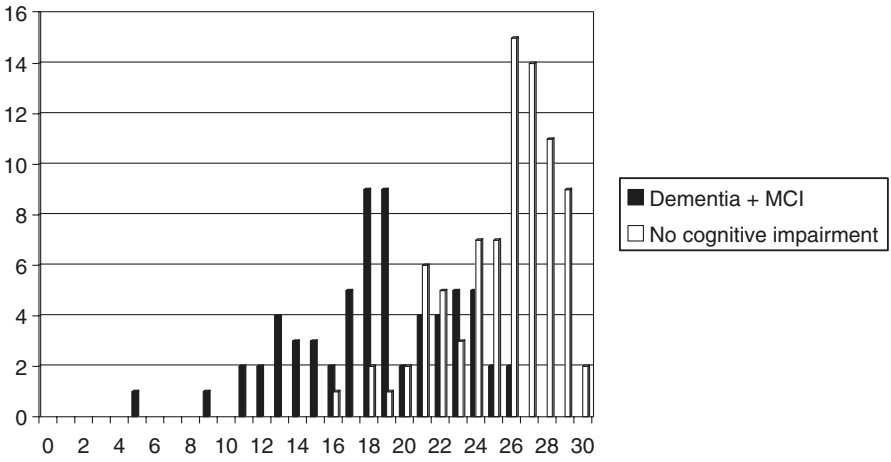

Fig. 4.7 MoCA scores vs diagnosis (cognitive impairment/no cognitive impairment) (Larner 2012a) reprinted with permission

The utility of MoCA in screening for cognitive impairment in day-to-day clinical practice has been assessed prospectively in two studies in CFC (September 2009 to March 2011: Storton and Larner 2011; Larner 2012a; and June 2015 to May 2016: Larner 2016b, c, 2017d), comparing MoCA with MMSE and MACE respectively (Chap. 6).

In the first of these studies (n = 150), MoCA proved easy to administer, no patient failing to complete the test. There was a weak negative correlation between age and MoCA score ($r = -0.38$; $t = 4.94$, df = 148, $p < 0.001$). MoCA and simultaneously recorded MMSE scores ($n = 148$) correlated highly ($r = 0.85$; $t = 19.2$, df = 146, $p < 0.001$). Using the test of agreement (Cohen's kappa statistic) for MMSE and MoCA, $\kappa = 0.39$ (95% CI 0.26–0.53), where 1 is perfect agreement between tests and 0 is agreement due to chance alone.

In the cognitively impaired (dementia and MCI) group, the mean MoCA score was 18.3 ± 4.5, and in the non-impaired group 25.2 ± 3.2 (Fig. 4.7; cf. Figure 4.2). The mean MoCA scores differed significantly between the two groups ($t = 12.0$, df = 148, $p < 0.001$). Mean MoCA scores in the demented and MCI groups were 16.6 ± 4.4 and 20.4 ± 3.8 respectively and differed significantly between the two groups ($t = 3.19$, df = 63, $p < 0.01$).

MoCA performance on measures of discrimination was initially examined for diagnosis of any cognitive impairment, i.e. both dementia and MCI combined (Larner 2012a; Fig. 4.8). Sensitivity and specificity of MoCA was examined at all cut-off values with the optimal cut-off being defined by maximal test accuracy for the differential diagnosis of cognitive impairment versus no cognitive impairment (Larner 2015d). Optimal accuracy for MoCA was 0.81 at a cut-off of ≥20/30 (a further example of the need to revise test cut-offs for pragmatic use from those defined in index studies; see also ACE and ACE-R, see Sects. 4.1.5.1 and 4.1.5.3 respectively). Using this revised cut-off reduced test sensitivity from that using the index paper cut-off (≥26/30; Nasreddine et al. 2005).

Subsequent further analysis of this study dataset (Larner 2016a, 2017e) allowed performance for diagnosis of dementia and MCI to be examined separately (Table 4.23).

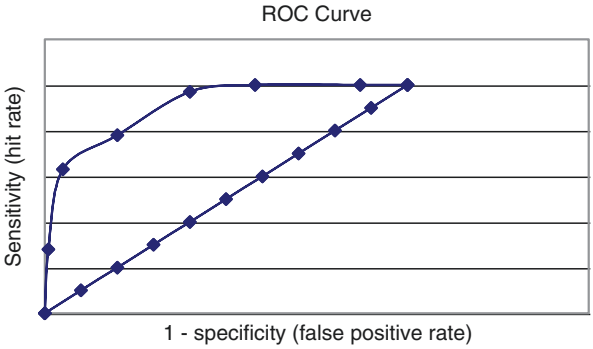

Fig. 4.8 ROC curve for MoCA (Larner 2012a) reprinted with permission

Table 4.23 Demographic and diagnostic parameters for MoCA cut-off ≥26/30 (data of Larner 2012a, reanalysed in Larner 2016a, 2017e)

	MoCA		
N	150		
F:M (% female)	57:93 (38)		
Age range (years)	20–87 (median 61)		
	Diagnosis of dementia vs. no dementia	**Diagnosis of dementia vs. MCI**	**Diagnosis of MCI vs. no cognitive impairment**
N	150 (36 vs 114)	65 (36 vs 29)	114 (29 vs 85)
Prevalence (= pre-test probability)	0.24	0.55	0.254
Pre-test odds = prevalence/(1 − prevalence)	0.315	1.24	0.341
Accuracy	0.59 (0.51–0.67)	0.58 (0.46–0.70)	0.68 (0.60–0.77)
Net Reclassification Improvement (NRI)	0.35	0.03	0.43
Sensitivity (Se)	1.00	1.00	0.93 (0.84–1.00)
Specificity (Sp)	0.46 (0.37–0.56)	0.07 (0–0.16)	0.60 (0.50–0.70)
Y	0.46	0.07	0.53
PPV (= post-test probability)	0.37 (0.27–0.47)	0.57 (0.45–0.69)	0.44 (0.32–0.57)
NPV	1.00	1.00	0.96 (0.91–1.00)
PSI	0.37	0.57	0.40
LR+	1.87 (1.57–2.22) = unimportant	1.07 (0.97–1.19) = unimportant	2.33 (1.76–3.08) = small
LR−	0 = large	0 = large	0.11 (0.09–0.15) = moderate
DOR	∞	∞	20.3 (15.3–26.8)
Post-test odds (= pre-test odds × LR+)	0.59	1.33	0.79
CUI+	0.37 (poor)	0.57 (adequate)	0.41 (poor)
CUI−	0.46 (poor)	0.07 (very poor)	0.58 (adequate)

This study of MoCA has been included in meta-analyses of MoCA (Tsoi et al. 2015; Ciesielska et al. 2016).

In the second CFC MoCA study (Larner 2017d; n = 260), MoCA again proved very sensitive for the diagnosis of both dementia and MCI (Table 4.24; Fig. 4.9).

The high sensitivity of the MoCA, compared to the MMSE, may be deemed one of the most desirable features of the test. Combining these tests has also been examined (see Sect. 6.2.1).

MoCA has also proved useful in individual cases to detect cognitive impairment (e.g. Connon and Larner 2017a).

Table 4.24 Demographic and diagnostic parameters for MoCA (cut-off ≥26/30) for diagnosis of dementia versus no dementia and MCI versus subjective memory complaint (SMC) (adapted and corrected from Larner 2017d)

	MoCA	
N	260	
F:M (% female)	118:142 (45)	
Age range (years)	22–89 (median 59)	
	Dementia vs no dementia (=MCI + SMC)	**MCI vs SMC**
N	260 (43 vs 217)	217 (75 vs 142)
Prevalence (= pre-test probability)	0.165	0.346
Pre-test odds = prevalence/(1 − prevalence)	0.198	0.528
Accuracy	0.43 (0.37–0.49)	0.60 (0.54–0.67)
Net Reclassification Improvement (NRI)	0.265	0.254
Sensitivity (Se)	1.00	0.92 (0.86–0.98)
Specificity (Sp)	0.31 (0.25–0.38)	0.44 (0.36–0.52)
Y	0.31	0.36
PPV (= post-test probability)	0.22 (0.16–0.28)	0.46 (0.38–0.54)
NPV	1.00	0.91 (0.84–0.98)
PSI	0.22	0.37
LR+	1.46 (1.33–1.59) = unimportant	1.63 (1.39–1.92) = unimportant
LR−	∞ = large	0.18 (0.16–0.21) = moderate
DOR	∞	8.91 (7.60–10.5)
Post-test odds (= pre-test odds × LR+)	0.289	0.860
CUI+	0.22 (very poor)	0.43 (poor)
CUI−	0.31 (very poor)	0.40 (poor)
AUC ROC curve	0.914 (0.892–0.937)	0.823 (0.794–0.851)
Effect size (Cohen's d)	2.01 (large)	1.25 (large)

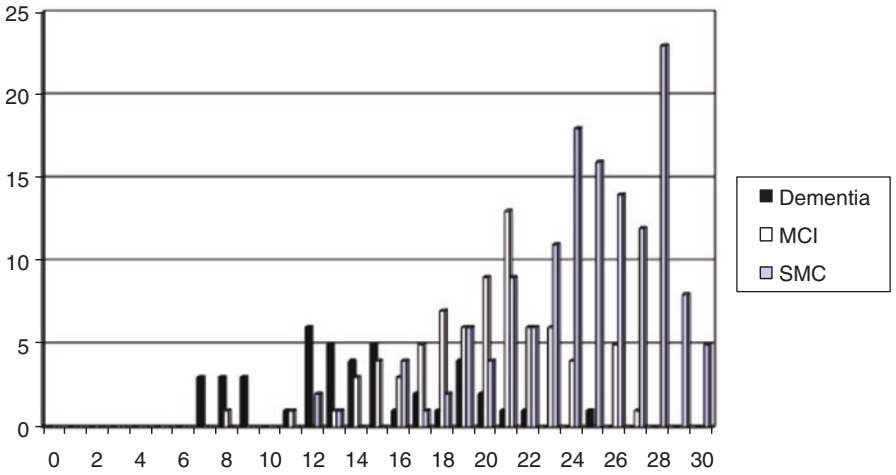

Fig. 4.9 MoCA scores vs diagnosis (dementia/MCI/SMC) (adapted from Larner 2017d) reprinted with permission

4.1.8.1 MoCA Subscores: MoCA Ala and MoCA VLOM Ratio

Like the MMSE (see Sect. 4.1.1) and the ACE (see Sect. 4.1.5.1), the item content of MoCA (Box 4.9) features tests of attention (score 6), memory/delayed recall (score 5) and construction (score 5). Hence, subscores may be derived from the MoCA which are analogous to the Ala subscore (Sect. 4.1.1.1) and the modified Ala subscore (see Sect. 4.1.5.2) and with the same score range (−5 to +10), thus:

$$\text{MoCA Ala subscore} = 5/6\left(\text{Attention}\right) - \text{Memory} + \text{Construction}$$

Likewise, MoCA has tests of verbal fluency (score 1), language (naming 3, repetition 2), and orientation (score 6) as well as delayed recall, such that a subscore analogous to the ACE VLOM ratio (see Sect. 4.1.5.2) may be derived, given thus:

$$\text{MoCA VLOM ratio} = \left(\text{verbal fluency} + \text{language}\right)/\left(\text{orientation} + \text{delayed recall}\right)$$

with possible maxima of (verbal fluency + language) = 6 and (orientation + delayed recall) = 11. (Derivation of a VLOM ratio to differentiate AD and FTLD has also been reported using the Cambridge Behavioural Inventory; see Sect. 5.2.1; Larner 2008b.)

Data from the first CFC MoCA pragmatic diagnostic accuracy study (Larner 2012a) were examined, specifically for those patients with a clinical diagnosis of AD, DLB, or FTLD (Rawle and Larner 2014). Of the cohort of 150 patients tested, 36 were identified with the target clinical diagnoses (AD = 22, DLB = 5, FTLD = 9). Of the FTLD cases, six had behavioural variant FTD and three had progressive non-fluent aphasia.

In the AD group the mean MoCA Ala subscore was 5.31 ± 2.53, and in the DLB group 3.80 ± 3.49. The mean MoCA Ala subscores did not differ significantly between the two groups ($t = 1.13$, df = 25, $p > 0.1$). At the specified Ala subscore cut-off of <5 used in the index paper (Ala et al. 2002), MoCA Ala subscore was neither sensitive (0.60) nor specific (0.59) for diagnosis (Table 4.25). Hence MoCA Ala subscore did not appear to be particularly helpful in differentiating DLB and AD, as noted in similar pragmatic studies of the analogous subscore derived from the MMSE and the ACE (Larner 2003, 2004).

Examining MoCA VLOM ratios, a cut-off of <1 identified 8/9 FTLD cases and 14/22 AD cases, hence was sensitive for a diagnosis of FTLD (0.89). At a cut-off of ≥0.67, overall test accuracy was identical (0.71), identifying 17/22 AD cases and 5/9 FTLD cases, hence was sensitive for a diagnosis of AD (0.77) (Table 4.26). MoCA

Table 4.25 Diagnostic parameters for MoCA Ala subscore (adapted from Rawle and Larner 2014)

	MoCA Ala subscore
N	27 (AD = 22, DLB = 5)
Cut-off	**MoCA Ala subscore < 5**
Accuracy	0.59 (0.41–0.78)
Sensitivity (Se)	0.60 (0.17–1.00)
Specificity (Sp)	0.59 (0.39–0.80)
Y	0.19
PPV	0.25 (0.01–0.50)
NPV	0.87 (0.69–1.00)
PSI	0.12
LR+	1.47 (0.62–3.52) = unimportant
LR−	0.68 (0.28–1.62) = unimportant
DOR	2.17 (0.90–1.65)
CUI+	0.15 (very poor)
CUI−	0.51 (adequate)

Table 4.26 Diagnostic parameters for MoCA VLOM ratio at different cut-offs (adapted from Rawle and Larner 2014)

	MoCA VLOM ratio	
N	31 (AD = 22, FTLD = 9)	
Cut-off	**≥0.67 (for diagnosis of AD)**	**<1 (for diagnosis of FTLD)**
Accuracy	0.71 (0.55–0.87)	0.71 (0.55–0.87)
Sensitivity (Se)	0.77 (0.60–0.95)	0.89 (0.68–1.00)
Specificity (Sp)	0.56 (0.23–0.88)	0.64 (0.44–0.84)
Y	0.33	0.53
PPV	0.81 (0.64–0.98)	0.50 (0.26–0.75)
NPV	0.50 (0.19–0.81)	0.93 (0.81–1.00)
PSI	0.31	0.43
LR+	1.74 (0.81–3.74) = unimportant	2.44 (1.34–4.45) = small
LR−	0.41 (0.19–0.88) = small	0.17 (0.09–0.32) = moderate
DOR	4.25 (1.98–9.13)	14.0 (7.69–25.5)
CUI+	0.63 (adequate)	0.44 (poor)
CUI−	0.28 (very poor)	0.59 (adequate)

VLOM ratio appeared useful in diagnosis, with greater sensitivity for FTLD or AD depending on the higher or lower cut-off respectively. This high sensitivity for FTLD diagnosis was encouraging, since some previous studies suggested that the ACE VLOM ratio was not sensitive for identifying FTLD (Bier et al. 2004; Larner 2007b).

4.1.8.2 Short MoCA (s-MoCA)

Various short forms of the MoCA have been described (see McDicken et al. 2018 for a systematic review). One of these, the short-MoCA (s-MoCA), was described by Roalf et al. (2016), based on the 8 items of the MoCA found to be most discriminative by item response theory and computerised adaptive testing (Box 4.9; score range 0–16, impaired to normal).

s-MoCA diagnostic accuracy for dementia vs MCI (Table 4.27) and for MCI vs SMC (Table 4.28) was examined in CFC (Larner 2017e) using data from a historical cohort of patients tested with the MoCA (Larner 2012a) for validation, and from an independent cohort (Larner 2017d) for reproducibility (Table 4.27).

s-MoCA was found to be highly sensitive for detection of cognitive impairment but with a much lower specificity, a pattern of performance similar to that

Table 4.27 Demographic and diagnostic parameters for s-MoCA (cut-off ≥12/16) for diagnosis of dementia versus MCI in validation and reproducibility cohorts (adapted from Larner 2017e)

	s-MoCA validation (Larner 2012a)	s-MoCA reproducibility (Larner 2017d)
N	150 (36 vs 29)	260 (43 vs 75)
F:M (% female)	57:93 (38)	118:142 (45)
Age range (years)	20–87 (median 61)	22–89 (median 59)
Prevalence of dementia (= pre-test probability)	0.55	0.36
Pre-test odds = prevalence/(1 − prevalence)	1.24	0.57
Accuracy	0.64 (0.52–0.76)	0.40 (0.31–0.49)
Net Reclassification Improvement (NRI)	0.09	0.04
Sensitivity (Se)	0.94 (0.87–1.00)	0.98 (0.93–1.00)
Specificity (Sp)	0.25 (0.09–0.41)	0.07 (0.01–0.12)
Y	0.19	0.05
PPV (= post-test probability)	0.62 (0.49–0.75)	0.38 (0.29–0.46)
NPV	0.78 (0.51–1.00)	0.83 (0.54–1.00)
PSI	0.40	0.21
LR+	1.26 (1.00–1.58) = unimportant	1.05 (0.97–1.13) = unimportant
LR−	0.22 (0.18–0.28) = small	0.35 (0.32–0.38) = small
DOR	5.73 (4.60–7.14)	3.00 (2.78–3.24)
Post-test odds (= pre-test odds × LR+)	1.56	0.60
CUI+	0.58 (adequate)	0.37 (poor)
CUI−	0.19 (very poor)	0.06 (very poor)
AUC ROC curve	0.67 (0.61–0.74)	0.83 (0.79–0.87)
Effect size (Cohen's d)	0.65 (medium)	1.33 (large)

Table 4.28 Demographic and diagnostic parameters for s-MoCA (cut-off ≥12/16) for diagnosis of MCI versus SMC in validation and reproducibility cohorts (adapted from Larner 2017e)

	s-MoCA validation (Larner 2012a)	s-MoCA reproducibility (Larner 2017d)
N	150 (29 vs 85)	260 (75 vs 142)
F:M (% female)	57:93 (38)	118:142 (45)
Age range (years)	20–87 (median 61)	22–89 (median 59)
Prevalence of MCI (= pre-test probability)	0.254	0.346
Pre-test odds = prevalence/(1 − prevalence)	0.341	0.528
Accuracy	0.68 (0.60–0.77)	0.71 (0.65–0.77)
Net Reclassification Improvement (NRI)	0.426	0.364
Sensitivity (Se)	0.75 (0.59–0.91)	0.93 (0.88–0.99)
Specificity (Sp)	0.66 (0.56–0.76)	0.60 (0.52–0.68)
Y	0.41	0.53
PPV (= post-test probability)	0.42 (0.28–0.56)	0.55 (0.46–0.64)
NPV	0.89 (0.81–0.97)	0.94 (0.90–0.99)
PSI	0.31	0.49
LR+	2.22 (1.54–3.21) = small	2.33 (1.89–2.87) = small
LR−	0.38 (0.26–0.54) = small	0.11 (0.09–0.14) = moderate
DOR	5.84 (4.05–8.43)	20.9 (16.9–25.7)
Post-test odds (= pre-test odds × LR+)	0.76	1.23
CUI+	0.32 (very poor)	0.51 (adequate)
CUI−	0.59 (adequate)	0.56 (adequate)
AUC ROC curve	0.83 (0.79–0.87)	0.83 (0.80–0.86)
Effect size (Cohen's d)	1.19 (large)	1.37 (large)

observed for the MoCA. Examining older patients only (>65 years) showed better results. The corollary of high negative predictive values suggested that normal scores on s-MoCA might be used in practice to rule out the need for further investigation. The generally larger effect sizes for distinguishing MCI from SMC may relate to the original purpose of the MoCA to detect MCI (Nasreddine et al. 2005).

4.1.9 Test Your Memory (TYM) Test

The Test Your Memory (TYM) test is a 10-item cognitive test instrument (Box 4.10) with scores ranging from 0 to 50, which is self-administered under medical supervision (Brown et al. 2009; Brown 2017). In the index study of TYM, a cross-sectional study of dementia patients and normal controls, the instrument was found to be highly sensitive and specific for the diagnosis of AD, and to detect more AD cases than the MMSE (Brown et al. 2009).

Box 4.10 Item Content of TYM

Orientation	10
Copying	2
Retrograde memory	3
Calculation	4
Fluency (phonemic)	4
Similarities	4
Naming	5
Visuospatial 1 and 2 (clock)	7
Anterograde memory	6
Executive	5
Total score	**50**

The diagnostic utility of TYM in the diagnosis of dementia in day-to-day clinical practice was assessed prospectively in new referrals to CFC and to the Brooker Centre, Runcorn (n = 224) seen over a 23-month period (February 2008 to December 2009; Hancock and Larner 2011). TYM proved easy to use, being completed in about 5–10 min by all but 10 cases (=4.5%); a higher drop-out rate would seem to be inevitable with self-administered, as opposed to clinician administered, tests. Subjectively, use of the TYM did not seem to slow the clinic down. Objectively, the patient supervision required (from patient relatives or carers, not clinic staff) was measured using the Executive item score of the TYM for the amount of help the patient needed, as observed by clinic staff, ranging from 1 (Major) to 5 (None). For the whole cohort, the mode, median and mean scores for this item were 5 (100/224 patients required no assistance at all in completing the TYM), 4, and 3.79 ± 1.38, respectively. For the group with dementia ($n = 78$), the figures were 3 (only three patients completed without any help), 3, and 2.51 ± 1.26.

TYM scores ranged from 0 to 50. For the group with dementia ($n = 78$), the mode, median, and mean TYM scores were 26, 26, and 23.2 ± 12.3, respectively: for the non-demented group ($n = 146$) the mode, median, and mean scores were 48, 42, and 40.2 ± 8.2 (Fig. 4.10, cf. Fig. 4.1). The mean TYM scores differed significantly between the demented and non-demented groups ($t = 44.1$, df = 222, $p < 0.001$). In the non-demented group, the mode, median and mean scores for the MCI patients ($n = 39$) were 41, 39, and 37.5 ± 6.2. The mean TYM scores differed significantly between the demented and MCI groups ($t = 6.9$, df = 115, $p < 0.001$).

At the TYM cut-off of ≤42/50 specified in the index paper (Brown et al. 2009), test sensitivity for the diagnosis of dementia was good (0.95) but specificity was suboptimal (0.45), with test accuracy of 0.63. At the TYM cut-off of ≤42/50, 98% of the AD/mixed dementia cases ($n = 54$) were detected, as compared to 93% in the index paper.

In view of the suboptimal TYM specificity at the ≤42/50 cut-off, and because of the different casemix in this population as compared to the index study, the

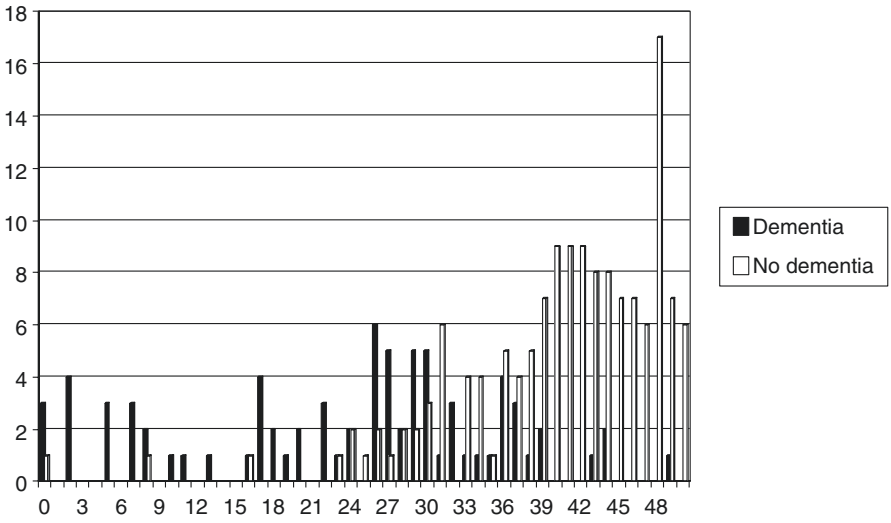

Fig. 4.10 TYM scores vs. diagnosis (dementia/no dementia) (Hancock and Larner 2011) reprinted with permission

sensitivity and specificity of TYM was examined at all cut-off values. Optimal test accuracy for the differential diagnosis of dementia/not dementia in this cohort was found to be 0.83 at the TYM cut-off of ≤30/50. Hence TYM cut-off was adjusted, as for the pragmatic CFC studies of ACE, ACE-R and MoCA (see Sects. 4.1.5.1, 4.1.5.3, and 4.1.8 respectively). At the revised cut-off, TYM specificity was greatly improved (0.88 vs 0.45) for some loss of sensitivity (0.73 vs 0.95) and ability to detect AD/mixed dementia cases (78% vs 98%) (Table 4.29; Fig. 4.11).

Although the sample size was relatively small, comparison of MCI ($n = 39$) and non-MCI non-demented patients ($n = 107$) was undertaken. In the latter group the mode, median and mean TYM scores were 48, 43, and 41.1 ± 8.6. Mean TYM scores differed significantly between the MCI and non-MCI non-demented groups ($t = 2.4$, df = 144, $p < 0.01$). However, diagnostic accuracy was relatively poor, maximal at TYM cut-off ≤36/50, with sensitivity 0.41, specificity 0.80, PPV 0.43, NPV 0.79, LR+ 2.1, and LR− 0.73.

The correlation between TYM scores and MMSE scores ($n = 210$) was highly positive ($r = 0.81$; $t = 19.9$, df = 208, $p < 0.001$), as was the correlation between TYM scores and ACE-R scores ($n = 140$; $r = 0.86$; $t = 20.0$, df = 138, $p < 0.001$). Using the test of agreement (Cohen's kappa statistic) which measures the percentage of agreement beyond chance, for TYM and MMSE $\kappa = 0.69$ (95% CI = 0.58–0.80), and for TYM and ACE-R $\kappa = 0.69$ (95% CI = 0.56–0.83). TYM is therefore a useful test which may be of particular value in situations where clinician time is limited,

Table 4.29 Demographic and diagnostic parameters for TYM (adapted from Hancock and Larner 2011)

	TYM
N	224
F:M (% female)	94:130 (42)
Age range (years)	20–90 (mean 63.3 ± 12.6)
Prevalence of dementia (= pre-test probability)	0.35
Pre-test odds = prevalence/(1 – prevalence)	0.54
Cut-off	**≤30/50**
Accuracy	0.83 (0.78–0.88)
Net Reclassification Improvement (NRI)	0.48
Sensitivity (Se)	0.73 (0.63–0.83)
Specificity (Sp)	0.88 (0.83–0.94)
Y	0.61
PPV (= post-test probability)	0.77 (0.67–0.87)
NPV	0.86 (0.80–0.92)
PSI	0.63
LR+	6.28 (3.94–10.0) = moderate
LR−	0.30 (0.19–0.49) = small
DOR	20.6 (12.9–32.8)
Post-test odds (= pre-test odds × LR+)	3.39
CUI+	0.56 (adequate)
CUI−	0.76 (good)
AUC ROC curve	0.89 (0.84–0.93)

Study undertaken in collaboration with Dr P Hancock, Memory Clinic, Brooker Centre, Runcorn

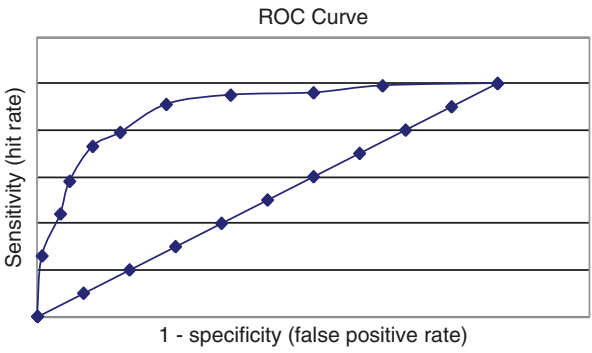

Fig. 4.11 TYM ROC curve (Hancock and Larner 2011) reprinted with permission

precluding performance of clinician-administered tests such as the MMSE or ACE-R (Hancock and Larner 2011).

TYM has also proved useful in individual cases to detect cognitive impairment (e.g. Ali et al. 2013).

4.1.9.1 Hard TYM (H-TYM) or TYM-MCI

A more stringent version of TYM, the Hard-TYM or H-TYM (Brown et al. 2014; Brown 2017), later renamed TYM-MCI (Brown et al. 2017), has subsequently been developed to detect mild AD and amnestic MCI (aMCI). H-TYM is another patient self-administered instrument which tests visual (0–15, impaired to normal) and verbal recall (0–15, impaired to normal) of newly learnt material, to give a total score of 0–30 impaired to normal (Brown 2017:225–7; Brown et al. 2014, 2017). The proof-of-concept study recruited patients with known diagnoses of aMCI/AD and normal controls, and H-TYM detected 95% of cases at a cut-off of ≤13/30, with sensitivity 0.95 and specificity 0.93 (Brown et al. 2014).

An independent pragmatic study of H-TYM was undertaken in CFC to examine its diagnostic accuracy in patients whose differential diagnosis at initial clinical assessment included MCI (Larner 2015g). Of 314 consecutive new outpatient referrals seen over a 12-month period (October 2013 to October 2014; F:M = 158:156), 80 were diagnosed with dementia (prevalence = 0.25) based on judgment of an experienced clinician applying widely accepted clinical diagnostic criteria for dementia (DSM-IV) and MCI (Petersen). In 38 cases (prevalence = 0.12 of whole cohort; 0.16 of non-demented patients; F:M = 17:21, median age 55.5 years) H-TYM was administered because of clinical uncertainty as to whether the diagnosis was MCI or subjective memory complaint. All these patients had scored ≥24/30 on MMSE (see Sect. 4.1.1) and/or ≤10/28 on the 6CIT (= "normal cognition" 0–4, or "questionable impairment" 5–9; Gale and Larner 2017; see Sect. 4.1.6) and were not demented. All patients completed H-TYM in around 5–10 min. H-TYM scores were not used in the final diagnostic judgment to avoid review bias. There was a low negative correlation between patient age and H-TYM scores ($r = -0.37$), as in the index study. There were low correlations between H-TYM scores and MMSE scores ($r = 0.22$) and 6CIT scores ($r = -0.45$, 6CIT negatively scored).

At the H-TYM cut-off of ≤13/30 specified in the index paper, test sensitivity for diagnosis of MCI was found to be 0.67 with specificity of 0.66 (Table 4.30, left hand column). Revising the cut-off to ≤15/30 to maximize test sensitivity (1.00), specificity was 0.50 (Table 4.30, right hand column).

As anticipated, the results in this pragmatic study were less impressive than in the case-control paradigm of the index study. H-TYM or TYM-MCI is a stringent test, which should be reserved for patients with evidence of cognitive impairment but no dementia. In the CFC patient cohort, H-TYM proved very sensitive for MCI when the diagnosis could not be made on initial consultation and cognitive testing (MMSE, 6CIT), although this situation was relevant to only a small number of patients since the clinical diagnosis of MCI was made in the majority of cases in this cohort (61/67 = 91%) without recourse to H-TYM. Cut-off revision to maximize test sensitivity reduced specificity (as in the index study) and increased false positive rate (0.34 rising to 0.50).

H-TYM has also proved useful in individual cases to monitor cognitive impairment (Ellis et al. 2017, case 2).

Table 4.30 Demographic and diagnostic parameters for H-TYM for diagnosis of MCI at different cut-offs (adapted from Larner 2015g)

	H-TYM	
N	38	
F:M (% female)	17:21 (45)	
Age range (years)	26–82 (median 55.5)	
Prevalence of mild cognitive impairment (= pre-test probability)	0.16	
Pre-test odds = prevalence/(1 – prevalence)	0.19	
H-TYM cut-off	**≤13/30**	**≤15/30**
Accuracy	0.66 (0.51–0.81)	0.58 (0.42–0.74)
Net Reclassification Improvement (NRI)	0.50	0.42
Sensitivity (Se)	0.67 (0.29–1.00)	1.00
Specificity (Sp)	0.66 (0.49–0.82)	0.50 (0.33–0.67)
Y	0.33	0.50
PPV (= post-test probability)	0.27 (0.04–0.49)	0.27 (0.09–0.46)
NPV	0.91 (0.80–1.00)	1.00
PSI	0.18	0.27
LR+	1.94 (0.92–4.07) = unimportant	2.00 = small
LR–	0.51 (0.24–1.07) = unimportant	0 = large
DOR	3.82 (1.82–8.01)	∞
Post-test odds (= pre-test odds × LR+)	0.37	0.38
CUI+	0.18 (very poor)	0.27 (very poor)
CUI–	0.60 (adequate)	0.50 (adequate)

4.1.10 Free-Cog

The Free-Cog scale, currently in development, is an attempt to incorporate assessment of cognition and function in a single instrument (Prof A Burns, personal communication, February 2017). Combining cognitive and functional scales may facilitate dementia diagnosis (see Sect. 6.2.3; Larner and Hancock 2012).

Preliminary experience with Free-Cog in CFC (n = 20 to end 2017) suggests that it is quick, acceptable to patients, easy to use and score. Overall Free-Cog scores correlated highly with MACE ($r = 0.91$), but subscores for the cognitive function and executive function components of Free-Cog showed only low correlation ($r = 0.47$; $t = 2.24$, df = 18, $p < 0.05$), as might be anticipated when testing different constructs (see Sect. 6.1.6).

4.1.11 Other Cognitive Screening Instruments: RBANS, MEAMS

Of the large number of other multidomain CSIs available in the literature (Burns et al. 2004; Tate 2010; Larner 2017f:317–8), only occasional experience has been gained in CFC.

The Repeatable Battery for the Assessment of Neuropsychological Status (RBANS; Randolph et al. 1998) was used to monitor cognitive function in a patient with GAD limbic encephalitis (Bonello et al. 2014).

The Middlesex Elderly Assessment of Mental State (MEAMS; Golding 1989) was used in a patient with behavioural variant frontotemporal dementia (see Case Study 4.3).

Case Study 4.3 Clinical Utility of Cognitive Screening Instruments in Diagnosis of Dementia: MEAMS

A 48 year-old woman presented with a 3-year history of altered social cognition and demeanour with decline in occupational function. Relatives noted her to be talkative, overfamiliar, "immature", and to have developed an appetite for sweet foods. The patient was anosognosic for all of these symptoms. There was a family history of "Pick's disease" in her father and paternal grandfather. On the ACE-R she scored 90/100, dropping points on memory and verbal fluency. On the Middlesex Elderly Assessment of Mental State (MEAMS), she passed in 8 of the 12 subtests, a borderline score. Subtests passed were orientation, name learning, remembering pictures, arithmetic, fragmented letters, unusual views, verbal fluency (cf. findings on ACE-R), and motor perseveration. Subtests failed were naming, comprehension, spatial awareness and usual views. MR brain imaging showed temporal lobe atrophy. Neurogenetic testing showed the MAPT gene splice site IVS10 + 16C > T mutation (see Sect. 7.3.2), confirming the clinical diagnosis of behavioural variant frontotemporal dementia.

4.2 Single Domain Cognitive Screening Instruments

All the CSIs described hitherto have been multidomain tests of cognitive function, attempting to address neuropsychological constructs. CSIs which attempt to address single specific cognitive domains may also have utility in particular clinical situations (Mitchell and Malladi 2010b; Larner 2017f:322–8).

4.2.1 Frontal Assessment Battery (FAB)

The Frontal Assessment Battery (FAB) is a bedside test which is reported to identify frontal lobe dysfunction in patients with a variety of neurodegenerative disorders (Box 4.11; Dubois et al. 2000). In selected patient cohorts, it has also been reported to assist in the differential diagnosis of the behavioural variant of FTD (bvFTD) from AD, including the early stages of disease (Slachevsky et al. 2004), although other groups have not found it as useful for this purpose

(Lipton et al. 2005; Castiglioni et al. 2006; Papageorgiou et al. 2009; Woodward et al. 2010).

Box 4.11 Item Content of FAB

Similarities (conceptualisation)	3
Lexical fluency (mental flexibility)	3
Motor series (programming)	3
Conflicting instructions (sensitivity to interference)	3
Go-No-Go (inhibitory control)	3
Prehension behaviour (environmental autonomy)	3
Total score	**18**

In a pragmatic study of the FAB in CFC, FAB was administered to patients (n = 45) whose diagnosis at first consultation was uncertain and in whom the possibility of a frontotemporal lobar degeneration (FTLD) was considered (Larner 2011, 2013e). For the whole group, there was a weak negative correlation between age and FAB score (r = −0.21), and a moderate correlation between FAB and MMSE scores (r = 0.59), as found by others (Castiglioni et al. 2006), but the correlation was weaker for the bvFTD cases (n = 16) only (r = 0.42).

Comparing patients with a final diagnosis of bvFTD with those with other (non-bvFTD) diagnoses, FAB scores ranged between 6 and 16 in the former group, and between 5 and 18 in the latter. Mean FAB scores in the two groups were 9.06 ± 3.34 and 11.66 ± 3.84 respectively, and differed significantly between the two groups (t = 2.27, df = 43, $p < 0.05$).

At the FAB cut-off of ≤12/18, which has been suggested to differentiate bvFTD from AD (Slachevsky et al. 2004), FAB score was very sensitive for the diagnosis of bvFTD vs. all other diagnoses (0.94), but not specific (0.55) (Table 4.31).

Papageorgiou et al. (2009) defined an "executive-to-global" (E/G) ratio:

$$\text{E / G ratio} = \text{FAB score} / \text{MMSE score}$$

E/G ratio was not significantly different between the bvFTD and non-bvFTD groups (Larner 2011) in the CFC cohort (t = 1.42, df = 32, $p > 0.1$).

It should be noted that in patients with other FTLD subtypes seen in this cohort, including progressive non-fluent aphasia (PNFA), FTLD with motor neurone disease, and FTDP-17 due to a tau gene mutation (splice site IVS10 + 16C > T; Larner 2009c, 2012c), FAB was often normal or even at ceiling. Hence, low FAB scores are only sensitive for bvFTD. For this reason, FAB may retain a place in clinical assessment when a diagnosis of bvFTD is being considered, especially since other screening tests for FTD such as the ACE VLOM subscore (see Sect. 4.1.5.2) have proved insensitive (Bier et al. 2004;

Table 4.31 Demographic and diagnostic parameters for FAB for diagnosis of bvFTD (adapted from Larner 2013e)

	FAB
N	45
F:M (% female)	14:31 (31)
Age range (years)	48–81 (median 61)
Prevalence of bvFTD	0.36
Pre-test odds = prevalence/(1 – prevalence)	0.56
Cut-off	**≤12/18**
Accuracy	0.69 (0.55–0.82)
Net Reclassification Improvement (NRI)	0.13
Sensitivity (Se)	0.94 (0.82–1.00)
Specificity (Sp)	0.55 (0.37–0.73)
Y	0.49
PPV (= post-test probability)	0.54 (0.35–0.72)
NPV	0.94 (0.83–1.00)
PSI	0.48
LR+	2.09 (1.37–3.19) = small
LR−	0.11 (0.07–0.17) = moderate
DOR	18.5 (12.1–28.2)
Post-test odds (= pre-test odds × LR+)	1.17
CUI+	0.50 (adequate)
CUI−	0.52 (adequate)
AUC ROC curve	0.70 (0.54–0.86)

Larner 2007b) because of failure to detect bvFTD cases. Other examples of the diagnostic utility of FAB have been noted (Aji et al. 2013; Case Studies 4.2, 7.3, 7.6, and 7.8).

4.2.2 FRONTIER Executive Screen (FES)

The FRONTIER Executive Screen (FES) is a test of executive function composed of three relatively simple items examining those domains of executive function which are typically impaired in bvFTD, namely verbal fluency, verbal inhibitory control, and working memory (see Box 4.12 for item content and scoring). Verbal fluency involves generating words beginning with the letters F and P in 1 min each

Box 4.12 Item content of FRONTIER Executive Screen (FES)

Verbal fluency (F, P)	0–5
Inhibition (sentence completion)	0–5
Working memory (letter span task)	0–5
Total	**0–15**

(phonological or lexical verbal fluency). Verbal inhibitory control is assessed with a sentence completion task which requires the inhibition of an automatic verbal response to generate the final missing word (e.g. "The cat sat on the …", where the anticipated final word, "mat", would be considered an incorrect response due to a failure of inhibition). Working memory requires repetition of strings of letters in the reverse order to which they are given (a "letter span task"; hence the response to "R-K-T" should be "T-K-R"). The FES can be administered in around 5–10 min. In the initial, proof-of-concept, study FES scores showed good discrimination between cases of established bvFTD and AD (Leslie et al. 2016). These encouraging early data, and the free availability of the test without copyright issues (at https://doi.org/10.1136/jnnp-2015-311917 or http://www.neura.edu.au/frontier/research), were suggested to make future test use and studies advisable (Larner and Bracewell 2016).

In CFC, FES has been used in three patients with genetically determined FTD, one with a tau (MAPT) gene mutation and two with C9orf72 hexanucleotide repeat expansions, two with behavioural presentations typical of bvFTD and one with a linguistic presentation suggestive of semantic dementia (McCormick and Larner 2018). All three patients scored below the suggested threshold for FES (≤8/15), whereas only two of the three cases were below the threshold score (≤12/18) for FAB (Table 4.32), although these latter scores were historical rather than contemporaneous (Larner 2017g).

4.2.3 Poppelreuter Figure

Another example of a specific, rather than general, cognitive function test which has been examined in CFC is the overlapping or Poppelreuter figure (Poppelreuter 1917a:165–6; 1917–1918; Fig. 4.12). This is a test of visual perceptual function (in Gestalt terms, a figure/ground discrimination task) which is acknowledged to be problematic for patients with apperceptive (but not associative) visual agnosia.

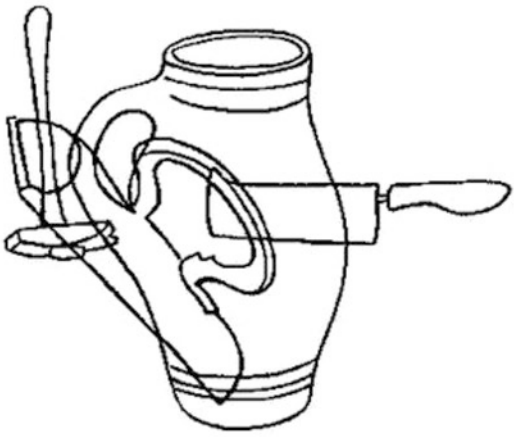

Fig. 4.12 Poppelreuter overlapping figure (Sells and Larner 2011) reprinted with permission

Table 4.32 Patient FES and FAB tests scores (adapted from Larner 2017g)

	Case 1: MAPT IVS10 + 16C > T mutation	**Case 2:** C9orf72 hexanucleotide repeat expansion	**Case 3:** C9orf72 hexanucleotide repeat expansion
FRONTIER Executive Screen (FES)			
Verbal fluency (F, P)	0/5	2/5	0/5
Inhibition (sentence completion)	3/5	2/5	2/5
Working memory (letter span task)	0/5	2/5	2/5
Total	**3/15**	**6/15**	**4/15**
Frontal Assessment Battery (FAB)			
Similarities (conceptualisation)	2/3	1/3	3/3
Lexical fluency (mental flexibility)	2/3	2/3	1/3
Motor series (programming)	3/3	3/3	1/3
Conflicting instructions (sensitivity to interference)	3/3	3/3	3/3
Go-No-Go (inhibitory control)	3/3	0/3	2/3
Prehension behaviour (environmental autonomy)	3/3	3/3	3/3
Total	**16/18**	**12/18**	**13/18**

Over the study period (March to September 2010), 101 patients were assessed of whom 28% had dementia by DSM-IV criteria (Table 4.33; Sells and Larner 2011). The Poppelreuter figure proved acceptable to patients and easy to use, being completed in less than 1 min by all patients. Poppelreuter scores ranged from 0 to 4, depending on the number of items correctly identified by name. For the demented group, the mode, median, and mean Poppelreuter scores were 4, 4, and 3.32 ± 1.09, respectively; for the non-demented group the mode, median, and mean scores were 4, 4, and 3.85 ± 0.36. The mean Poppelreuter scores differed significantly between the demented and non-demented groups ($t = 3.67$, df = 99, $p < 0.001$).

There was a very weak negative correlation between age and Poppelreuter score ($r = -0.13$). Comparing Poppelreuter scores and the other specific (dot counting and fragmented letters from ACE-R; intersecting pentagons from MMSE) and general tests (complete MMSE), correlations were moderate or high for other visual perceptual tasks (dot counting and fragmented letters respectively) and poor for the visuomotor task (intersecting pentagons) and for complete MMSE.

Optimal test sensitivity for the differential diagnosis of dementia/not dementia in this cohort was found to be 0.39 at the Poppelreuter cut-off of ≤3/4, and optimal test specificity was 1.00 at the cut-off of ≤2/4, with similar test accuracy at both cut-offs

Table 4.33 Demographic and diagnostic parameters for Poppelreuter figure (adapted from Sells and Larner 2011)

	Poppelreuter
N	101
F:M (% female)	48:53 (48)
Age range (years)	23–89 (median 61)
Prevalence of dementia	0.28
Pre-test odds = prevalence/(1 – prevalence)	0.39
Cut-off	**≤3/4**
Accuracy	0.72 (0.64–0.81)
Net Reclassification Improvement (NRI)	0.44
Sensitivity (Se)	0.39 (0.21–0.57)
Specificity (Sp)	0.85 (0.77–0.93)
Y	0.24
PPV (= post-test probability)	0.50 (0.29–0.71)
NPV	0.78 (0.69–0.88)
PSI	0.28
LR+	2.61 (1.28–5.32) = small
LR−	0.71 (0.35–1.46) = unimportant
DOR	3.65 (1.79–7.44)
Post-test odds (= pre-test odds × LR+)	1.02
CUI+	0.20 (very poor)
CUI−	0.67 (good)
AUC ROC curve	0.63 (0.53–0.74)

(0.72, 0.77 respectively). Traditional parameters of test diagnostic utility were calculated at the ≤3/4 cut-off (Table 4.33). Of particular note, the clinical utility indices indicated that the Poppelreuter figure was more useful for ruling out a diagnosis of dementia (good negative utility index) than for ruling it in (very poor positive utility index). A retrospective study of Poppeleuter figure performance in a non-overlapping cohort ($n = 50$; dementia prevalence 56%) showed similar results (Sells and Larner 2011).

The Poppelreuter figure might therefore be useful as a visual perceptual task in a general dementia screening test, or as one component of a broader assessment battery. It might also prove to be a useful and quick stand-alone screen for dementia, perhaps readily applicable in primary care where time available for testing is brief.

4.3 Summary and Recommendations

The diagnostic utility of various CSIs has been examined in CFC in pragmatic diagnostic test accuracy studies. Clearly only a very limited number of the large number of CSIs available has been assessed, with perhaps the most glaring omission relating to computerised test batteries, such as the CANTAB-PAL, where only limited experience has been acquired (Hancock et al. 2007).

Cognitive screening tests are not stand-alone diagnostic measures. Their use as a supplement to clinical judgement based on history taking and neurological examination (Chap. 3) may need to be supplemented by further assessment of non-cognitive factors (Chap. 5) and other diagnostic investigations (Chap. 7). How to compare, combine, and convert these various CSIs in the hope of finding the optimal test or test battery is examined in Chap. 6.

References

Abdel-Aziz K, Larner AJ. Six-Item Cognitive Impairment Test (6CIT) for detection of dementia and cognitive impairment. Int Psychogeriatr. 2015;27:991–7.

Aji BM, Ghadiali EJ, Jacob A, Larner AJ. Passage of an iron bar through the head: 50-year follow-up. J Neurol. 2012;259:1247–8.

Aji BM, Medley G, O'Driscoll K, Larner AJ, Alusi SH. Perry syndrome: a disorder to consider in the differential diagnosis of parkinsonism. J Neurol Sci. 2013;330:117–8.

Aji BM, Milburn-McNulty P, Larner AJ. Epilepsy: when family history holds the key to diagnosis. Prog Neurol Psychiatry. 2016;20(5):11–2.

Ala T, Hughes LF, Kyrouac GA, Ghobrial MW, Elble RJ. The Mini-Mental State exam may help in the differentiation of dementia with Lewy bodies and Alzheimer's disease. Int J Geriatr Psychiatry. 2002;17:503–9.

Ali R, Barborie A, Larner AJ, White RP. Psychiatric presentation of sporadic Creutzfeldt-Jakob disease: a challenge to current diagnostic criteria. J Neuropsychiatry Clin Neurosci. 2013; 25:335–8.

Allison RS. The senile brain. A clinical study. London: Edward Arnold; 1962.

Banerjee S, Willis R, Matthews D, Contell F, Chan J, Murray J. Improving the quality of care for mild to moderate dementia: an evaluation of the Croydon Memory Service Model. Int J Geriatr Psychiatry. 2007;22:782–8.

Belmin J, Pariel-Madjlessi S, Surun P, Bentot C, Feteanu D, Lefebvre des Noettes V, et al. The cognitive disorders examination (Codex) is a reliable 3-minute test for detection of dementia in the elderly (validation study in 323 subjects). Presse Med. 2007;36:1183–90.

Bier JC, Ventura M, Donckels V, et al. Is the Addenbrooke's Cognitive Examination effective to detect frontotemporal dementia? J Neurol. 2004;251:428–31.

Bonello M, Larner AJ, Marson AG, et al. Profound amnesia after temporal lobectomy: an autoimmune process resembling patient H.M.? Case Rep Neurol. 2014;6:251–5.

Bowie P, Branton T, Holmes J. Should the Mini Mental State Examination be used to monitor dementia treatments? Lancet. 1999;354:1527–8.

Brooke P, Bullock R. Validation of a 6 item cognitive impairment test with a view to primary care usage. Int J Geriatr Psychiatry. 1999;14:936–40.

Brown J. The use and misuse of short cognitive tests in the diagnosis of dementia. J Neurol Neurosurg Psychiatry. 2015;86:680–5.

Brown JM. TYM (Test Your Memory) testing. In: Larner AJ, editor. Cognitive screening instruments. A practical approach. 2nd ed. London: Springer; 2017. p. 209–29.

Brown J, Pengas G, Dawson K, Brown LA, Clatworthy P. Self administered cognitive screening test (TYM) for detection of Alzheimer's disease: cross sectional study. BMJ. 2009;338:b2030.

Brown J, Wiggins J, Dong H, Harvey R, Richardson F, Dawson K, Parker RA. The H-TYM. Evaluation of a short cognitive test to detect mild AD and amnestic MCI. Int J Geriatr Psychiatry. 2014;29:272–80.

Brown JM, Lansdall CJ, Wiggins J, et al. The Test Your Memory for Mild Cognitive Impairment (TYM-MCI). J Neurol Neurosurg Psychiatry. 2017;88:1045–51.

Brugnolo A, Nobili F, Barbieri MP, et al. The factorial structure of the mini mental state examination (MMSE) in Alzheimer's disease. Arch Gerontol Geriatr. 2009;49:180–5.

Burkhardt H, Karaminejad E, Gladisch R. A short performance test can help to predict adherence to self-administration of insulin in elderly patients with diabetes. Age Ageing. 2006;35:449–50.
Burns A, Lawlor B, Craig S. Assessment scales in old age psychiatry. 2nd ed. London: Martin Dunitz; 2004.
Buschke H, Kuslansky G, Katz M, et al. Screening for dementia with the Memory Impairment Screen. Neurology. 1999;52:231–8.
Cagliarini AM, Price HL, Livemore ST, Larner AJ. Will use of the Six-Item Cognitive Impairment Test help to close the dementia diagnosis gap? Aging Health. 2013;9:563–6.
Can SS, Gencay-Can A, Gunendi Z. Validity and reliability of the clock drawing test as a screening tool for cognitive impairment in patients with fibromyalgia. Compr Psychiatry. 2012;53:81–6.
Cannon P, Larner AJ. Errors in the scoring and reporting of cognitive screening instruments administered in primary care. Neurodegener Dis Manag. 2016;6:271–6.
Carnero-Pardo C. Should the Mini-Mental State Examination be retired? Neurologia. 2014;29:473–81.
Carnero Pardo C, editor. Test cognitivos breves. Madrid: Ediciones SEN; 2015.
Caslake R, Summers F, McConachie D, et al. The Mini-Mental Parkinson's (MMP) as a cognitive screening tool in people with Parkinson's disease. Curr Aging Sci. 2013;6:273–9.
Castiglioni S, Pelati O, Zuffi M, et al. The Frontal Assessment Battery does not differentiate frontotemporal dementia from Alzheimer's disease. Dement Geriatr Cogn Disord. 2006;22:125–31.
Ciesielska N, Sokolowski R, Mazue E, Podhorecka M, Polak-Szabela A, Kedziora-Kornatowska K. Is the Montreal Cognitive Assessment (MoCA) test better suited than the Mini-Mental State Examination (MMSE) in mild cognitive impairment (MCI) detection among people aged over 60? Meta-analysis. Psychiatr Pol. 2016;50:1039–52.
Connon P, Larner AJ. Fragile X-associated tremor/ataxia syndrome: cognitive presentations. Br J Hosp Med. 2017a;78:230–1.
Connon P, Larner AJ. Six-item Cognitive Impairment Test (6CIT): diagnostic test accuracy study in primary care referrals. Int J Geriatr Psychiatry. 2017b;32:583–4.
Copeland JR, Davidson IA, Dewey ME, et al. Alzheimer's disease, other dementias, depression and pseudodementia: prevalence, incidence and three-year outcome in Liverpool. Br J Psychiatry. 1992;161:230–9.
Copeland JR, McCracken CF, Dewey ME, Wilson KC, Doran M, Gilmore C, Scott A, Larkin BA. Undifferentiated dementia, Alzheimer's disease and vascular dementia: age- and gender-related incidence in Liverpool. The MRC-ALPHA study. Br J Psychiatry. 1999;175:433–8.
Cox C, Larner AJ. Recurrent hypoglycaemia and cognitive impairment: a 14-year follow-up. Br J Hosp Med. 2016;77:540–1.
Crawford S, Whitnall L, Robertson J, Evans JJ. A systematic review of the accuracy and clinical utility of the Addenbrooke's Cognitive Examination and the Addenbrooke's Cognitive Examination-Revised in the diagnosis of dementia. Int J Geriatr Psychiatry. 2012;27:659–69.
Crum RM, Anthony JC, Bassett SS, Folstein MF. Population-based norms for the Mini-Mental State Examination by age and educational level. JAMA. 1993;269:2386–91.
Cullen B, O'Neill B, Evans JJ, Coen RF, Lawlor BA. A review of screening tests for cognitive impairment. J Neurol Neurosurg Psychiatry. 2007;78:790–9.
Davey RJ, Jamieson S. The validity of using the mini mental state examination in NICE dementia guidelines. J Neurol Neurosurg Psychiatry. 2004;75:343–4.
Davies RR, Dawson K, Mioshi E, Erzinclioglu S, Hodges JR. Differentiation of semantic dementia and Alzheimer's disease using the Addenbrooke's Cognitive Examination (ACE). Int J Geriatr Psychiatry. 2008;23:370–5.
Delaney BC, Hyde CJ, McManus RJ, et al. Systematic review of near patient test evaluations in primary care. BMJ. 1999;319:824–7.
Dick JPR, Guiloff RJ, Stewart A, et al. Mini-mental state examination in neurological patients. J Neurol Neurosurg Psychiatry. 1984;47:496–9.
Doran M, Larner AJ. EEG findings in dementia with Lewy bodies causing diagnostic confusion with sporadic Creutzfeldt-Jakob disease. Eur J Neurol. 2004;11:838–41.

Dubois B, Slachevsky A, Litvan I, Pillon B. The FAB: a Frontal Assessment Battery at bedside. Neurology. 2000;55:1621–6.
Dubois B, Touchon J, Portet F, Ousset PJ, Vellas B, Michel B. "The 5 words": a simple and sensitive test for the diagnosis of Alzheimer's disease [in French]. Presse Med. 2002;31: 1696–9.
Dudas RB, Berrios GE, Hodges JR. The Addenbrooke's Cognitive Examination (ACE) in the differential diagnosis of early dementias versus affective disorder. Am J Geriatr Psychiatry. 2005;13:218–26.
Duff Canning SJ, Leach L, Stuss D, Ngo L, Black SE. Diagnostic utility of abbreviated fluency measures in Alzheimer disease and vascular dementia. Neurology. 2004;62:556–62.
Ellis RJ, Mbizvo GK, Jacob A, Doran M, Larner AJ. Relapsing polychondritis complicated by cognitive dysfunction: two distinct clinical phenotypes? Int J Neurosci. 2017;127:124–34.
Feher EP, Mahurin RK, Doody RS, Cooke N, Sims J, Pirozzolo FJ. Establishing the limits of the Mini-Mental State Examination. Arch Neurol. 1992;49:87–92.
Ferran J, Wilson K, Doran M, Ghadiali E, Johnson F, Cooper P, McCracken C. The early onset dementias: a study of clinical characteristics and service use. Int J Geriatr Psychiatry. 1996; 11:863–9.
Fisher CAH, Larner AJ. Frequency and diagnostic utility of cognitive test instrument use by general practitioners prior to memory clinic referral. Fam Pract. 2007;24:495–7.
Folstein MF, Folstein SE, McHugh PR. "Mini-Mental State." A practical method for grading the cognitive state of patients for the clinician. J Psychiatr Res. 1975;12:189–98.
Freedman M, Leach L, Kaplan E, Winocur G, Shulman K, Delis DC. Clock drawing. A neuropsychological analysis. New York: Oxford University Press; 1994.
Galasko D, Klauber MR, Hofstetter CR, Salmon DP, Lasker B, Thal LJ. The Mini-Mental State Examination in the early diagnosis of Alzheimer's disease. Arch Neurol. 1990;47:49–52.
Gale TM, Larner AJ. Six-Item Cognitive Impairment Test (6CIT). In: Larner AJ, editor. Cognitive screening instruments. A practical approach. 2nd ed. London: Springer; 2017. p. 241–53.
Galvin JE, Roe CM, Powlishta KK, et al. The AD8. A brief informant interview to detect dementia. Neurology. 2005;65:559–64.
Ganguli M, Ratcliff G, Huff FJ, et al. Serial sevens versus world backwards: a comparison of the two measures of attention from the MMSE. J Geriatr Psychiatry Neurol. 1990;3:203–7.
Ghadiri-Sani M, Larner AJ. Cognitive screening instrument use in primary care: is it changing? Clin Pract. 2014;11:425–9.
Golding E. The Middlesex Elderly Assessment of Mental State. Bury St Edmunds: Thames Valley Test Company; 1989.
Grober E, Buschke H. Genuine memory deficits in dementia. Dev Neuropsychol. 1987;3:13–36.
Han L, Cole M, Bellevance F, McCusker J, Primeau F. Tracking cognitive decline in Alzheimer's disease using the Mini-Mental State Examination: a meta-analysis. Int Psychogeriatr. 2000;12: 231–47.
Hancock P, Larner AJ. The diagnosis of dementia: diagnostic accuracy of an instrument measuring activities of daily living in a clinic-based population. Dement Geriatr Cogn Disord. 2007;23:133–9.
Hancock P, Larner AJ. Diagnostic utility of the Informant Questionnaire on Cognitive Decline in the Elderly (IQCODE) and its combination with the Addenbrooke's Cognitive Examination-Revised (ACE-R) in a memory clinic-based population. Int Psychogeriatr. 2009;21:526–30.
Hancock P, Larner AJ. Test Your Memory (TYM) test: diagnostic utility in a memory clinic population. Int J Geriatr Psychiatry. 2011;26:976–80.
Hancock P, Larner AJ. Cornell Scale for Depression in Dementia: clinical utility in a memory clinic. Int J Psychiatry Clin Pract. 2015;19:71–4.
Hancock P, Wike J, Larner AJ. Clinical experience with CANTAB-PAL in the diagnosis of Alzheimer's disease. Poster presentation, 17th Alzheimer Europe Conference, Estoril, Portugal, 9–11 May 2007.
Hatfield CF, Dudas RB, Dening T. Diagnostic tools for dementia. Maturitas. 2009;63:181–5.
Healey E. Elizabeth is missing. London: Penguin; 2015.

Hennerici MG, Daffertshofer M, Caplan LR, Szabo K. Case studies in stroke. Common and uncommon presentations. Cambridge: Cambridge University Press; 2006.
Henry JD, Crawford JR, Phillips LH. Verbal fluency performance in dementia of the Alzheimer type: a meta-analysis. Neuropsychologia. 2004;42:1212–22.
Hessler J, Bronner M, Etgen T, et al. Suitability of the 6CIT as a screening test for dementia in primary care patients. Aging Ment Health. 2014;18:515–20.
Hodges JR, Larner AJ. Addenbrooke's Cognitive Examinations: ACE, ACE-R, ACE-III, ACEapp, and M-ACE. In: Larner AJ, editor. Cognitive screening instruments. A practical approach. 2nd ed. London: Springer; 2017. p. 109–37.
Hodges JR, Patterson K, Ward R, et al. The differentiation of semantic dementia and frontal lobe dementia (temporal and frontal variants of frontotemporal dementia) from early Alzheimer's disease: a comparative neuropsychological study. Neuropsychology. 1999;13:31–40.
Hoehn MM, Yahr MD. Parkinsonism: onset, progression and mortality. Neurology. 1967;17:427–42.
Holmes C, Lovestone S. Long-term cognitive and functional decline in late onset Alzheimer's disease: therapeutic implications. Age Ageing. 2003;32:200–4.
Hsieh S, Schubert S, Hoon C, Mioshi E, Hodges JR. Validation of the Addenbrooke's Cognitive Examination III in frontotemporal dementia and Alzheimer's disease. Dement Geriatr Cogn Disord. 2013;36:242–50.
Hsieh S, McGrory S, Leslie F, et al. The Mini-Addenbrooke's Cognitive Examination: a new assessment tool for dementia. Dement Geriatr Cogn Disord. 2015;39:1–11.
Ibrahim I, Young CA, Larner AJ. Fornix damage from solitary subependymal giant cell astrocytoma causing postoperative amnesic syndrome. Br J Hosp Med. 2009;70:478–9.
Ismail Z, Mulsant BH, Herrmann N, Rapoport M, Nilsson M, Shulman K. Canadian Academy of Geriatric Psychiatry survey of brief cognitive screening instruments. Can Geriatr J. 2013; 16:54–60.
Julayanont P, Nasreddine ZS. Montreal Cognitive Assessment (MoCA): concept and clinical review. In: Larner AJ, editor. Cognitive screening instruments. A practical approach. 2nd ed. London: Springer; 2017. p. 139–95.
Kalbe E, Kessler J. DemTect. In: Larner AJ, editor. Cognitive screening instruments. A practical approach. 2nd ed. London: Springer; 2017. p. 197–208.
Kalbe E, Calabrese P, Schwalen S, Kessler J. The Rapid Dementia Screening Test (RDST): a new economical tool for detecting possible patients with dementia. Dement Geriatr Cogn Disord. 2003;16:193–9.
Kalbe E, Kessler J, Calabrese P, et al. DemTect: a new, sensitive cognitive screening test to support the diagnosis of mild cognitive impairment and early dementia. Int J Geriatr Psychiatry. 2004;19:136–43.
Larner AJ. MMSE subscores and the diagnosis of dementia with Lewy bodies. Int J Geriatr Psychiatry. 2003;18:855–6.
Larner AJ. Use of MMSE to differentiate Alzheimer's disease from dementia with Lewy bodies. Int J Geriatr Psychiatry. 2004;19:1209–10.
Larner AJ. "Dementia unmasked": atypical, acute aphasic, presentations of neurodegenerative dementing disease. Clin Neurol Neurosurg. 2005a;108:8–10.
Larner AJ. An audit of the Addenbrooke's Cognitive Examination (ACE) in clinical practice. Int J Geriatr Psychiatry. 2005b;20:593–4.
Larner AJ. An audit of the Addenbrooke's Cognitive Examination (ACE) in clinical practice. 2. Longitudinal change. Int J Geriatr Psychiatry. 2006;21:698–9.
Larner AJ. Of clocks and mirrors: the Backward Clock Test. Eur J Neurol. 2007a;14(Suppl 1):100. (abstract P1265)
Larner AJ. Addenbrooke's Cognitive Examination (ACE) for the diagnosis and differential diagnosis of dementia. Clin Neurol Neurosurg. 2007b;109:491–4.
Larner AJ. Addenbrooke's Cognitive Examination-Revised (ACE-R) in day-to-day clinical practice. Age Ageing. 2007c;36:685–6.
Larner AJ. DemTect in the diagnosis of dementia: first 100 patients. In: Iqbal K, Winblad B, Avila J, editors. Alzheimer's disease: new advances. Collection of selected articles of papers

presented at the 10th International Conference on Alzheimer's disease and related disorders. Madrid, Spain, July 15–20, 2006. Medimond: Bologna; 2007d. p. 177–81.
Larner AJ. DemTect: 1-year experience of a neuropsychological screening test for dementia. Age Ageing. 2007e;36:326–7.
Larner AJ. Addenbrooke's Cognitive Examination-Revised in day-to-day clinical practice. Reply. Age Ageing. 2008a;37:350–1.
Larner AJ. Cambridge Behavioural Inventory: diagnostic and differential diagnostic utility. J Neurol Neurosurg Psychiatry. 2008b;79:351–2. (abstract 61)
Larner AJ. ACE-R: cross-sectional and longitudinal use for cognitive assessment. In: Fisher A, Hanin I, editors. New trends in Alzheimer and Parkinson related disorders: ADPD 2009. Collection of selected free papers from the 9th International Conference on Alzheimer's and Parkinson's disease AD/PD. Prague, Czech Republic, March 11–15, 2009. Bologna: Medimond International Proceedings; 2009a. p. 103–7.
Larner AJ. Addenbrooke's Cognitive Examination-Revised: cross-sectional and longitudinal use for cognitive assessment. Neurodegener Dis. 2009b;6(Suppl 1):194.
Larner AJ. Intrafamilial clinical phenotypic heterogeneity with *MAPT* gene splice site IVS10+16C>T mutation. J Neurol Sci. 2009c;287:253–6.
Larner AJ. Is Mini-Mental Parkinson (MMP) a useful screening test in a cognitive clinic population? Eur J Neurol. 2010;17(Suppl 3):205. (abstract P1342)
Larner AJ. Frontal Assessment Battery (FAB): a pragmatic study. Neurodegener Dis. 2011; 8(Suppl 1):565.
Larner AJ. Screening utility of the Montreal Cognitive Assessment (MoCA): in place of—or as well as—the MMSE? Int Psychogeriatr. 2012a;24:391–6.
Larner AJ. Mini-Mental Parkinson (MMP) as a dementia screening test: comparison with the Mini-Mental State Examination (MMSE). Curr Aging Sci. 2012b;5:136–9.
Larner AJ. FTDP-17: 2-year follow-up of motor and cognitive features after autologous stem-cell transplantation. J Neuropsychiatry Clin Neurosci. 2012c;24(2):E1–2.
Larner AJ, editor. Cognitive screening instruments. A practical approach. London: Springer; 2013a.
Larner AJ. Addenbrooke's Cognitive Examination-Revised (ACE-R): pragmatic study of cross-sectional use for assessment of cognitive complaints of unknown aetiology. Int J Geriatr Psychiatry. 2013b;28:547–8.
Larner AJ. Codex (cognitive disorders examination) for the detection of dementia and mild cognitive impairment. Codex pour la détection de la démence et du mild cognitive impairment. Presse Med. 2013c;42:e425–8.
Larner AJ. Addenbrooke's Cognitive Examination standardized verbal fluency scores for differential diagnosis of AD and FTLD. J Neurol Sci. 2013d;333:e292.
Larner AJ. Can the Frontal Assessment Battery (FAB) help in the diagnosis of behavioural variant frontotemporal dementia? A pragmatic study. Int J Geriatr Psychiatry. 2013e;28:106–7.
Larner AJ. AD8 informant questionnaire for cognitive impairment: pragmatic diagnostic test accuracy study. J Geriatr Psychiatry Neurol. 2015a;28:198–202.
Larner AJ. Mini-Addenbrooke's Cognitive Examination: a pragmatic diagnostic accuracy study. Int J Geriatr Psychiatry. 2015b;30:547–8.
Larner AJ. Mini-Addenbrooke's Cognitive Examination diagnostic accuracy for dementia: reproducibility study. Int J Geriatr Psychiatry. 2015c;30:1103–4.
Larner AJ. Optimizing the cutoffs of cognitive screening instruments in pragmatic diagnostic accuracy studies: maximising accuracy or Youden index? Dement Geriatr Cogn Disord. 2015d;39:167–75.
Larner AJ. Implications of changing the Six-item Cognitive Impairment Test cutoff. Int J Geriatr Psychiatry. 2015e;30:778–9.
Larner AJ. Six Item Cognitive Impairment Test: suitable for the visually impaired? Prog Neurol Psychiatry. 2015f;19(6):20–2.
Larner AJ. Hard-TYM: a pragmatic study. Int J Geriatr Psychiatry. 2015g;30:330–1.
Larner AJ. Cognitive screening instruments for the diagnosis of mild cognitive impairment. Prog Neurol Psychiatry. 2016a;20(2):21–6.

Larner AJ. Correlation or limits of agreement? Applying the Bland-Altman approach to the comparison of cognitive screening instruments. Dement Geriatr Cogn Disord. 2016b;42:247–54.
Larner AJ. M-ACE vs. MoCA: a weighted comparison. Int J Geriatr Psychiatry. 2016c;31:1089–90.
Larner AJ, editor. Cognitive screening instruments. A practical approach. 2nd ed. London: Springer; 2017a.
Larner AJ. Introduction to cognitive screening instruments: rationale and desiderata. In: Larner AJ, editor. Cognitive screening instruments. A practical approach. 2nd ed. London: Springer; 2017b. p. 3–13.
Larner AJ. MMSE variants and subscores. In: Larner AJ, editor. Cognitive screening instruments. A practical approach. 2nd ed. London: Springer; 2017c. p. 49–66.
Larner AJ. MACE versus MoCA: equivalence or superiority? Pragmatic diagnostic test accuracy study. Int Psychogeriatr. 2017d;29:931–7.
Larner AJ. Short Montreal Cognitive Assessment: validation and reproducibility. J Geriatr Psychiatry Neurol. 2017e;30:104–8.
Larner AJ. The usage of cognitive screening instruments: test characteristics and suspected diagnosis. In: Larner AJ, editor. Cognitive screening instruments. A practical approach. 2nd ed. London: Springer; 2017f. p. 315–39.
Larner AJ. FRONTIER Executive Screen (FES). Poster P0034, Association of British Neurologists annual meeting, Liverpool, 3–5 May 2017g.
Larner AJ. Assessment of cognitive function. In: Severn A, editor. Cognitive changes after surgery. London: Springer; 2018a.
Larner AJ. Metamemory: a construct with diagnostic utility in a cognitive disorders clinic? Int J Geriatr Psychiatry. 2018b;33:553–4.
Larner AJ, Bracewell RM. A new FRONTIER in dementia differential diagnosis? J R Coll Physicians Edinb. 2016;46:172–3.
Larner AJ, Doran M. Broader assessment needed for treatment decisions in AD. Prog Neurol Psychiatry. 2002;6(3):5–6.
Larner AJ, Hancock P. Does combining cognitive and functional scales facilitate the diagnosis of dementia? Int J Geriatr Psychiatry. 2012;27:547–8.
Larner AJ, Hancock P. ACE-R or MMSE? A weighted comparison. Int J Geriatr Psychiatry. 2014;29:767–8.
Larner AJ, Mitchell AJ. A meta-analysis of the accuracy of the Addenbrooke's Cognitive Examination (ACE) and the Addenbrooke's Cognitive Examination-Revised (ACE-R) in the detection of dementia. Int Psychogeriatr. 2014;26:555–63.
Larner AJ, Young CA. Acute amnesia in multiple sclerosis revisited. Int MS J. 2009;16:102–4.
Larner AJ, Moffat MA, Ghadiali E, Majid S, English P, Williams G. Amnesia following profound hypoglycaemia in a type 1 diabetic patient. Eur J Neurol. 2003a;10(Suppl 1):92. (abstract P1170)
Larner AJ, Downes JJ, Hanley JR, Tsivilis D, Doran M. Developmental prosopagnosia: a clinical and neuropsychological study. J Neurol. 2003b;250(Suppl 2):II156. (abstract P591)
Larner AJ, Ray PS, Doran M. The R269H mutation in presenilin-1 presenting as late-onset autosomal dominant Alzheimer's disease. J Neurol Sci. 2007;252:173–6.
Law E, Connelly PJ, Randall E, et al. Does the Addenbrooke's Cognitive Examination-revised add to the Mini-Mental State Examination in established Alzheimer disease? Results from a national dementia research register. Int J Geriatr Psychiatry. 2013;28:351–5.
Leslie FVC, Foxe D, Daveson N, Flannagan E, Hodges JR, Piguet O. FRONTIER Executive Screen: a brief executive battery to differentiate frontotemporal dementia and Alzheimer's disease. J Neurol Neurosurg Psychiatry. 2016;87:831–5.
Levin P, editor. The Penguin book of the sonnet. 500 years of a classic tradition in English. London: Penguin; 2001.
Lezak MD, Howieson DB, Bigler ED, Tranel D. Neuropsychological assessment. 5th ed. New York: Oxford University Press; 2012.
Lindeboom J, Schmand B, Tulner L, Walstra G, Jonker C. Visual association test to detect early dementia of the Alzheimer type. J Neurol Neurosurg Psychiatry. 2002;73:126–33.

Lipton AM, Ohman KA, Womack KB, Hynan LS, Ninman ET, Lacritz LH. Subscores of the FAB differentiate frontotemporal lobar degeneration from AD. Neurology. 2005;65:726–31.
Lozsadi DA, Larner AJ. Prevalence and causes of seizures at the time of diagnosis of probable Alzheimer's disease. Dement Geriatr Cogn Disord. 2006;22:121–4.
Magni E, Binetti G, Padovani A, Cappa SF, Bianchetti A, Trabucchi M. The Mini-Mental State Examination in Alzheimer's disease and multi-infarct dementia. Int Psychogeriatr. 1996; 8:127–34.
Mahieux F, Michelet D, Manifacier M-J, Boller F, Fermanian J, Guillard A. Mini-Mental Parkinson: first validation study of a new bedside test constructed for Parkinson's disease. Behav Neurol. 1995;8:15–22.
Mainland BJ, Shulman KI. Clock Drawing Test. In: Larner AJ, editor. Cognitive screening instruments. A practical approach. 2nd ed. London: Springer; 2017. p. 67–108.
Malloy PF, Cummings JL, Coffey CE, et al. Cognitive screening instruments in neuropsychiatry: a report of the Committee on Research of the American Neuropsychiatric Association. J Neuropsychiatry Clin Neurosci. 1997;9:189–97.
Maruta C, Guerreiro M, de Mendonca A, Hort J, Scheltens P. The use of neuropsychological tests across Europe: the need for a consensus in the use of assessment tools for dementia. Eur J Neurol. 2011;18:279–85.
Mathuranath PS, Nestor PJ, Berrios GE, Rakowicz W, Hodges JR. A brief cognitive test battery to differentiate Alzheimer's disease and frontotemporal dementia. Neurology. 2000;55:1613–20.
McCormick LJ, Larner AJ. "Could you repeat that?": Not always a hearing problem! Br J Hosp Med. 2018;79. (in press)
McDicken JA, Blayney G, Elliott E, Makin S, Ali M, Larner AJ. Quinn TJ. Accuracy of the short form Montreal Cognitive Assessment: systematic review and external validation; 2018. (submitted).
Menon R, Larner AJ. Use of cognitive screening instruments in primary care: the impact of national dementia directives (NICE/SCIE, National Dementia Strategy). Fam Pract. 2011;28:272–6.
Mioshi E, Dawson K, Mitchell J, Arnold R, Hodges JR. The Addenbrooke's Cognitive Examination Revised: a brief cognitive test battery for dementia screening. Int J Geriatr Psychiatry. 2006;21:1078–85.
Mitchell AJ. The Mini-Mental State Examination (MMSE): update on its diagnostic accuracy and clinical utility for cognitive disorders. In: Larner AJ, editor. Cognitive screening instruments. A practical approach. 2nd ed. London: Springer; 2017. p. 37–48.
Mitchell AJ, Malladi S. Screening and case-finding tools for the detection of dementia. Part I: evidence-based meta-analysis of multidomain tests. Am J Geriatr Psychiatry. 2010a;18:759–82.
Mitchell AJ, Malladi S. Screening and case-finding tools for the detection of dementia. Part II: evidence-based meta-analysis of single-domain tests. Am J Geriatr Psychiatry. 2010b; 18:783–800.
Mitrushina M, Boone KB, Razani J, D'Elia LF. Handbook of normative data for neuropsychological assessment. 2nd ed. Oxford: Oxford University Press; 2005.
Möller WD, Vetter P, Sprenger S, Kropp P. Importance of tests for diagnosing dementia. Eur J Neurol. 2009;16(Suppl3):368. (abstract P2090)
Nasreddine ZS, Phillips NA, Bédirian V, Charbonneau S, Whitehead V, Collin I, et al. The Montreal Cognitive Assessment, MoCA: a brief screening tool for mild cognitive impairment. J Am Geriatr Soc. 2005;53:695–9.
National Institute for Clinical Excellence. Guidance on the use of donepezil, rivastigmine, and galantamine for the treatment of Alzheimer's disease (Technology Appraisal Guidance No. 19). London: NICE; 2001.
Newman CGJ, Bevins AD, Zajicek JP, et al. Improving the quality of cognitive screening assessments: ACEmobile, an iPad-based version of the Addenbrooke's Cognitive Examination-III. Alzheimers Dement (Amst). 2017;10:182–7.
Newman JC, Feldman R. Copyright and open access at the bedside. N Engl J Med. 2011;365:2447–9.
Nieuwenhuis-Mark RE. The death knoll for the MMSE: has it outlived its purpose? J Geriatr Psychiatry Neurol. 2010;23:151–7.

Olazaran J, Hoyos-Alonso MC, del Ser T, et al. Practical application of brief cognitive tests. Neurologia. 2016;31:183–94.

Papageorgiou S, Nikaki M, Kontaxis T, et al. Can the frontal assessment battery differentiate between frontotemporal dementia (FTD) and Alzheimer's disease (AD)? Eur J Neurol. 2009;16(Suppl 3):442. (abstract P2317)

Petersen RC, Thomas RG, Grundman M, et al. Vitamin E and donepezil for the treatment of mild cognitive impairment. N Engl J Med. 2005;352:2379–88.

Poppelreuter W (Zihl J, Weiskrantz L, transl.). Disturbances of lower and higher visual capacities caused by occipital damage with special reference to the psychopathological, pedagogical, industrial, and social implications. Oxford: Clarendon Press; 1917a.

Poppelreuter W. Die psychischen Schädigungen durch Kopfschuss im Kriege 1914/17: mit besonderer Berücksichtigung der pathopsychologischen, pädagogischen, gewerblichen und sozialen Beziehungen (2 volumes: Band 1: Die Störungen der niederen und höheren Sehleistungen durch Verletzungen des Okzipitalhirns; Band 2: Die Herabsetzung der körperlichen Leistungsfähigkeit und des Arbeitswillens durch Hirnverletzung im Vergleich zu Normalen und Psychogenen). Leipzig: Voss; 1917b–1918.

Randolph C, Tierney MC, Mohr E, Chase TN. The Repeatable Battery for the Assessment of Neuropsychological Status (RBANS): preliminary clinical validity. J Clin Exp Neuropsychol. 1998;20:310–9.

Rawle MJ, Larner AJ. NARP syndrome: a 20-year follow-up. Case Rep Neurol. 2013;5:204–7.

Rawle M, Larner A. MoCA subscores to diagnose dementia subtypes: initial study. J Neurol Neursurg Psychiatry. 2014;85:e4.

Ridha B, Rossor M. How to do it. The Mini Mental State Examination. Pract Neurol. 2005; 5:298–303.

Roalf DR, Moore TM, Wolk DA, et al. Defining and validating a short form Montreal Cognitive Assessment (s-MoCA) for use in neurodegenerative disease. J Neurol Neurosurg Psychiatry. 2016;87:1303–10.

Scheurich A, Muller MJ, Slessmeier T, et al. Validating the DemTect with 18-fluoro-2-deoxy-glucose positron emission tomography as a sensitive neuropsychological screening test for early Alzheimer disease in patients of a memory clinic. Dement Geriatr Cogn Disord. 2005;20:271–7.

Sells R, Larner AJ. The Poppelreuter figure visual perceptual function test for dementia diagnosis. Prog Neurol Psychiatry. 2011;15(2):17–8, 20–1.

Seshadri M, Mazi-Kotwal N. A copyright-free alternative is needed. BMJ. 2012;345:e8589.

Slachevsky A, Villalpando JM, Sarazin M, Hahn BV, Pillon B, Dubois B. Frontal assessment battery and differential diagnosis of frontotemporal dementia and Alzheimer disease. Arch Neurol. 2004;61:1104–7.

Smithson E, Larner AJ. Glioblastoma multiforme masquerading as herpes simplex encephalitis. Br J Hosp Med. 2013;74:52–3.

St John L, Larner AJ. Muscle wasting, bone pain and cognitive decline: a unifying diagnosis. Br J Hosp Med. 2015;76:602–3.

Stagg B, Larner AJ. Zarit Burden Interview: pragmatic study in a dedicated cognitive function clinic. Prog Neurol Psychiatry. 2015;19(4):23–7.

Storton K, Larner AJ. Montreal Cognitive Assessment (MoCA): diagnostic utility in a cognitive clinic population. Alzheimers Dement. 2011;7(Suppl1):S166. (abstract P1–171)

Strauss E, Sherman EMS, Spreen O. A compendium of neuropsychological tests: administration, norms, and commentary. 3rd ed. New York: Oxford University Press; 2006.

Tangalos EG, Smith GE, Ivnik RJ, et al. The Mini-Mental State Examination in general medical practice: clinical utility and acceptance. Mayo Clin Proc. 1996;71:829–37.

Tate RL. A compendium of tests, scales, and questionnaires. The practitioner's guide to measuring outcomes after acquired brain impairment. Hove: Psychology Press; 2010.

Tombaugh TN, McIntyre NJ. The Mini-Mental State Examination: a comprehensive review. J Am Geriatr Soc. 1992;40:922–35.

Tsoi KK, Chan JY, Hirai HW, Wong SY, Kwok TC. Cognitive tests to detect dementia. A systematic review and meta-analysis. JAMA Intern Med. 2015;175:1450–8.

Valcour VG, Masaki KH, Blanchette PL. The phrase: “no ifs, ands, or buts” and cognitive testing. Lessons from an Asian-American community. Hawaii Med J. 2002;61:72–4.
Werner P, Heinik J, Lin R, Bleich A. “Yes” ifs, ands or buts: examining performance and correlates of the repetition task in the mini-mental state examination. Int J Geriatr Psychiatry. 1999;14:719–25.
Williamson J, Larner AJ. Fibromyalgia: cognitive aspects. Br J Hosp Med. 2016;77:116.
Williamson J, Larner AJ. MACE for diagnosis of dementia and MCI: 3-year pragmatic diagnostic test accuracy study. Dement Geriatr Cogn Disord. 2018;45. (in press)
Wilson M, Doran M, Enevoldson TP, Larner AJ. Cognitive profiles associated with intracranial dural arteriovenous fistula. Age Ageing. 2010;39:389–92.
Wojtowicz A, Larner AJ. General Practitioner Assessment of Cognition: use in primary care prior to memory clinic referral. Neurodegener Dis Manag. 2015;5:505–10.
Wojtowicz A, Larner A. Scoring errors in cognitive screening instruments administered in primary care. J Neurol Neurosurg Psychiatry. 2016;87:e1.
Wojtowicz A, Schott JM, Larner AJ. CSF biomarkers and the diagnosis of variant forms of Alzheimer’s disease. Prog Neurol Psychiatry. 2017;21(2):13–5.
Wong S, Hart IK, Larner AJ. Revised Addenbrooke’s Cognitive Examination in the assessment of voltage-gated potassium channel antibody-positive non-paraneoplastic limbic encephalitis. Eur J Neurol. 2008;15(Suppl 3):303. (abstract P2368)
Wong SH, Saunders M, Larner AJ, Das K, Hart IK. An effective immunotherapy regimen for VGKC antibody-positive limbic encephalitis. J Neurol Neurosurg Psychiatry. 2010;81:1167–9.
Woodford HJ, George J. Cognitive assessment in the elderly: a review of clinical methods. Q J Med. 2007;100:469–84.
Woodward M, Brodaty H, Boundy K, Ames D, Blanch G, Balshaw R. PRIME Study Group. Does executive impairment define a frontal variant of Alzheimer’s disease? Int Psychogeriatr. 2010;22:1280–90.
Zaccai J, McCracken C, Brayne C. A systematic study of prevalence and incidence studies of dementia with Lewy bodies. Age Ageing. 2005;34:561–6.
Ziso B, Larner AJ. Codex (cognitive disorders examination) for the detection of dementia and mild cognitive impairment: diagnostic utility. J Neurol Neurosurg Psychiatry. 2013;84:e2.
Ziso B, Larner A. Levodopa response in paroxysmal exercise-induced dystonia without GLUT1 deficiency. Eur J Neurol. 2015;22(Suppl1):394.
Ziso B, Larner AJ. STOP-Bang: screening for obstructive sleep apnoea in a cognitive disorders clinic. J Sleep Disord Ther. 2016;5:223.