A. J. Larner
Editor

Cognitive Screening Instruments

A Practical Approach

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Preface

Although there have been some previous publications examining cognitive screening instruments, and books partially devoted to their examination, texts entirely devoted to this subject are few. For demographic, and hence economic and political, reasons, namely the aging of the human population and the increasing numbers of individuals afflicted with dementia, it seems timely to provide an overview of some cognitive screening instruments.

Of the very large number of published cognitive screening instruments, only a small number could be selected for discussion in this volume. This selection, though not arbitrary, is not systematic. Choices have been made mindful of the requirements of clinicians working particularly in the nonacademic arena, where time and support in the clinic may be limited. Emphasis has therefore been placed on tests requiring little more than pen and paper; computerized tests have not been discussed.

Some of the tests included are very well-known (e.g., the Mini-Mental State Examination discussed by Alex Mitchell in Chap. 2; the Clock Drawing Test discussed by Brian Mainland and Ken Shulman in Chap. 5), others perhaps less familiar (e.g., DemTect discussed by Elke Kalbe and Josef Kessler in Chap. 7; derivates of the MMSE discussed by Rhys Davies and myself in Chap. 3). Some are designed for or suitable for use in primary care settings (GPCOG discussed by Katrin Seeher and Henry Brodaty in Chap. 10; 6CIT discussed by Kiri Jefferies, and Tim Gale in Chap. 11; and possibly DemTect), others are more suitable for secondary care settings because of their length (e.g., Montreal Cognitive Assessment discussed by Ziad Nasreddine in Chap. 6; Addenbrooke's Cognitive Examination discussed by Rhys Davies and myself in Chap. 4). Most tests are clinician-administered (MMSE, Clock Drawing Test, DemTect, ACE, MoCA, GPCOG, 6CIT) but the possible role of patient administered testing under medical supervision using the Test Your Memory (TYM) test is discussed by Jerry Brown in Chap. 9. The important area of informant testing with the IQCODE is addressed by Nicolas Cherbuin and Tony Jorm in Chap. 8.

The idea for this volume came to me while listening to lectures on a bright Spring Saturday morning in Munich (April 9, 2011) at a conference entitled "Changing

times in Alzheimer's disease: Overcoming challenges and embracing advances." The conference was held at the Ludwig-Maximilians University, and afforded the opportunity to visit the historical Alois Alzheimer exhibition room in what used to be Alzheimer's laboratory. So, albeit indirectly, I like to think that Alzheimer has inspired this work. I hope the resulting volume will prove user-friendly to clinicians at all levels of experience who are required to assess patients with cognitive function complaints.

Thanks are due to all the contributors for their timely production of chapters, and all at Springer, past and present, who have supported the production of this volume, namely Manika Power, Melissa Morton, and particularly Joanna Bolesworth.

Andrew J. Larner

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Chapter 1
Introduction to Cognitive Screening Instruments: Rationale, Desiderata, and Assessment of Utility

Andrew J. Larner

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Abstract Cognitive disorders are common and likely to become more so as the world population ages. Pending the definition of reliable biomarkers, the identification of such disorders, as a prelude to effective management, involves the use of cognitive screening instruments. The desiderata for effective cognitive screening instruments and the methods for assessment of their utility are considered in this chapter, prior to the in-depth analysis of specific instruments in subsequent chapters. The potential role of factors such as age, education, and culture on test performance and interpretation is also considered.

Keywords Cognitive screening instruments • Desiderata • Sensitivity and specificity STARD • QUADAS

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1.1 Introduction

Cognitive screening instruments may be encountered by practitioners in many branches of clinical medicine, in both primary and secondary care. However, not all clinicians may feel themselves either familiar with or competent in the use of such instruments. This may stem in part from lack of appropriate training, or even frank neurophobia, perhaps exacerbated by the profusion of potential tests available.

Although there have been publications examining cognitive screening instruments (e.g., [1–4]), and books which are partially devoted to their examination (e.g., [5, 6]), texts entirely devoted to this subject are few (e.g., [7]). This book aims to give practical advice on a few of the cognitive screening instruments suitable for day-to-day use in assessing patients with possible cognitive impairments.

The rationale for this use of cognitive screening instruments relates, at least in part, to the increasing numbers of individuals with cognitive impairment, related to the ageing of the population, numbers which are predicted to increase dramatically worldwide in the coming decades [8–10]. Although population screening for dementia is not currently advocated, there being insufficient evidence of benefit to justify such an undertaking [11, 12], nonetheless, early diagnosis of dementia is a stated health goal in some countries, such as the United Kingdom (UK) [13, 14]. Screening of at-risk groups (e.g., older people, individuals with subjective memory complaints) may be more appropriate than global population screening.

Underdiagnosis of dementia remains a significant issue. In the UK, a comparison of estimated numbers of people with dementia (based on applying prevalence rates to corresponding age groups) with the actual number of people with dementia recorded on the National Health Service (NHS) Quality and Outcomes Framework dementia register (based in primary care) suggested that only around 40 % of people with dementia have a diagnosis [15]. Closing this "diagnostic gap" or "dementia gap" may be facilitated by appropriate use of cognitive screening instruments.

Conversely, current clinical practice indicates that many individuals who attend cognitive/memory clinics are found not to have dementia, but purely subjective memory impairment. Physiological cognitive decline may be evident in early middle age (45–49 years [16]). Although the UK National Institute for Health and Clinical Excellence (NICE) [17] suggested a memory clinic base rate for dementia of 54 %, this may greatly overestimate current clinical experience, where rates around 25 % may be seen [18, 19]. A report from 30 Alzheimer's centres in the USA reported 50 % of patients seen were diagnosed as having normal cognition [20]. Identification and reassurance of those individuals with purely subjective memory impairment is an important function of such clinics, a task which may also be facilitated by use of cognitive screening instruments.

1.2 Rationale of Cognitive Screening

What is the purpose of cognitive screening? This issue may be addressed by considering the classic criteria for disease screening published under the auspices of the World Health Organization (WHO; see Box 1.1) [21, 22].

Box 1.1: WHO Screening Criteria (After [21, 22])

- The disease/condition sought should be an important public health problem.
- There should be a recognizable latent or presymptomatic stage of the disease.
- The natural history of the disease should be adequately understood.
- There should be a treatment for the condition, which should be more beneficial when applied at the presymptomatic stage compared to the later symptomatic stage.
- There should be a suitable test or examination to detect the disease with reasonable sensitivity and specificity.
- The test should be acceptable to the population.
- The health-care system should have the capacity and policies in place to test for the condition and deal with the consequences.
- The cost of case finding, including diagnosis and treatment of patients diagnosed, should be economically balanced in relation to possible expenditure on medical care as a whole.
- Case finding should be a continuing process and not a "once and for all" project.

Many of these conditions are fulfilled for dementia as a syndrome and for specific subtypes of dementia, most importantly Alzheimer's disease (AD). For example, the public health implications of dementia [8–10] and its huge economic costs [23] are unequivocally established. It is also evident that the natural history of most forms of dementia encompasses a presymptomatic phase, with disease evolution occurring over years before clinical presentation. Longitudinal epidemiological studies suggest almost 10 years of cognitive decline in AD preceding dementia [24]. Neuroimaging studies indicate hippocampal volume loss preceding dementia [25, 26], and amyloid accumulation in the brain, thought to be a key pathogenetic event in AD, may precede the first clinical symptoms by at least a decade [27]. This long presymptomatic phase presents a potential window of opportunity for intervention should disease modifying drugs become available.

Equally, many of these screening criteria are yet to be fulfilled for dementia. For example, it has yet to be established that any of the available pharmacotherapies for AD are more beneficial when applied at the presymptomatic stage compared to the later symptomatic stage. Application of pharmacotherapies in presymptomatic AD has, to my knowledge, yet to be reported, but there is no evidence that cholinesterase inhibitors, a symptomatic treatment for AD, prevent conversion of prodromal AD (mild cognitive impairment) to AD in the long term [28–30]. It is not clear that health-care systems have the capacity and policies to test for dementia and deal with the consequences, nor that the cost of case finding, including diagnosis and treatment, would be economically balanced in relation to possible expenditure on medical care as a whole.

Putting aside these issues, which may possibly be resolved by ongoing research, the key screening criterion considered in this book is whether there are suitable tests or examinations available to detect dementia and its subtypes with reasonable sensitivity and specificity, and which are acceptable to the population. The population in question needs careful definition in this context since prevalence rates of dementia may differ greatly in different populations. Hence, a cognitive screening instrument to be applied at the whole population level might be very different to one applied to at-risk groups (e.g., older persons) or to the highly selected population attending cognitive/memory clinics. The latter have, at minimum, subjective memory impairment. It is to the constituency of those presenting to clinical attention with memory complaints that the current volume is addressed.

As with all medical activities, such as investigation and treatment, a screening process may be associated with both clinical benefits and risks, which should be recognized at the outset. Screening for dementia is not equivalent to diagnosis, which remains at least in part a clinical judgement made by those experienced in the diagnosis of these conditions, a process which needs to take into account the marked clinical and aetiological heterogeneity of the dementia syndrome [19, 31–35] and the inadvisability of accepting "one-size-fits-all" approaches [36, 37]. Screening can therefore never replace the clinical interview.

Because screening tests for dementia can never have perfect sensitivity and specificity (i.e. = 1), there will always be a risk of false positive and false negative diagnoses (see Sect. 1.4). Highly sensitive tests, which are generally thought desirable for screening purposes, will ensure that early cases are not missed but at the risk of making false positive diagnoses (with all the attendant, and ultimately unnecessary, anxiety, treatment risks, etc., that these may entail). Highly specific tests minimize incorrect diagnoses but may miss early cases (false negatives). Screening tests that disclose abnormalities only when a disease is clinically obvious are of limited applicability, indeed, measures of test performance (see Sect. 1.4) may be inflated by using patients with established diagnoses.

1.3 Desiderata for Cognitive Screening Instruments

What features would be desirable for the optimal cognitive screening instrument?

A number of criteria for such an instrument were enunciated by the Research Committee of the American Neuropsychiatric Association [38]:

1. Ideally it should take <15 min to administer by a clinician at any level of training.
2. Ideally it should sample all major cognitive domains, including memory, attention/concentration, executive function, visual-spatial skills, language, and orientation.
3. It should be reliable, with adequate test-retest and inter-rater validity.
4. It should be able to detect cognitive disorders commonly encountered by neuropsychiatrists.

To these criteria, one may add:

- Ease of test administration, that is, not much equipment required beyond pencil and paper or laptop computer.
- Ease of interpretation, that is, clear test cutoffs, perhaps operationalized, for example, a particular score on the test should lead to particular actions, such as patient reassurance, continued monitoring of cognitive function over specified times periods, or immediate initiation of further investigations and/or treatment.

Other issues may also require consideration when selecting a cognitive screening instrument, for example, the location in which testing is undertaken (primary or secondary care) and the suspected dementia diagnosis being screened for (see Sects. 12.2.1 and 12.3, respectively). In primary care settings, briefer tests may be optimal [39, 40]. If the suspected diagnosis being screened for is AD, then tests which focus on the examination of episodic memory, to the relative exclusion of other cognitive domains, may be preferred.

A variety of factors may influence patient performance on cognitive screening instruments. These include patient age, educational status, culture, language, presence of primary psychiatric disorder (anxiety, depression), and presence of primary sensory deficits. For example, one study found that poor performance on the Mini-Mental State Examination (MMSE; [41]) due to causes other than dementia was recorded in around 10 % of an elderly population, increasing with age (>40 % in those ≥85 years), most commonly due to poor vision and hearing, deficient schooling, and the consequences of stroke [42]. It is well recognized that test performance may vary with factors such as the environment in which testing is undertaken (e.g., the alien surroundings of an impersonal clinic room vs. the familiar location of the patient's home) and tester (e.g., perceived to be sympathetic and encouraging vs. brusque and impatient). All these factors may need to be taken into account when using cognitive screening instruments, rather than relying solely on raw test scores. Corrections to test scores or revision of cutoffs may be applicable to allow for patient age and education [43, 44].

Educational and cultural biases are evident in many typical screening test items [45]. For example, tests which rely heavily on literacy will be challenging for individuals with limited education or from cultures using a different language. Screening tests may thus need adaptation for these factors and also patient ethnicity. Cultural modifications have been reported for a variety of cognitive screening instruments, including the MMSE, the Short Portable Mental Status Questionnaire, and the Short Orientation-Memory-Concentration Test [45]. Cultural factors may also affect willingness to be screened for cognitive impairment [46]. Ideally culture-free cognitive screening tests may be developed: claims for such status have been made for the Mini-Cog [47] and the Time and Change Test [48]. Patient assessment by means of informant reports may be relatively culture-free, as may also be the case for functional assessments.

Cognitive screening instruments are not equivalent to a neuropsychological assessment administered by a clinical neuropsychologist, which remains the gold standard for cognitive assessment. The tests used in neuropsychological assessment

Fig. 1.1 2×2 table (Reproduced with permission from [19])

		True status	
		Condition present	**Condition absent**
Test outcome	**Positive**	True positive (*a*)	False positive (*b*)
	Negative	False negative (*c*)	True negative (*d*)

are potentially many [5, 49–51] and tend to focus on function within individual cognitive domains or give a global measure of intelligence (verbal, performance, and full-scale IQ). Requirement for a trained neuropsychologist to administer such tests means that access is not universal. The test battery administered is often time-consuming (much greater than the 15 min suggested by the Research Committee of the American Neuropsychiatric Association [38]), fatiguing for patients, and may sometimes require multiple outpatient visits. Hence, neuropsychological assessment is not a plausible means for screening cognitive function, although it may be necessary to clarify diagnosis in those identified as cognitively impaired by screening instruments.

1.4 Assessment of Utility of Cognitive Screening Instruments

How might the utility of cognitive screening instruments be assessed? There are a variety of parameters based on the classic 2×2 table (Fig. 1.1) which are traditionally used to evaluate diagnostic tests (see Box 1.2). These parameters are mentioned in many of the chapters in this book.

Box 1.2: Some Measures of Test Utility Applicable to Cognitive Screening Instruments

Sensitivity (Se): a measure of the correct identification of true positives:

$$\text{Se} = \text{True positives}/\text{True positives} + \text{False negatives}$$
$$= a/(a+c)$$

Specificity (Sp): a measure of the correct identification of true negatives:

$$\text{Sp} = \text{True negatives}/\text{True negatives} + \text{False positives}$$
$$= d/(b+d)$$

Overall test accuracy (Acc):

$$\begin{aligned}\text{Acc} &= \text{True positives} + \text{True negatives}/\text{Total number tested} \\ &= (a+d)/(a+b+c+d)\end{aligned}$$

Positive predictive value (PPV): a measure of the probability of disease in a patient with a positive test:

$$\begin{aligned}\text{PPV} &= \text{True positives}/\text{True positives} + \text{False positives} \\ &= a/(a+b)\end{aligned}$$

Negative predictive value (NPV): a measure of the absence of disease in a patient with a negative test:

$$\begin{aligned}\text{NPV} &= \text{True negatives}/\text{True negatives} + \text{False negatives} \\ &= d/(c+d)\end{aligned}$$

Youden index (Y), or Youden J statistic:

$$\text{Y} = \text{Sensitivity} + \text{Specificity} - 1$$

Predictive summary index (PSI):

$$\text{PSI} = \text{PPV} + \text{NPV} - 1$$

False positive rate:

$$= \left(b/b+d\right) = \left(1 - \text{specificity}\right)$$

False negative rate:

$$= \left(c/a+c\right) = \left(1 - \text{sensitivity}\right)$$

False alarm rate:

$$= \left(b/a+b\right) = \left(1 - \text{PPV}\right)$$

False reassurance rate:

$$= \left(c/c+d\right) = \left(1 - \text{NPV}\right)$$

Diagnostic odds ratios (DOR):

$$\begin{aligned}\text{DOR} &= \text{True positives} \times \text{True negatives} / \text{False positives} \times \text{False negatives} \\ &= ad/bc\end{aligned}$$

Positive likelihood ratio (LR+): a measure of the change in pretest to post-test odds:

$$\text{LR}+ = \text{Sensitivity} / \left(1 - \text{Specificity}\right)$$

Negative likelihood ratio (LR−): a measure of the change in pretest to post-test odds:

$$\text{LR}- = \left(1 - \text{Sensitivity}\right) / \text{Specificity}$$

Clinical utility index (UI+, UI−): calculates the value of a diagnostic method:

$$\text{UI}+ = \text{Se} \times \text{PPV}\left(\text{ruling in a diagnosis}\right)$$

$$\text{UI}- = \text{Sp} \times \text{NPV}\left(\text{ruling out a diagnosis}\right)$$

Receiver operating characteristic (ROC) curve: plot of false positive rate (1 − specificity) on the *x*-axis against sensitivity ("hit rate") on the *y*-axis; area under the curve (AUC) is a measure of test diagnostic accuracy, where AUC = 0.5 indicates that a test provides no added information, and AUC = 1 indicates a test providing perfect discrimination.

Of these various parameters, sensitivity and specificity are those most usually quoted for cognitive screening instruments (as for other clinical tests), although they are difficult to apply to individual patients. As previously mentioned, tests with high sensitivity are generally thought desirable for screening purposes in order to ensure that cases are not missed (false negatives) but at the risk of including unaffected individuals (false positives). Conversely, a negative result with a highly sensitive test is likely to rule out a disorder. With a highly specific test, a positive result is likely to rule a disorder in, albeit that some cases may be missed (false negatives).

Predictive values (PPV and NPV) are influenced by the prevalence of the disease in the population being tested, and hence their use as a basis for diagnostic decisions is limited. A distinction may be drawn between case finding, identification of a condition with minimal false negatives often measured by PPV, and screening, identification with minimal false positives often measured by NPV [52].

Likelihood ratios, measures of diagnostic gain, may be more useful for application to individual patients than sensitivity and specificity since they are measures of how tests modify the pretest to post-test odds of disease. A positive likelihood ratio (LR+; range 1–∞) indicates a change in probability which favours the presence of a disorder if the test is positive, whilst a negative likelihood ratio (LR−; range 0–1) indicates a change in probability which favours the absence of a disorder if the test is negative. The receiver operating characteristic (ROC) curve is a measure of overall diagnostic accuracy (for further details on these various parameters see [19, 53–56]).

Longitudinal, rather than cross-sectional, assessment of cognitive function is sometimes necessary to establish diagnosis. Such assessment may include repeated use of cognitive tests. Meaningful cognitive change over time may be established through use of reliable change indices which have been defined for a number of neuropsychological tests but for few of the cognitive screening instruments used in day-to-day practice (MMSE, modified MMSE [57]).

Comparisons between different diagnostic instruments may be undertaken using the test of agreement or kappa statistic, where $\kappa = 1$ is perfect agreement between tests and $\kappa = 0$ is agreement due to chance alone [58]; by convention, $\kappa > 0.6$–0.8 is interpreted as substantial agreement [59].

1.5 Assessment of Studies of Diagnostic Accuracy of Cognitive Screening Instruments

With the availability of many cognitive screening instruments, the decision as to which should be incorporated into clinical practice is potentially difficult. The quality of diagnostic accuracy studies may be evaluated using two methodological quality assessment tools, STARD and QUADAS [55, 60]. The Scottish Intercollegiate Guidelines Network (SIGN) also has a methodological checklist for diagnostic studies [61].

The STAndards for the Reporting of Diagnostic accuracy studies (STARD) checklist [62, 63] comprises 25 items and a flow chart which should be followed for optimal study design and reporting. This is a prospective tool which may be used to plan and implement well-designed studies, relatively free of bias. Calculation of sample sizes before undertaking assessments of diagnostic accuracy studies has also been recommended [64]. Evaluation of the entire diagnostic test-treatment pathway has also been advocated [65], although it is currently difficult to envisage how this might be done in the context of dementia and cognitive disorders where treatments are few.

The Quality Assessment of Diagnostic Accuracy Studies (QUADAS) is a tool developed to assess the quality of research studies of diagnostic accuracy, comprising 14 criteria [66, 67], which has been recently revised (QUADAS-2; [68]). This is a retrospective instrument used to assess the methodological rigour of diagnostic accuracy studies. STARD and QUADAS share a number of items (and authors).

Systematic reviews of the accuracy and clinical utility of diagnostic accuracy studies may also help to guide the clinical practice of cognitive screening. Such reviews use defined search strategies and apply specific inclusion and exclusion

criteria. These criteria may of course vary between systematic reviews, dependent on the authors' wishes, for example, sometimes articles in a language other than English may be excluded [69], thus potentially influencing the conclusions reached.

It is universally acknowledged that double-blind placebo-controlled randomized controlled trials (RCTs) are the touchstone for decisions about the licensing of new medications. However, because of their inclusion/exclusion criteria, RCT results may not necessarily reflect therapeutic efficacy in day-to-day practice. Hence, pragmatic studies may better address the uncertainties faced by clinicians in practice [70]. In a similar way, diagnostic accuracy studies undertaken in selected populations may score highly on the STARD/QUADAS ratings but may not necessarily reflect the situations encountered by clinicians in daily practice. For example, patients do not present to the cognitive/memory clinic with the aetiology of their cognitive impairment already defined, and there is no control group in clinical practice. Pragmatic studies of cognitive screening instruments may therefore be required, since in day-to-day practice tests are essentially used to provide arguments for a given diagnosis that is suspected by clinical assessment [19].

1.6 Conclusion

In the age in which dementia biomarkers, based on the findings of sophisticated neuroimaging and biochemical testing, are beginning to be used to define disease entities even before the onset of dementia per se [71–73], it may be questioned what role there may be for cognitive screening instruments in dementia diagnosis. The interrelationships of cognitive screening instruments and biomarkers are only beginning to be investigated [74].

Other investigations certainly play a role in the definition of the aetiology of cognitive impairment and dementia [19]. Since the dementia construct encompasses non-cognitive as well as cognitive impairments [75], assessment of other domains (functional, behavioural, neurovegetative, global) may also be required [19]. However, it has been reported that cognitive testing may be as good as, if not better than, neuroimaging and CSF tests in predicting conversion and decline in patients with mild cognitive impairment at risk of progressing to dementia [76]. Moreover, the newer diagnostic criteria incorporating biomarkers are more applicable to research environments than to daily clinical practice, since many of the investigations recommended are not widely available. Hence, cognitive screening instruments are likely to remain an integral part of clinical assessment of cognitive complaints for the foreseeable future. Their appropriate application and interpretation are therefore of paramount importance to ensure early and correct diagnosis.

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Chapter 2
The Mini-Mental State Examination (MMSE): An Update on Its Diagnostic Validity for Cognitive Disorders

Alex J. Mitchell

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Abstract The Mini-Mental State Examination (MMSE) is the most commonly used brief cognitive tool in the assessment of a variety of cognitive disorders. The tool comprises a short battery of 20 individual tests covering 11 domains and totalling 30 points. Typical completion time is 8 min in cognitively unimpaired individuals rising to 15 min in those with dementia. Internal consistency appears to be moderate and test-retest reliability good. However, the main psychometric issue concerns the MMSE's diagnostic validity against dementia, mild cognitive impairment, and delirium. This chapter updates previous meta-analytic summary analyses for the performance of the MMSE in specialist and nonspecialist settings. Summary sensitivity, specificity, positive, and negative predictive values are presented. Results suggest against dementia, mild cognitive impairment, and delirium it did not perform well as a confirmatory (case-finding) tool, but it did perform adequately in a rule-out (screening) capacity. In clinical practice, this means that a high score on the

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MMSE would lead to about a 10 % false negative rate, and further, a low (positive) score must be followed by more extensive neuropsychological or clinical evaluation. The MMSE is neither the most accurate nor more efficient tool with which to evaluate cognitive disorders, but it has provided a benchmark against which all newer tools can be measured.

Keywords Mini-Mental State Examination (MMSE) • Dementia • Mild cognitive impairment • Delirium • Diagnostic accuracy • Reliability • Sensitivity • Clinical utility

2.1 Introduction: History and Development

The Mini-Mental State Examination (MMSE) was published in 1975 by Folstein et al. [1] as a practical method of grading cognitive impairment and has become the most commonly used rapid cognitive screening instrument [2]. While it is true that the MMSE may never have been intended as a diagnostic tool, it has been very extensively investigated as a diagnostic test of dementia and related cognitive disorders. Many are attracted by the brevity of the instrument and the belief that it offers broad coverage of cognitive domains. Its ubiquitous use was no doubt helped by its royalty free distribution up to 2001 when copyright was acquired by Psychological Assessment Resources (http://www.minimental.com/). In clinical practice, the main applications of the MMSE are to help clinicians in the diagnosis of dementia and delirium [3]. It has been investigated in a case-finding role (i.e. confirmatory diagnosis) as well as in a screening role (largely rule-out application designed to minimize false negatives). Recent work has also investigated its performance in detecting mild cognitive impairment (MCI). A subsidiary aim, not discussed here, is grading severity of cognitive impairment in those with known disorders [4]. It is worth noting that while a typical application time of 10 min seems short to neuropsychologists, many working in primary care would consider this much too long [5, 6].

At least 100 validation studies exist, but most are underpowered and many lack an adequate criterion standard and, hence, can give a misleading impression of accuracy [7]. For example, Folstein, Folstein, and McHugh validated the MMSE in two samples of patients which included only 38 with dementia [1]. However, it can be argued that even with suboptimal accuracy, the large evidence base surrounding the MMSE is advantageous because scores on the MMSE are fairly well understood by health professionals. This is most applicable to normative data. Folstein et al. [1] tested a population sample in Baltimore and found 4.2 % of those aged 18–64 scored <24/30 compared to 20.8 % of those over 65. Crum et al. [8] tested an extensive group of 18,056 participants in US Epidemiologic Catchment Area (ECA) study and presented distributions by age and educational levels. Some groups have provided norms for each item on the MMSE by age group [9]. Yet there remains controversy about its clinical applications in case finding and screening, as well as the optimal cut-off threshold [10, 11]. A cut-off of <24/30 was recommended as significant by Folstein and colleagues in persons with at least 8 years of education

[1]. But in reality, individuals with early dementia but with a background of extensive education are likely to experience a ceiling effect with the MMSE (see Sect. 2.4 on early dementia). Numerous other cut-offs have been calculated from receiver operating characteristic curve (ROC) analysis of specific populations together with adjustments for age and education [12, 13]. Here, I will review the accuracy of the MMSE when considering one of the common cognitive disorders in clinical practice: dementia, mild cognitive impairment, and delirium.

2.2 Structure and Reliability of the MMSE

The MMSE has an internal structure of 20 individual tests covering 11 domains including orientation, registration, attention or calculation (serial sevens or spelling), recall, naming, repetition, comprehension (verbal and written), writing, and construction. Internal consistency appears to be moderate with Cronbach alpha scores reported between 0.6 to 0.9 [14, 15]. Test-retest reliability has been examined in several studies and in those where re-examination took place within 24-h reliability by Pearson correlation was usually above 0.85. Scoring emphasizes orientation (time – 5 points; place – 5 points) and attention/concentration/calculation (5 points) with lower emphasis on registration memory (3 points) and recall (3 points). Little weight is placed on naming (2 points), repetition (1 point), following a three-stage command (3 points), reading (1 point), writing (1 point), or copying intersecting pentagons (1 point). Factor-analytic and item-response studies suggest up to five factors [16, 17]. Using Rasch analysis, it is possible to grade the completion difficulty of each item on the MMSE. Relatively difficult items are the recall of three words, citing the correct date, coping the pentagon design, and spelling world backwards or completing serial sevens. Conversely, relatively simple items are naming the correct country, registering three words, following the command and naming an object (pencil).

A significant issue is that the individual questions are not particularly applied, which reduces acceptability of the test to those who suspect impairment. In other words, uptake of the test may be low in those with impairment. It is generally accepted that much of the content of the MMSE was derived from existing instruments [18]. All questions are designed to be asked in the order listed, with omissions scored as errors giving a maximum score of 30. However, there is some ambiguity in several items leading to the Standardized Mini-Mental State Examination from Molloy et al. [19] (see Sect. 3.2.1). The MMSE has helped in the development of newer potentially improved cognitive instruments discussed in other chapters (e.g. Chap. 4).

2.3 Diagnostic Validity in Unselected Dementia

This is probably the MMSE's most common application and hence the most important question. Does the MMSE enable clinicians to accurately rule-in or rule-out dementia? Further, does this depend on prevalence of dementia, for example, when

dementia is less common such as in primary care settings? O'Connor et al. [20] conducted one of the first adequately powered tests of the MMSE using a cut-off <24/30 in 2,302 primary care patients; 586 received a CAMDEX/CAMCOG interview as a gold standard (criterion reference). O'Connor et al. found that sensitivity of the MMSE was 86 % and specificity 92 % [20]. There have been at least eight other primary studies, and these documented somewhat differing results (see Table 2.1).

To clarify uncertainty, our group undertook a meta-analysis of MMSE dementia studies published prior to 2009 [21]. In the original paper, after excluding studies relying upon modified forms of the MMSE, as well as those focussing on specific sub-tests, there were 34 diagnostic validity studies against dementia (typically using DSM criteria, not robust post-mortem data). This is now updated to 45 studies (Table 2.1; [20, 22–64]) comprising 12 community studies, 7 primary care studies and 26 from specialist settings where the prevalence of dementia is relatively high. It is important to remember that the prevalence of a condition strongly influences test performance. High prevalence settings favor few false positives but at the expense of false negatives. Three studies were difficult to classify as they were conducted in the community but recruited from primary care lists. The most common reference standard in making a diagnosis of dementia was used in 20 studies. These results are now updated in Table 2.1 with the addition of eight new studies. A random effects meta-analysis model was used to calculate summary sensitivity, specificity, and PPV and NPV calculated using a prevalence of 25 %.

Looking at specialist settings, meta-analysis showed that the MMSE's sensitivity for diagnosing dementia was 76.9 % (95 % CI = 70.1–83.1 %) and its specificity was 89.9 % (95 % CI = 82.5–95.4 %). More meaningfully, that converts into a positive predictive value (PPV) of 89.3 % and a negative predictive value (NPV) of 74.8 % at a prevalence of 55 %, but 71.7 % (PPV) and 92.1 % (NPV) at 25 %. Thus, there would be a 25 % false negative rate for every 24 or above MMSE score in clinics where the prevalence of dementia was high, but only an 8 % error rate when prevalence was low. Clinical utility can be considered to be a function of both occurrence and discrimination of a test. MMSE may be suitable to be used as a first step screening tool in specialist clinics.

Looking next at nonspecialist settings, meta-analytic pooled sensitivity was 81.4 % (95 % CI = 75.2–86.8 %), and the meta-analytic pooled specificity proportion was 87.2 % (95 % CI = 84.0–90.1 %). These studies were conducted in populations where the prevalence of dementia was only 10 %. PPV was approximately 40 % and the NPV 98 %. This generates a concerning 60 % false positive rate for every <24 score. However, at 25 % prevalence, the false positive rate is reduced to one in three. Clinical utility calculation suggests the MMSE would be suitable as a screening test in primary care, based on accuracy, provided instrument length was not problematic. Further separating community studies from primary care studies revealed only a slightly better rule-in ability of the MMSE in primary care. These data are likely to somewhat flatter the MMSE by making comparisons largely without including patients with MCI. In clinical settings, a more important question may be who has early dementia in a group complaining of memory problems? This introduces two further analyses, namely early dementia and MCI.

Table 2.1 Diagnostic validity of MMSE in diagnosing dementia

Reference	Reference standard	Sample description	Setting	Cut off	Sensitivity (%)	Specificity (%)	PPV (%)	NPV (%)	Prevalence
McDowell et al. [22]	DSM-III-R and ICD-10 revised	$N = 1{,}120$ including 368 with dementia	Community and institutions	24v25	85.9	77.0	64.6	91.8	0.33
Huppert et al. [23]	AGECAT dementia	Large CFAS study includes 795 with dementia and 11,885 without seen over multiple waves	Community multicenter population study in those aged 65 years and older	23v24	88.9	87.9	32.9	99.2	0.06
Callahan et al. [24]	DSM IV and ICD10 dementia	Cohort one consists of 344 community-dwelling black persons identified from a random sample of 2,212 black persons aged 65 and older residing in Indianapolis	Community sample	23v24	93.3	86.6	24.2	99.7	0.04
Gagnon et al. [25]	DSM-III dementia	2,792 community elderly 65 years or older	Community sample	23v24	100.0	78.0	14.9	100.0	0.04
Ganguli et al. [26]	DSM-III-R dementia	1,367 > 65 years	Community sample	23v24	65.2	88.9	55.1	92.4	0.17
Heun et al. [27]	DSM-III-R dementia	37 dementia, 250 no dementia from general population; psychiatric disorders included	Community sample	23v24	83.8	98.8	91.2	97.6	0.13

(continued)

Table 2.1 (continued)

Reference	Reference standard	Sample description	Setting	Cut off	Sensitivity (%)	Specificity (%)	PPV (%)	NPV (%)	Prevalence
Kay et al. [28]	DSM-III dementia	274 older persons living in community including 116 over 70 years	Community sample	23v24	69.2	88.9	50.9	94.6	0.14
Schultz-Larsen et al. [29]	DSM-IV dementia	68/242 with dementia at baseline, mostly mild	Community sample	23v24	36.8	98.3	89.3	79.9	0.28
Fountoulakis et al. [30]	DSM-IV, NINCDS-ADRDA	22 with dementia, 52 without plus 195 assumed intact	Community sample	23v24	100.0	47.9	13.0	100.0	0.07
Clarke et al. [31]	Cambridge Mental Disorders of the Elderly Examination (CAMDEX)	$n=161$ with mixed dementia vs. 152 without (114 with minimal dementia excluded)	Community sample from a single general practice	23v24	88.8	80.9	83.1	87.2	0.51
Brayne and Calloway [32]	Cambridge Mental Disorders of the Elderly Examination (CAMDEX)	29 with dementia, 336 without	Community study	21v22	82.8	86.9	35.3	98.3	0.08
Cullen et al. [33]	AGECAT dementia	Over 65 years	Community study from a primary care sample	23v24	90.9	86.4	21.5	99.6	0.04

Larner [34]	DSM-IV dementia and Petersen MCI criteria combined	150 patients including 36 with dementia, 29 with MCI and 85 without cognitive impairment	Specialist memory clinic	25v26	65	89	82	78	0.43
Callahan et al. [24]	DSM IV and ICD10 dementia	Cohort two consists of 651 subject referrals to the Alzheimer Disease Center	Specialist memory clinic	23v24	81.4	93.5	93.4	81.7	0.53
Hoops et al. [35]	Movement Disorder Society diagnostic criteria for probable PDD	132 patients: 92 with no cognitive disorder, 23 with MCI and 17 with dementia	Specialist outpatients at movement clinic	28v29	82.3	63.0	29.2	95.1	0.15
Dalrymple-Alford et al. [36]	Movement Disorder Society diagnostic criteria for probable PDD	114 patients with idiopathic PD including 21 with dementia and 21 with MCI and 47 healthy controls	Specialist outpatients at movement clinic	26v27	86.0	75.0	60.0	93.0	0.18
Borson et al. [37]	Mini-Cog DSM-III-R NINCDS CERAD applied	1,119 age stratified random sample	Primary care	24v25	71.0	94.0	44.9	97.9	0.06
Brodaty et al. [38]	DSM-IV dementia	82 with dementia and 201 without	Primary care	24/25	81.7	76.1	58.3	91.1	0.29

(continued)

Table 2.1 (continued)

Reference	Reference standard	Sample description	Setting	Cut off	Sensitivity (%)	Specificity (%)	PPV (%)	NPV (%)	Prevalence
Hooijer et al. [39]	GMS/AGECAT 4 or 5+CAMDEX	13 with dementia and 345 without	Primary care	23/24	76.9	96.5	45.5	99.1	0.04
Kalida et al. [40]	DSM-III-R dementia	BLSA sample with severe dementia excluded. Ninety-seven patients enrolled 67 % AD 13 %. Mixed 8 % Parkinson's 12 % dementia unspecified. Matched with randomly selected controls. ADRC sample 159 dementia 159 controls	Primary care	26v27	76.0	90.0	84.7	83.8	0.42
Kirby et al. [41]	Diagnosis by DSM-III-R GMS-AGECAT	Total 648, dementia-41, depression-84, normal-523	Primary care	23v24	87.8	87.6	35.6	98.9	0.07

Wind et al. [42]	GMS/AGECAT	Total = 533, 391 = minimal dementia, 106 = mild dementia, 36 = mod/severe dementia	Primary care	23v24	69.3	89.3	63.7	91.4	0.21
Grober et al. [43]	DSM-IV and expert consensus	55 with dementia, 262 without dementia All have MMSE > 18; 62 % were CDR = 0.5	Primary care (urban)	23v24	52.7	90.1	52.7	90.1	0.17
O'Connor et al. [20]	Cambridge Mental Disorders of the Elderly Examination (CAMDEX)	51 with dementia, 430 without	Primary care sample	23v24	86.3	92.1	56.4	98.3	0.11
Kalbe et al. [44]	Diagnosis by DSM IV , NINCDS-ADRDA	289 dementia 201 controls	Secondary care	25v26	62.6	91.5	91.4	63.0	0.59
Brooke and Bullock [45]	Psychiatrists expert diagnosis dementia	70 mild dementia (GDS3-5) and 82 moderate to severe	Secondary care memory clinic and community	23v24	78.9	100	100	80.8	0.53

(continued)

Table 2.1 (continued)

Reference	Reference standard	Sample description	Setting	Cut off	Sensitivity (%)	Specificity (%)	PPV (%)	NPV (%)	Prevalence
Tariq et al. [46]	DSM-IV dementia	440 normal, 180 mild cognitive impairment, 82 dementia	Secondary care OPC	23v24	45.5	100.0	100.0	91.0	0.15
O'Bryant et al. [47]	"Published criteria" dementia	1,141 educated individuals including 307 (164 men and 143 women) patients with dementia (any type), 176 (106 men and 70 women) patients with MCI and 658 (242 men and 416 women) control participants	Secondary care: archival data from the Mayo Clinic Alzheimer Disease Research Center	26v27	88.6	91.0	82.2	94.5	0.32
Chopard et al. [48]	DSM-IV and NINCDS-ADRDA for AD	282 with dementia (including 187 with AD), 206 without. No significant differences in age, sex, or level of education between patients and controls Dementia included 41 % CDR = 1.0	Secondary care: memory clinic	24v25	92.9	85.9	90.0	89.8	0.58

Flicker et al. [49]	DSM-III-R dementia	216 with dementia, 84 without	Secondary care: memory clinic	23v24	84.7	60.2	84.7	60.2	0.72
Kalbe et al. [50]	NINCDS-ADRDA for AD	88 with mild AD MMSE >21 plus 97 older controls > 59 years	Secondary care: memory clinic	26v27	67.0	76.3	86.4	50.7	0.69
Mendiondo et al. [51]	Expert diagnosis CDR 0.5 or 1	503 patients with mild possible AD and 70 non-clinic patients without dementia	Secondary care: memory clinic	23v24*	76.9	77.1	96.0	31.8	0.88
Narasimhalu et al. [52]	DSM-IV dementia	87 with AD and 82 with VaD versus 407 controls	Secondary care: memory clinic	17v18 if no education else 21v22	72.8	76.0	55.7	87.1	0.29
Yoshida et al. [53]	CDR and NINCDS-ADRDA	242 memory clinic patients: dementia ($n=130$), mild cognitive impairment (MCI) ($n=39$) and a control group ($n=73$)	Secondary care: memory clinic	26v27	41.0	96.9	99.2	94.7	0.64

(continued)

Table 2.1 (continued)

Reference	Reference standard	Sample description	Setting	Cut off	Sensitivity (%)	Specificity (%)	PPV (%)	NPV (%)	Prevalence
Yoshida et al. [54]	Early dementia by NINCDS-ADRDA	201 subjects (Alzheimer's disease (AD) = 65, frontotemporal dementia (FTD) = 24, vascular dementia = 26, dementia with Lewy bodies = 11, mild cognitive impairment (MCI) = 13, and controls = 62) participated in this study	Secondary care: memory clinic	23v24	76.2	97.3	97.9	70.8	0.627
Terpening et al. [55]	Diagnosis by DSM IV, AD by NINCDS-ADRDA	82 with dementia 40 with no dementia	Secondary care: memory clinic	NR	80.0	78.0	88.9	64.0	0.672
Meulen et al. [56]	Diagnosis by DSM IV, AD by NINCDS-ADRDA	AD-177 VD-62 LBD-17 other dementia-30 +35 MCI-87 depression-31 controls-45	Secondary care: memory clinic, geriatric medicine clinic	22v23	64.7	96.8	98.6	43.9	0.78

Galvin et al. [57]	CDR 0.5 or 1 and NINCDS-ADRDA	101 with dementia (CDR 1 and 0.5); 156 without dementia	Secondary care: University Alzheimer's Disease Research Center	25v26	72.4	90.4	80.8	85.4	0.358
Tang et al. [58]	DSM-IV dementia	83 stroke patients including 10 with dementia	Specialist acute stroke unit	18v19	93.3	80.0	36.0	98.0	0.12
Borson et al. [59]	CERAD, DSM IV and NINCDS-ADRDA	129 with AD and 120 non-AD. Five ethnic groups. All 129 who met criteria for probable dementia	Specialist AD Research Center	23v24	90.7	91.7	92.1	90.2	0.52
Borson et al. [60]	NINCDS-ADRDA for AD	112 with probable AD, 71 with MCI and 140 healthy controls	Specialist AD Research Center	23v24	94.6	84.3	82.8	95.2	0.44
Tangalos et al. [61]	DSMIIIR dementia	105 with dementia vs. 227 without	Specialist Mayo Clinic serving primary internal medicine	23v24	69.2	99.1	98.5	79.8	0.45
Ganzer et al. [62]	DSM-IV and NINCDS-ADRDA for AD	105 AD patients and 68 controls	Specialist memory and neurology clinics	25v26	93.3	75.0	85.2	87.9	0.61

(continued)

Table 2.1 (continued)

Reference	Reference standard	Sample description	Setting	Cut off	Sensitivity (%)	Specificity (%)	PPV (%)	NPV (%)	Prevalence
Aprahamian et al. [63]	DSM-IV and NINCDS-ADRDA for AD	121 outpatients previously diagnosed with AD and 99 normal controls (NC), older than 60 years	Specialist outpatients	26v27	88.4	75.8	88.7	84.3	0.55
de Silva and Gunatilake [64]	CAMCOG	57 patients including 31 positive on the CAMCOG	Specialist university hospital in Sri Lanka	17v18	93.5	84.6	87.9	91.7	0.54

Updated from [21]
DSM-IV Diagnostic and Statistical Manual of Mental Disorders (DSM IV), *CERAD* Consortium to Establish a Registry for Alzheimer's Disease, *CDR* Clinical Dementia Rating

2.4 Diagnostic Validity in Early Dementia

One critical question is whether the MMSE retains sufficient accuracy when looking for early dementia. People with early dementia are particularly at risk of being overlooked and undertreated [65]. Provisional evidence from three studies suggests that sensitivity is lower when attempting to diagnose those with mild dementia. From memory clinic studies, Meulen and colleagues [56] found that the area under the ROC was 0.95 for all dementias but only 0.87 for mild dementia. Yoshida et al. [54] also found relatively low sensitivity (and low NPV) when looking for mild dementia in a Japanese memory clinic. Mendiondo et al. [51] found reasonable rule-in accuracy but poor rule-out accuracy using the MMSE in a very high prevalence memory clinic sample of those with mild dementia scoring 20 or above. Yet in a sub-analysis of 88 people with mild Alzheimer's scoring >20 on the MMSE, Kalbe and colleagues [50] found that the MMSE had a sensitivity of 92 % and a specificity of 86 % (PPV 85.2 %, NPV 92.2 %).

Regarding diagnosis of mild dementia in primary care, Kalida and colleagues [40] found adjusting the cut-off to 26v27 was required. Grober et al. [43] examined the value of MMSE in 317 primary care attendees with an MMSE score above 18 including 134 patients with a CDR of 0.5 without MCI (equivalent to MCI). In this study, at a cut-off of 23v24, the PPV was 52.7 % and the NPV 90.1 %, but at a cut-off of 26v27, the PPV was 36.0 % and the NPV 92.7 %. Taken together, these data suggest that there is little basis for case-finding (confirmatory) role for the MMSE in early dementia presenting in primary care, but there is a rule-out (reassurance) role. However, its accuracy is lower when compared with the diagnosis of moderate-severe dementia, and a higher cut-off is recommended.

2.5 Diagnostic Validity in Specific Dementias

The MMSE has been used in the diagnosis of several types of dementias, most notably Alzheimer's disease, vascular dementia, Lewy body dementia, and Parkinson's dementia. It should be noted that with the possible exception of the Cambridge CFAS group, no study has yet followed such patients through to post-mortem. Thus, any results are dependent upon the diagnosis of a specific dementia being accurate in life.

At face value, the MMSE lacks the detail to differentiate between dementias. For example, it is relatively insensitive to the early stages of AD when the deficits are confined to amnestic syndromes [66]. Similarly, it may lack assessment of attention necessary for DLB and does not include executive function thought to be involved in Parkinson's dementia. As all tests are combined in a summary score, it is not usual to extract subtest scores. However, if subtest scores are extracted, some groups have reported success in differentiating Lewy body dementia from probable Alzheimer's disease [67–69] and from Parkinson's dementia [70].

At least nine diagnostic validity studies have tested the MMSE against probable Alzheimer's disease according to NINCDS-ADRDA criteria (Table 2.1). Results seem to parallel those in dementia as a whole, although the prevalence of Alzheimer's disease is slightly lower than dementia taken as a whole.

Several studies have looked at the application of the MMSE for post-stroke cognitive impairment [71] and post-stroke MCI (Table 2.2) but only one specifically recorded post-stroke dementia (Table 2.1). Two studies have examined Parkinson's dementia (Table 2.1), and both showed low specificity and low PPV for the MMSE. One additional study has also looked at Parkinson's related MCI versus amnesic MCI unrelated to Parkinson's based on MMSE's pentagon copying test [72]. Overall, it seems premature to conclude whether the MMSE is more or less accurate in specific subtypes of dementia.

2.6 Diagnostic Validity in MCI

An earlier analysis of MMSE studies against MCI identified only five studies published before 2009 [21]. Rerunning the search now reveals 11 qualifying studies (see Table 2.2; [73–77]). The majority use the Mayo Clinic criteria suggested by Petersen and colleagues [78]. These core criteria are essentially the combination of subjective memory complaints, objective impairment short of dementia and minimal functional decline. It is important to realize many patients with pre-dementia cognitive decline will not fulfill these rules largely because of high problems with activities of daily living or lack of subjective complaints. Thus, MCI should be considered as one of several possible pre-dementia categories. Indeed, many with MCI do not progress but actually improve. As shown in Table 2.2, the optimal cut-point when looking for MCI is not <24 but higher, possibly <27. However, age and education again influence this cut-point making one recommendation difficult.

There are three ways the MMSE would be commonly used in the diagnosis of MCI. First, to attempt to identify MCI in those who have subjective memory complaints but clearly do not have dementia. These would be similar to the memory clinic studies listed in Table 2.2. Second, to identify people with MCI among otherwise unimpaired individuals living in the community. This use has not yet been adequately tested in the literature. Third, to identify dementia in a population with memory complaints, essentially to find those with dementia among a group with MCI. Taking the first aim, a meta-analysis of 11 studies reveals an overall sensitivity of 66.9 % (95 % CI = 50.1–81.8 %) and a specificity of 77.6 % (95 % CI = 62.3–89.8 %) when MCI is the target in specialist settings. Assuming a prevalence of 25 %, then the PPV is about 50 % and NPV about 88 %. Further, assessing clinical applicability using the clinical utility index shows that the MMSE has poor rule-in value (CUI+ = 0.334) but good rule-out value (CUI− = 0.679). Taking the third objective, from six qualifying studies, the MMSE has a pooled sensitivity of 87.2 % (95 % CI = 80.9–92.5 %) and a specificity of 59.7 % (95 % CI = 34.9–82.1 %) when helping clinicians separate dementia from MCI. Again, if prevalence were 25 %,

Table 2.2 Diagnostic validity of MMSE in diagnosing mild cognitive impairment

Reference	Reference standard	Sample description	Setting	Cut off	Sensitivity (%)	Specificity (%)	PPV (%)	NPV (%)	Prevalence
Xu et al. [73]	MCI by prospective conversion to dementia	351 patients	Memory clinic	26v27	85.7	80.1	57.6	94.7	0.24
Tang-Wai et al. [74]	MCI by Petersen et al. (1997) criteria	917 patients	Specialist Mayo Clinic	28v29	82.2	48.0	20.5	94.3	0.14
Borson et al. [60]	MCI defined as CDR = 0.5 without functional deficits	112 with probable AD, 71 with MCI and 140 healthy controls	Specialist AD Research Center	23v24	50.7	84.3	62.1	77.1	0.34
Kalbe et al. [50]	MCI by Petersen et al. (1997) criteria	97 older controls >59 years vs. 97 with MCI	Memory clinic	26v27	69.1	77.3	75.3	71.4	0.50
Nasreddine et al. [75]	MCI by Petersen et al. (1997) criteria	184 individuals	Memory clinic	25v26	18.1	100.0	100.0	53.9	0.51
De Marchis et al. [76]	Neuropsychological battery	70 inpatients 55–85 years; 55 with MCI and 15 without	Medical inpatients	27v28	85.5	66.7	90.4	55.6	0.79
Yoshida et al. [53]	Adapted Petersen et al. (1997) MCI criteria	Mild cognitive impairment (MCI) ($n = 39$) and a control group ($n = 73$)	Memory clinic	26v27	41.0	98.6	84.1	75.8	0.39

(continued)

Table 2.2 (continued)

Reference	Reference standard	Sample description	Setting	Cut off	Sensitivity (%)	Specificity (%)	PPV (%)	NPV (%)	Prevalence
Pendlebury et al. [77]	Winblad consensus MCI criteria	39 with MCI and 52 without	Population-based Oxford Vascular Study	28v29	76.9	80.7	75.0	82.0	0.43
Hoops et al. [35]	Adapted Petersen et al. (1997) MCI criteria	132 patients, 92 with no cognitive disorder, 23 with Parkinson's MCI and 17 with Parkinson's dementia	Outpatients at movement clinic	28v29	91.3	38.0	26.9	94.6	0.20
Dalrymple-Alford et al. [36]	Neuropsychological battery	114 patients with idiopathic PD including 21 with Parkinson's dementia and 21 with Parkinson's MCI, 72 without cognitive impairment and 47 healthy controls	Outpatients at movement clinic	28v29	90.5	51.3	44.0	93.0	0.22

O'Bryant et al. [47]	"Published criteria"	1,141 educated individuals including 307 (164 men and 143 women) patients with dementia (any type), 176 (106 men and 70 women) patients with MCI and 658 (242 men and 416 women) control participants	Archival data from the Mayo Clinic Alzheimer Disease Research Center and Alzheimer Disease Patient Registry	26v27	34.7	91.0	50.8	83.9	0.21

Updated from [21]

then the PPV and NPV would be 41.9 and 93.3 %, respectively. This means that the MMSE would not be a good choice to confirm the presence of dementia in typical memory clinics where most patients had MCI as 60 % of positives would be erroneous. However, it could once again be used as a screening test with a 7 % false positive rate in this context.

2.7 Diagnostic Validity in Delirium

Delirium is a mental disorder usually characterized by acute onset, impaired attention, an altered level of consciousness and a fluctuating course. Frequently, there are widespread cognitive deficits in orientation, memory, attention, thinking, perception, and insight. It occurs in approximately 10–30 % of vulnerable patients admitted to hospital. If unresolved, delirium is strongly associated with poor outcomes such as disability and death [79–81]. Randomized trials have shown multi-component preventive strategies to be effective in preventing and treating delirium [82]. However, it remains under-recognized suggesting a role for screening instruments [83–85].

A recent review of 11 instruments in 25 studies highlighted potentially favorable accuracy for Global Attentiveness Rating (GAR), Memorial Delirium Assessment Scale (MDAS), Delirium Rating Scale Revised-98 (DRS-R-98), Clinical Assessment of Confusion (CAC), Delirium Observation Screening Scale (DOSS), and Nursing Delirium Screening Scale (Nu-DESC) [86]. The Confusion Assessment Method (CAM) was the most thoroughly investigated, but the Mini-Mental State Examination (MMSE) was omitted from this review [87]. The MMSE may not seem the ideal choice for delirium but nevertheless has the potential to be useful because of its broad cognitive remit.

A search of the literature suggests there are currently ten valid studies of the MMSE for the detection of delirium in medical settings involving a total of 1,477 patients. These studies are summarized in Table 2.3 [88–97]. Running a diagnostic validity meta-analysis gives an overall sensitivity estimate of 83.5 % (95 % CI = 73.9–91.3 %) and a specificity of 76.5 % (95 % CI = 59.7–89.9 %). Assuming delirium was present in 25 % of high risk patients, then the PPV and NPV would be 54.2 and 93.3 %, respectively. Using the clinical utility index to calculate both occurrence and discrimination suggests that the MMSE is not a particularly good test to identify delirium although it has some value when negative. A negative test occurs in approximately three out of four people without delirium, and when negative there is a 93 % chance delirium is not present.

2.8 Conclusion: Implementation

This chapter updates the earlier findings concerning the application of the MMSE as a diagnostic test for dementia and related disorders. It is worth acknowledging that the MMSE has a number of obvious limitations [3]. It has a floor effect (imprecise

Table 2.3 Diagnostic validity of MMSE in diagnosing delirium

Reference	Reference standard	Sample description	Setting	Cut-off	Sensitivity (%)	Specificity (%)	PPV (%)	NPV (%)	Prevalence
Anthony et al. [88]	Delirium or dementia DSM-III by psychiatrist	97 patients (37 male) 46 over 60 years	Hospital	23v24	0.87	0.824	0.606	0.953	0.237
Trzepacz et al. [89]	DSMIII delirium	108 consecutive liver transplant candidates	Hospital	NR	0.556	0.822	0.385	0.902	0.167
Dyer et al. [90]	Confusion Assessment Method (CAM)	60 patients 97 % male, mean age 70.1 year	Hospital	NR	0.771	0.56	0.711	0.636	0.583
Hart et al. [91]	DSM-III-R delirium by psychiatrists	103 patients	Hospital (controls included outpatients)	18v19	1	0.938	0.815	1	0.214
Rockwood et al. [92]	DSMIIIR delirium by psychiatrists	104 patients, mean age 79 years	Hospital	23v24	0.885	0.526	0.383	0.932	0.25
Rolfson et al. [93]	DSMIIIR delirium by psychiatrists	71 patients; 80 % male, mean age 71 years	Hospital in patients undergoing cardiac surgery	23v24	0.348	0.813	0.471	0.722	0.324

(continued)

Table 2.3 (continued)

Reference	Reference standard	Sample description	Setting	Cut-off	Sensitivity (%)	Specificity (%)	PPV (%)	NPV (%)	Prevalence
Grassi et al. [94]	DSM-III-R delirium	105 patients, 55 males 67.7 years	Hospital	23v24	0.955	0.385	0.724	0.833	0.629
O'Keeffe et al. [95]	Confusion Assessment Method (CAM)	160 patients, mean 79 years	Hospital	Fall of 2 points	0.917	0.9	0.727	0.974	0.225
Ringdal et al. [96]	Confusion Assessment Method (CAM)	364 patients over 65 years	Hospital patients with hip fracture	23v24	0.882	0.542	0.337	0.945	0.209
Fayers et al. [97]	ICD10 Delirium	305 patients mean 80 years 42 % male	Hospital	23v24	0.894	1	1	0.916	0.466

Updated from [21]

measurement in the very severe range) [17, 98] which is notable in advanced dementia, in those with little formal education, and in those with severe language problems. Perhaps more importantly, there is a ceiling effect meaning it cannot easily gauge severity in people with very mild disease [99]. This is largely due to its crude testing of recall based solely on three objects. The ceiling effect is reflected in a low sensitivity when diagnosing early dementia as well a low sensitivity for MCI [100]. This problem is amplified when testing highly educated individuals. Further, several MMSE items are strongly influenced by age, education, and ethnicity [17]. Twelve percent of the variance in MMSE scores can be attributed to age and education alone [101]. Tables of adjustment by age and education have been published but are often overlooked [102]. As a rule of thumb, education-adjusted cut-off points for an abnormal score are <21 for patients with a basic school education, <23 for a high school education, and <24 for graduate/university education. A final limitation is its length, particularly in primary care [5, 6], and while it can be completed and scored in about 8 min in unimpaired individuals, it often takes more than 15 min in patients with dementia [56].

The focus of this chapter is the accuracy of the MMSE when used diagnostically. Results from the meta-analyses above suggest that the main role of the MMSE should be as a screening test and not as a case-finding tool. Further, it functions best in this capacity when the prevalence of the condition in question is low. Providing its length was not a barrier to use, then it could be used as an initial screening test for dementia in primary care and in memory clinics although the false negative rate would be about 8 % of all negative screens or about 5 % of consecutive attendees. However, sub-analysis concerning the diagnosis of dementia in patients with pre-existing MCI (arguably a more realistic test of memory clinic conditions) reduces its accuracy considerably and prevents a recommendation. When looking for MCI among otherwise unimpaired individuals, the MMSE achieves reasonable performance, but it can certainly be improved upon by other newer instruments as well as neuropsychological testing [103]. Finally, for the detection of delirium in hospital settings, the MMSE performs reasonably well but again cannot be used in a case-finding role. As an initial screen for delirium, it can rule-out delirium with 93 % accuracy (NPV) when negative. These findings generally concur with the recommendation from the original authors that MMSE should not be used to substitute for systematic evaluation including history taking, examination, and laboratory tests. I recommend that even if the MMSE is used as an initial first step to rule out dementia, delirium, or MCI, then the rate of false negative and false positive rate should be carefully considered.

Some may argue that data on the accuracy of a tool do not prove that it is effective in clinical practice. Very few studies have actually evaluated whether the MMSE improves outcomes when implemented in a clinical setting. Although one early study incorporating the MMSE showed no beneficial effect of delirium screening [104], a second larger randomized study of delirium screening and treatment was effective [105]. Regarding implementation of MMSE screening for dementia, in a nonrandomized study of diagnostic practices of 64 general practitioners in the Netherlands, Van Hout and colleagues found general practitioners opted to use the MMSE in only 18 out of 93 cases and use of the MMSE was not associated with better diagnostic accuracy [106].

The MMSE has gained tremendous popularity as a relatively quick "bedside" cognitive test, but its diagnostic accuracy has been hitherto unclear. The best evidence available to date suggests it is not the ideal tool for case finding especially for early dementia and MCI. It does have a role as a first step screener for dementia, MCI, or delirium, provided its other limitations are not problematic (Table 2.4). A number of groups have evaluated possible improvements to the MMSE by using a structured format, by repeated application, by refining the discriminating items or by adding additional tests [52, 100, 107, 108]. While neither the accuracy nor the brevity of the MMSE is entirely optimal, it has helped encourage the development of numerous other alternative brief cognitive tests, some of which are discussed elsewhere in this volume.

Table 2.4 Summary table of diagnostic accuracy of the MMSE for cognitive impairment

	Basic diagnostic accuracy statistics				Advanced diagnostic accuracy statistics						Clinical utility statistics			
Purpose of test (prevalence)	Sensitivity	Specificity	PPV	NPV	Youden J	Diagnostic odds ratio	Error diagnostic ratio	Overall correct	LR+	LR−	CUI+ score	CUI+ qualitative	CUI− score	CUI− qualitative
Diagnosis of dementia in primary care at 10 %	0.814	0.872	0.414	0.977	0.686	29.814	39.209	86.62	6.359	0.210	0.337	Poor	0.852	Excellent
Diagnosis of dementia in primary care at 25 %	0.814	0.872	0.679	0.934	0.686	29.814	39.209	85.750	6.359	0.213	0.553	Average	0.814	Excellent
Diagnosis of dementia in specialist settings at 25 %	0.769	0.899	0.717	0.921	0.668	29.631	36.663	86.650	7.614	0.257	0.552	Average	0.828	Excellent
Diagnosis of dementia in specialist settings at 55 %	0.769	0.899	0.903	0.761	0.668	29.631	36.663	86.620	7.614	0. 257	0.694	Good	0.684	Good
Diagnosis of dementia in patients with MCI at 25 %	0.872	0.597	0.419	0.933	0.469	10.092	28.316	66.575	2.164	0.214	0.365	Poor	0.557	Average

(continued)

Table 2.4 (continued)

	Basic diagnostic accuracy statistics				Advanced diagnostic accuracy statistics						Clinical utility statistics			
Purpose of test (prevalence)	Sensitivity	Specificity	PPV	NPV	Youden J	Diagnostic odds ratio	Error diagnostic ratio	Overall correct	LR+	LR−	CUI+ score	CUI+ qualitative	CUI− score	CUI− qualitative
Diagnosis of MCI in specialist settings at 25 %	0.669	0.776	0.499	0.876	0.445	7.002	11.628	74.925	2.987	0.427	0.334	Poor	0.679	Good
Diagnosis of delirium in specialist settings at 25 %	0.835	0.765	0.542	0.933	0.600	16.474	28.150	78.250	3.553	0.216	0.453	Poor	0.714	Good

Updated from [21]

PPV positive predictive value, *NPV* negative predictive value, *LR+* (likelihood ratio+) = sensitivity/(1 − specificity), *LR−* (likelihood ratio−) = (1 − sensitivity)/specificity, CUI+ (clinical utility index+) = sensitivity × PPV, clinical utility index − (clinical utility index−) = specificity × NPV

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Chapter 3
MMSE Variants and Subscores

R. Rhys Davies and Andrew J. Larner

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Abstract The Mini-Mental State Examination (MMSE) is long established as an instrument for the screening of cognitive complaints. Its utility has prompted the development of a number of variants and subscores. Of the MMSE variants, many are shorter than the original MMSE to facilitate use in time-limited situations but hopefully without loss of clinical utility. In contrast, the modified MMSE or 3MS is longer, assessing a broader range of cognitive functions. MMSE adaptations for those with hearing or visual impairment, for telephone use, and to identify cognitive problems in Parkinson's disease have been described. MMSE subscores which may help to identify vascular dementia and dementia with Lewy bodies have also been

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described. These MMSE variants and subscores provide additional tools for the assessment of cognitive complaints, sometimes related to specific clinical situations. There are fewer data regarding their use than for the MMSE.

Keywords Mini-Mental State Examination • Variant • Subscore • Hearing impaired Visually impaired • Telephone

3.1 Introduction

It is now more than 35 years since the Mini-Mental State Examination (MMSE) was first published [1]. Over this time period, the MMSE has become the most widely used cognitive screening instrument, with many studies published examining its utility in identifying individuals with cognitive impairment and thousands of citations [2, 3] (see Chap. 2). It has also been translated into a variety of different languages (e.g., [4]), but these will not be discussed in this chapter nor other reported cultural modifications [5].

Despite its ubiquity, shortcomings in the diagnostic ability of the MMSE have been noted (e.g., [6, 7]). It has limited ability to generate a cognitive profile [8] with only perfunctory testing of memory (cases of amnesia can be missed: [9]) and visuoperceptual function, and executive function testing is largely eschewed. The MMSE is very much oriented to language in the verbal domain, but some of the language tests are of low sensitivity and correlate poorly with neuropsychological test scores [8]. Ideally, MMSE scores should be corrected for age and level of education [10] although this is seldom done in clinical practice.

Theoretically motivated revisions of the MMSE which try to address the neuropsychological omissions and improve screening performance include the Addenbrooke's Cognitive Examination and its revision, ACE and ACE-R [11, 12] (see Chap. 4). In addition, other MMSE variants have been reported which aim to improve test performance, as well as subscores derived from elements of the MMSE which aim to help in the identification of specific pathological causes of cognitive decline. Such diagnostic subscores have also been described using the ACE and ACE-R (see Chap. 4).

3.2 MMSE Variants

3.2.1 Standardized Mini-Mental State Examination (sMMSE)

Newly developed cognitive screening instruments now generally come with a scoring manual which operationalizes the test, but this was not normative when the MMSE was first described. There was therefore scope for inter- and intra-rater

variance when performing the MMSE. Molloy and colleagues sought to redress this problem by providing specific instructions as to how the MMSE should be administered and scored, in the hope that such strict guidelines would improve reliability. Using this standardized MMSE (sMMSE), they found reduced inter- and intra-rater variance and improved intra-class correlation as compared to the original MMSE, changes characterized as resulting from reduced measurement noise. Of note, use of the standardized MMSE was found to take less time that the traditional MMSE [13, 14].

Baseline sMMSE scores have been reported to correlate with function in activities of daily living: scores between 30/30 and 26/30 are deemed in the normal range, while scores between 25/30 and 20/30 are found in patients with mild cognitive impairment, between 20/30 and 10/30 in moderate cognitive impairment, and 9/30 or less in severe cognitive impairment [15]. Baseline sMMSE scores have also been reported to predict progression in Alzheimer's disease [16]. It has also been suggested that analysis of the pattern of deficits in sMMSE can help to differentiate between AD, vascular dementia, and dementia with Lewy bodies [15].

3.2.2 Modified Mini-Mental State Examination (3MS)

The Modified Mini-Mental State Examination (3MS) was designed to sample a broader range of cognitive functions than the MMSE [17]. By adding test items, making some changes in item content, and using graded scoring, a final score which ranged from 0 to 100 was generated, so extending ceiling and floor effects. Despite these changes, 3MS was said to retain the brevity of the original MMSE [17].

Later studies have confirmed the high correlation of MMSE and 3MS scores, as well as test-retest reliability [18]. In the Cardiovascular Health Study, an observational prospective cohort study of risk factors for coronary heart disease and stroke in individuals ≥65 years of age, a cross-sectional assessment found that users of certain anti-hypertensive medications (calcium channel blockers and loop diuretics but not beta-blockers) had more severe white matter hyperintensity seen on MR imaging and worse performance on 3MS [19]. In the Women's Health Initiative Memory Study (WHIMS), 3MS was administered to over 7,000 women aged 65–80 years who had volunteered for the study. Mean 3MS scores decreased with age and increased with education, associations which varied among ethnic groups [20].

3MS has been used in community screening for dementia [21, 22], most notably in the Canadian Study of Health and Aging (e.g., [23, 24]). McDowell et al. [21] found that in comparison to the MMSE, the 3MS had better alpha internal consistency and greater diagnostic accuracy in identifying dementia as measured by the area under the ROC curve, superiority attributed to the extended scoring system rather than to its additional questions per se. Bland and Newman [22] found 3MS to be highly sensitive (0.88) and specific (0.90) at a cutoff score of 77/78 for the identification of mild dementia and cognitive impairment.

A revised version of the modified MMSE, 3MS-R, has been described [25]. It should be noted that not all reports of a "modified mini-mental state examination" relate to 3MS (e.g., [26]).

3.2.3 Short Forms of the MMSE

One complaint sometimes levelled at the MMSE is that it takes too long to administer [27], perhaps particularly in primary care and general medical and neurological settings where time available for cognitive assessment may be limited (i.e. less than 5–10 min). Hence, there has been comment upon and interest in developing abbreviated forms of the MMSE which can be applied in a briefer time, yet hopefully retain much of the sensitivity and specificity of the original [28].

One option to shorten administration times is to predict total MMSE performance based on performance on selected items only. Magaziner et al. [29] found that seven items of the MMSE could predict total scores. More recently, Matthews et al. [30], examining a cohort in which cognitive impairment was rare, found that an 11-item abbreviated version of the MMSE could be used to derive full-scale MMSE scores fairly accurately by assuming high functioning on excluded items.

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 7 s, and orientation to time) while other items (registration, naming, repetition, three-step verbal command, written command, writing a sentence) are only weak predictors [31]. Based on their observations of the predictive power of individual MMSE components for the diagnosis of AD, Galasko et al. [31] developed a two-item score (recall memory and orientation to place, score range 0–8) which, in a restricted sample of well-educated patients and controls, showed comparable sensitivity and only slightly decreased specificity to the complete MMSE. Three-word recall and spatial orientation from the MMSE were incorporated into a decision tree, along with a simplified clock drawing test, called the cognitive disorders examination or Codex which had high sensitivity and specificity for dementia (0.92 and 0.85, respectively) in a validation study, a better sensitivity than the MMSE [32].

Other attempts to produce short MMSE derivatives include the study of Onishi et al. [33] who reported that the summed scores of time orientation and serial sevens were found to have high sensitivity (0.98) but lesser specificity (0.69) for cognitive impairment in older adults using a cutoff of 7/7+. Paveza et al. [34] developed a "brief MMSE" using four items (orientation to time, orientation to place, memorizing and repeating three nonrelated items, spelling "world" backward) with a score range of 0–18, with high sensitivity (0.98) with a cutoff of 14. The potential value of this brief MMSE in medically ill older people has been reported [35].

The six-item screener (SIS), described by Callahan et al. [36], comprises the three-item recall and three of the temporal orientation items (day of week, month, year) from the MMSE, with the score being the number of errors (range 0–6). In a

community-based sample of elderly African-Americans, using a cutoff of three or more errors gave sensitivity and specificity for a diagnosis of dementia of 0.89 and 0.88, respectively. Performance on the SIS was found to be comparable to the MMSE (sensitivity 0.95, specificity 0.87 at cutoff 23/30). A study from a memory clinic in China [37] found the SIS to have similar sensitivity (0.89) but lower specificity (0.78) for the detection of mild AD compared to the study of Callahan et al. [36], but limited ability to detect mild cognitive impairment. SIS has been used to identify cognitive impairment in older persons in the emergency department, wherein its sensitivity (0.63) proved somewhat lower than in the index study [38], although it does appear to be superior to the caregiver- or patient-administered AD8 [39, 40] to identify cognitive dysfunction in this setting [41].

Similar to the SIS, summation of MMSE subscores for orientation to time and three-word recall has been suggested as a marker of episodic memory function and was strongly associated with diagnosis of dementia and AD [42], more so than scores on the Free and Cued Selective Reminding Test, another test of episodic memory [43]. By adding three-object recall and orientation to time to the MMSE score, Commenges et al. [44] reported increased specificity of the MMSE without loss of sensitivity. Three-word recall and time orientation form part of the Memory Orientation Screening Test (MOST™), along with list memory and clock drawing, which is reported to be more sensitive and accurate than MMSE for identifying early dementia [45].

Schultz-Larsen et al. [46] used Rasch analysis of MMSE items to produce an abbreviated version of the MMSE ("D8-MMSE") consisting of nine items and using a simpler (polytomous) scoring of three-item recall. Items in D8-MMSE included those known to be important discriminators of dementia, such as orientation to place, recall memory, and copying. This version proved to have almost identical performance values as the original MMSE, with slightly lower sensitivity and specificity but equal area under the receiver operating characteristic curve. Total scores were not affected by age, sex, or educational level. This modified design of the MMSE post hoc has excluded this instrument from a meta-analysis of multi-domain cognitive screening tests [47].

Haubois et al. [48] hypothesized that the six memory items of the MMSE could be used to build a short form of the MMSE, calculated using the formula [free recall of three words + cued recall of three words], with a score range of 0–6 (the exact cueing technique was not specified in their publication). In some ways, this approach seems similar to that of the Free and Cued Selective Reminding Test, or five-word test of Dubois et al. [43] which is said to test episodic memory (hippocampal amnesia) specifically. In a case control study examining patients diagnosed as demented or cognitively healthy (patients with mild cognitive impairment were excluded), Haubois et al. [47] found a short MMSE cutoff score of ≤4/6 had similar sensitivity to MMSE cutoff score ≤24/30 (0.90) and similar area under the ROC curve (0.93 vs. 0.95). A validation study of this short form of the MMSE has reported excellent sensitivity (ca. 80 %) and specificity (ca. 90 %) [49].

Shortened forms of translated versions of the MMSE have also been reported (e.g., the Korean MMSE; [50]).

3.2.4 Severe MMSE

The severe MMSE was designed to assess cognitive domains which remain relatively preserved in moderate to severe AD [51]. The ten items examine orientation to person (name, birthdate), language (follow verbal command, repeat three words, name three objects, spell a word, write own name, category fluency for animals), and construction (copy square, draw circle) generating a score of 0–30. Dedicated memory tests are absent. It has been pointed out that there is little similarity between MMSE and severe MMSE other than the score range [52].

Severe MMSE and MMSE performance in 182 patients with possible or probable AD was found to correlate significantly only when MMSE score fell below 9/30. As MMSE performance approached floor levels, severe MMSE scores were still at half maximal levels. Severe MMSE performance also correlated with functional staging of AD using the Clinical Dementia Rating Scale and the Global Deterioration Scale [51].

3.2.5 MMSE for the Hearing Impaired

As MMSE is presented verbally, performance problems may be anticipated in those with hearing impairment; indeed, poor hearing was one of the most common causes of poor performance on the MMSE in elderly patients without dementia [53].

A study of AD patients found lower MMSE scores in those who were hearing impaired compared to unimpaired. Using a written version of the MMSE, scores were lower than the standard MMSE scores in the hearing impaired, while in the hearing unimpaired patients, written MMSE scores were slightly higher than standard MMSE scores. Although these differences, which were contrary to expectations, did not reach statistical significance, they nonetheless suggested that poor cognitive performance in the hearing impaired was not an artefact of the cognitive testing procedure [54]. Using a written MMSE, De Silva et al. [55] found no significant difference between written and standard MMSE scores in a hearing-impaired group (although they expressed a preference for the former), but normal hearing individuals performed slightly better on the standard MMSE (contrary to findings of Uhlmann et al. [54]). Time to perform the two versions was similar. Hence, although hearing-impaired individuals are impaired on standard MMSE performance, using a written version of the MMSE makes no difference. Nevertheless, written MMSE may be the only option for those with profound hearing loss if they require cognitive testing [55].

3.2.6 MMSE-Blind or "MMblind"

Primary sensory deficits, particularly visual, may be one of the factors which contributes to impaired performance on cognitive screening (see Chap. 1).

A number of MMSE items explicitly require vision for their performance: naming two visually presented objects, following a written command, writing a sentence, and copying intersecting pentagons. Vision is also required for the praxis of the three-stage command. Removing these tasks from the MMSE to give a denominator of 22 (rather than 30) has been described as the "MMSE-blind" [56] or "MMblind" [57]. Age- and education-specific norms have been validated for this instrument [56]. A study of older individuals (85+ years) found no difference in MMblind scores between those registered sight impaired or severely sight impaired and those not registered, whereas standardized MMSE scores (see Sect. 3.2.1) did differ between these groups, with the former group scoring lower not only on the recognized visual items but also on orientation and repetition of a phrase [57].

Adaptation of the standardized MMSE for use in blind people has been described (omitting the naming of objects, reading a command, writing a sentence, and copying a diagram) to give a denominator of 25 [15].

3.2.7 Telephone Adaptations of the MMSE

Administration of cognitive screening instruments by telephone may be a useful method for detecting individuals with cognitive impairment, particularly for community studies or where distances might preclude attendance at an outpatient facility. However, telephone administration of a cognitive screening instrument poses similar challenges to administration to visually impaired individuals. A number of telephone versions of the MMSE have been reported. A telephone adaptation of the modified MMSE (3MS; see Sect. 3.2.2) has been described [58]. The Six-Item Screener (see Sect. 3.2.3) can be administered by telephone [36].

Roccaforte et al. [59] tested the validity of a telephone-administered MMSE compared with face-to-face administration to geriatric outpatients and found excellent correlation of test scores for both cognitively impaired and intact individuals. Hearing impairment was associated with lower test scores. Similar correlations across the spectrum of cognitive impairment were found with an Italian telephone version of the MMSE, Itel-MMSE (*sic*), although this was weakest in severely demented patients [60]. Newkirk et al. [61] undertook a study using a 26-point telephone MMSE adapted from the Roccaforte study and face-to-face administration of the original MMSE in AD patients. Total scores were highly correlated, but neither hearing impairment nor education level significantly affected scores. Similar findings were reported in demented patients with a Spanish telephone MMSE [62]. In healthy elderly individuals, Itel-MMSE proved to be a useful screening instrument to identify poor cognitive performance [63].

MMSE may also be reliably administered via a telehealth link. A study found no differences between MMSE scores given by face-to-face and distant assessors when the test was administered by an interactive videoconferencing link [64].

3.2.8 Mini-Mental Parkinson (MMP)

The Mini-Mental Parkinson (MMP) was specifically devised as a derivative of the MMSE which would detect cognitive impairment in patients with Parkinson's disease (PD). Orientation and attention items from the MMSE were retained, but in order to examine the visual and executive cognitive functions which are recognized to be impaired in PD (e.g., [65]), the other MMSE items were substituted with tests of visual registration and recall, two set fluency, shifting, and concept processing, producing a test with a denominator score of 32 [66]. MMP scores show a weak negative correlation with patient age [66, 67] but no correlation with PD duration or modified Hoehn and Yahr score [68].

A few studies of the MMP have been published, indicating its utility in detecting cognitive impairment in PD patients compared to PD patients with dementia or cognitive impairment short of dementia [69, 70], or in comparison with normal controls [71]. It may also be used to track cognitive change over time in PD patients [72].

As the changes in MMP address many of the theoretical neuropsychological shortcomings of the MMSE, in a manner not dissimilar to the changes in the Addenbrooke's Cognitive Examination and its revision (ACE and ACE-R; see Chap. 4), the utility of MMP has also been examined as cognitive screening instrument in unselected consecutive patients referred to a memory clinic. MMP was found to be equivalent to MMSE in this setting [67].

3.3 MMSE Subscores

Subscores derived from elements of the MMSE have been suggested to help in the differential diagnosis of AD from multi-infarct dementia [73] and from dementia with Lewy bodies [74]. Examples of MMSE subscores reported to facilitate diagnosis of cognitive impairment or dementia have been mentioned previously in the discussion of short forms of the MMSE (see Sect. 3.2.3).

3.3.1 Vascular Dementia

Magni et al. [73] compared MMSE performance in patients with AD ($n=70$) and multi-infarct dementia (MID; $n=31$) using component factor analysis and found that a derived measure of episodic memory differed statistically between the two groups, being worse in the AD patients. Whether such a measure could be easily derived and used in day-to-day clinical practice remains open to question. Compared to AD patients, vascular dementia patients scored lower on MMSE items testing motor/constructional and working memory functions, whereas AD patients scored lower on temporal orientation and declarative memory tests [65]. While these

findings may be pointers to guide more detailed examination of cognitive function, they are insufficient of themselves to permit reliable discrimination between AD and vascular dementia. Moreover, considering the frequent overlap between vascular and neurodegenerative pathologies in neuropathological studies of elderly demented individuals, attempts at such categorisation may not be appropriate.

3.3.2 Dementia with Lewy Bodies: Ala Score

Dementia with Lewy bodies (DLB) is recognized to be associated with more marked impairment of attentional and visuospatial functions than AD but with relative preservation of orientation and memory function (e.g., [75–77]). Mindful of these distinctions, a weighted subscore derived from elements of the MMSE was reported by Ala et al. [74] to be helpful in the differential diagnosis of AD from DLB, given by the formula:

$$\text{Attention} - 5/3.(\text{Memory}) + 5.(\text{Construction})$$

The subscore therefore ranged from −5 to +10. In a series of patients with pathologically confirmed AD ($n=27$) or DLB ($n=17$), a subscore of <5 was associated with the diagnosis of DLB with sensitivity of 0.82 and specificity of 0.81 in patients with an MMSE ≥ 13/30 [74].

A subsequent study of selected patients with diagnoses of probable AD and probable DLB also found that the MMSE subscore defined by Ala et al. was helpful in discriminating the two conditions [78].

Encouraging as these results were, they do not particularly reflect clinical practice, where preselection by patient diagnosis is not possible. An attempt to evaluate the diagnostic utility of the Ala score in a prospective cohort of unselected consecutive patients ($n=271$) seen in a cognitive clinic found very few patients with a clinical diagnosis of DLB, and so no meaningful statement could be made as to the sensitivity of the Ala subscore, but the specificity (0.51) did not encourage the view that prospective use of this subscore would be useful for clinical diagnosis of DLB [79, 80].

3.4 Conclusion

The MMSE variants described in this chapter have not been as widely adopted as the original MMSE, with the possible exception of the 3MS. A number of reasons may account for this, including unfamiliarity with these variants amongst clinicians and possible lack of clinical utility. It is fair to say that many of the described variants have not been subjected to the extent of investigation which the original MMSE has attracted. Likewise, MMSE subscores have found only limited application.

Shortened versions of the MMSE with good test metrics may be particularly attractive as cognitive screening instruments because of their brevity and ease of applicability, not only in clinic-based situations but also possibly at a population level. Likewise, telephone versions might facilitate more widespread population screening. The impact of the enforcement of copyright restrictions on the use of the MMSE [81] on the use of MMSE variants and subscores is yet to be determined.

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Chapter 4
Addenbrooke's Cognitive Examination (ACE) and Its Revision (ACE-R)

R. Rhys Davies and Andrew J. Larner

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Abstract The Addenbrooke's Cognitive Examination (ACE) and its revised version (ACE-R) are theoretically motivated revisions of the Mini-Mental State Examination (MMSE) which attempt to address the neuropsychological omissions and improve the screening performance of the latter. Though taking longer to administer than the MMSE, and therefore best suited to specialist settings, both ACE and ACE-R have proved to be acceptable to patients and have shown excellent performance in identifying cognitive impairment in a variety of clinical situations (Alzheimer's disease, frontotemporal lobar degenerations, parkinsonian syndromes, stroke and vascular

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dementia, brain injury). Subscores of the ACE/ACE-R may be useful for the differentiation of Alzheimer's disease from frontotemporal lobar degeneration (the VLOM ratio) and of Alzheimer's disease from semantic dementia (the SI index). ACE/ACE-R utility has prompted translation into various languages.

Keywords Addenbrooke's Cognitive Examination • Cognitive screening • Subscore Alzheimer's disease • Frontotemporal lobar degenerations

4.1 Introduction

Although the Mini-Mental State Examination (MMSE; [1]) is perhaps the best known and globally the most widely used Cognitive Screening Instrument (CSI), it is recognized not to be without shortcomings (see Chap. 2). It has also sometimes been applied or recommended in situations for which it was not designed or is inadequate, such as measuring meaningful change following treatment of Alzheimer's disease patients with cholinesterase inhibitors [2].

From the neuropsychological viewpoint, the MMSE is recognized to be deficient in its coverage of certain cognitive domains, specifically memory, visuoperceptual function and executive function, despite such coverage being one of the recommendations for the optimal CSI as enunciated by the Research Committee of the American Neuropsychiatric Association [3] (see Sect. 1.3). Developments of the MMSE to try to address these shortcomings have been made, for example, the Modified Mini-Mental State Examination or 3MS [4] (see Sect. 3.2.2).

Another theoretically motivated revision of the MMSE which attempts to address the neuropsychological omissions and improve screening performance is the Addenbrooke's Cognitive Examination (ACE) [5] and its revision, the Addenbrooke's Cognitive Examination-Revised (ACE-R) [6]. These CSIs have gained wide acceptance and use over the past decade. Not only does ACE/ACE-R appear to be useful in detecting cognitive impairment [7] in Alzheimer's disease (AD) and other causes of cognitive decline but also subscores derived from elements of the ACE have been suggested to help in the differential diagnosis of AD from frontotemporal lobar degenerations (FTLD) in general [5, 6] and specifically from the semantic dementia variant [8], as well as from dementia with Lewy bodies [9].

4.2 Development and Index Studies

4.2.1 Addenbrooke's Cognitive Examination (ACE)

ACE encompasses tests of attention/orientation, memory, language, visual perceptual and visuospatial skills, and executive function, with a total score out of 100 [5]

(Box 4.1). Reliability of the ACE was evident from its high internal consistency (Cronbach's alpha coefficient = 0.78). ACE encompasses the MMSE, so this score may also be generated. There is also a clock drawing test (see Chap. 5), the scoring of which is comparable to other standardized scoring methods [10]. The design of the ACE aimed to allow sensitivity to the early stages of Alzheimer's disease (AD) and frontotemporal dementia (FTD).

Box 4.1: Item Content of ACE

Orientation	10
Registration	3
Attention/concentration (serial 7s, DLROW)	5
Recall	3
Memory:	
Anterograde	28
Retrograde	4
Verbal fluency:	
Letters	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*

In the index study [5], ACE was acceptable to patients and relatively quick to administer (ca. 15 min). A patient group ($n = 139$, of 210 screened, excluding patients with dual pathology, depression, and nondegenerative, nonvascular pathology) was examined, of whom most had dementia (115; non-dementia = 24), along with a control group ($n = 127$; education-matched individuals attending orthopedic or gynecology clinics and their spouses and members of the Medical Research Council subject panel). At cutoff scores of 88/100 and 83/100, ACE was reported to have good sensitivity and specificity for identifying dementia (0.93 and 0.71; 0.82 and 0.96, respectively), figures which compared favorably to the MMSE at a cutoff of 24/30 (0.52 and 0.96, respectively). Subsequent studies of patients with mild cognitive impairment (MCI) suggested that an ACE cutoff of 80/100 distinguished very well between convertors and non-convertors [11].

Mathuranath et al. [5] observed that patients with AD and with frontotemporal dementia (FTD) showed significant differences on performance of different components of the ACE: orientation, attention, and memory were worse in AD, while

letter fluency, language, and naming were worse in FTD. This scoring pattern was translated into an index useful for the differentiation of AD and FTD, $(V+L)/(O+M)$ or the VLOM ratio, given by the formula:

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

For the ACE, the maximum scores for each of these components give a ratio of 42/17. A VLOM ratio >3.2 showed sensitivity of 0.75 and specificity of 0.84 for the diagnosis of AD compared to non-AD. A VLOM ratio <2.2 showed sensitivity of 0.58 and specificity of 0.97 for the diagnosis of FTD versus non-FTD [5].

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

ACE-R is a development of the earlier ACE which also incorporates the MMSE. Like the ACE, the overall ACE-R score is 100, from which domain scores for attention and orientation, memory, fluency, language, and visuospatial abilities can be generated (Box 4.2). Reliability was very good (Cronbach's alpha coefficient = 0.8).

In the index study [6], ACE-R was acceptable to patients and relatively quick to administer (ca. 15 min). The cohort examined ($n = 241$; dementia 142, MCI 36, controls 63) was selected using exclusion criteria as for the ACE study (psychiatric disorder, mixed pathology, non-neurodegenerative disease process). At cutoff scores of 88/100 and 82/100, ACE-R was reported to have good sensitivity and specificity for identifying dementia (0.94 and 0.79; 0.84 and 1.00, respectively). MCI group performance fell between that of controls and AD patients.

Box 4.2: Domain Scores of ACE-R

Attention and orientation	18
Memory	26
Fluency	14
Language	26
Visuospatial	16
Total score	*100*

As with the ACE, a subscore was derived from the ACE-R, the VLOM ratio, which was reported to be helpful in differentiating AD from FTD. The same criteria were applied for calculating the VLOM ratio (although not explicitly stated, the maximum score for each of these components in the ACE-R gives a ratio of 40/17). ACE-R VLOM ratio >3.2 showed sensitivity of 0.74 and specificity of 0.85 for the diagnosis of AD compared to non-AD, while VLOM ratio <2.2 showed sensitivity of 0.58 and specificity of 0.95 for the diagnosis of FTD versus non-FTD [6]. The findings were therefore similar to those with the VLOM ratio derived from the ACE.

Table 4.1 Translations of the Addenbrooke's Cognitive Examination and its revision

Language	References
French	Bier et al. [12, 13]
Malayalam (southern India)	Mathuranath et al. [14, 15]
Spanish	Garcia-Caballero et al. [16]; Roca et al. [17]; Torralva et al. [18]
German	Alexopoulos et al. [19, 20]
Danish	Stokholm et al. [21]
Greek	Konstantinopoulou et al. [22]
Japanese	Yoshida et al. [23, 24]
Korean	Kwak et al. [25]
Persian	Pouretemad et al. [26]
Hebrew	Newman [27]
Portuguese (Brazilian)	Carvalho et al. [28]; Amaral-Carvalho and Caramelli [29]
Dutch	Robben et al. [30]
Arabic	Al Salman et al. [31]

4.3 ACE Translations

The excellent performance of the ACE has prompted its translation into a number of languages [12–31] (Table 4.1). These translations have facilitated the examination of ACE performance in a large number of independent patient cohorts.

4.4 Diagnostic Utility

4.4.1 Dementia and Mild Cognitive Impairment

Prospective studies on the ACE and ACE-R in independent patient cohorts have been reported. Examining cohorts with cognitive complaints of unknown etiology, rather than groups preselected by diagnosis with or without a control group, is more reflective of the idiom of clinical practice and may also minimize verification bias.

In a study conducted over 42 months in consecutive new patient referrals to a cognitive function clinic ($n=285$; dementia prevalence = 49 %), ACE proved easy to use with very few patients failing to complete the test [32–34]. ACE scores and MMSE scores were highly correlated ($r=0.92$). Using the ACE cutoffs specified in the index paper (88/100 and 83/100) [5], test sensitivity for dementia was high (1.00 and 0.96 at 88/100 and 83/100, respectively) but specificity less good (0.43 and 0.63, respectively). These specificities were considerably poorer than those documented in the index study (see Sect. 4.2.1). Analysis of the first 2 years of data [32] indicated that ACE was more sensitive but less specific than MMSE for dementia

Table 4.2 Summary of results (with 95 % confidence intervals) at various ACE cutoff scores ($n=285$)

ACE cutoff	<88/100	<83/100	<75/100
Test accuracy:	0.71 (0.66–0.76)	0.79 (0.75–0.84)	0.84 (0.80–0.88)
Sensitivity:	1.00	0.96 (0.93–0.99)	0.85 (0.79–0.91)
False-positive rate:	0.57 (0.48–0.65)	0.37 (0.29–0.45)	0.17 (0.11–0.23)
Specificity:	0.43 (0.35–0.42)	0.63 (0.55–0.71)	0.83 (0.77–0.89)
Youden index (*Y*):	0.43	0.59	0.68
False-negative rate:	0	0.04 (0.01–0.07)	0.15 (0.09–0.21)
Positive predictive value (PPV):	0.63 (0.57–0.69)	0.71 (0.65–0.78)	0.83 (0.77–0.89)
False alarm rate:	0.37 (0.31–0.43)	0.29 (0.22–0.35)	0.17 (0.11–0.23)
Negative predictive value:	1	0.95 (0.90–0.99)	0.85 (0.79–0.91)
Predictive summary index (PSI):	0.63	0.66	0.68
False reassurance rate:	0	0.05 (0.01–0.09)	0.15 (0.09–0.21)
Diagnostic odds ratio (DOR):	∞	45.5	28.6
Positive likelihood ratio (LR+):	1.77 (1.53–2.04)	2.59 (2.10–3.21)	5.14 (3.54–7.45)
Negative likelihood ratio (LR−):	0	0.06 (0.05–0.07)	0.18 (0.12–0.26)
Positive utility index (UI+):	0.63 Adequate	0.68 Good	0.71 Good
Negative utility index (UI−):	0.43 Poor	0.60 Adequate	0.71 Good

Adapted from [33]

diagnosis. Using a lower ACE cutoff of 75/100 [35], 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, ACE sensitivity and specificity were both greater than 80 % as was positive predictive value (PPV; Table 4.2). Area under the receiver operating characteristic (ROC) curve, a measure of diagnostic accuracy, was 0.93 (95 % confidence intervals 0.90–0.96). Other studies have also found lower ACE cutoffs to be necessary to maximize diagnostic utility, for example, in a rural Spanish patient cohort with low educational level [16].

In a study of the ACE-R conducted over 36 months ($n=243$; dementia prevalence = 35 %), ACE-R proved easy to administer, with very few patients failing to complete the test [34, 36, 37]. ACE-R scores and MMSE scores were highly correlated ($r=0.90$). Initial results using the ACE-R cutoffs specified in the index paper (88/100 and 82/100) [6] showed excellent sensitivity for dementia (1.00 and 0.96 at 88/100 and 82/100, respectively) but poor specificity (0.48 and 0.72, respectively), much poorer than those documented in the index study (see Sect. 4.2.2). Using a lower ACE-R cutoff of 75/100, as previously used with ACE [33, 35], sensitivity and specificity were both greater than 90 %, and PPV approached this value (Table 4.3). Subsequently, sensitivity and specificity of ACE-R were examined at all cutoff values and an optimal cutoff defined by maximal test accuracy for the differential diagnosis of dementia/not dementia (= 73/100). At this cutoff, results were similar to those in the initial analysis with cutoff 75/100 and better than those for the MMSE at its similarly defined optimal cutoff (24/100; Table 4.4). Area under the ACE-R ROC curve was 0.94 (95 % confidence intervals 0.91–0.97).

Table 4.3 Summary of results (with 95 % confidence intervals) at various ACE-R cutoff scores ($n = 100$)

ACE-R cutoff	<88/100	<82/100	<75/100
Test accuracy:	0.72 (0.63–0.81)	0.83 (0.76–0.90)	0.91 (0.85–0.97)
Sensitivity:	1	0.96 (0.90–1.0)	0.91 (0.83–0.99)
False-positive rate:	0.52 (0.39–0.65)	0.28 (0.16–0.40)	0.09 (0.02–0.17)
Specificity:	0.48 (0.35–0.61)	0.72 (0.60–0.84)	0.91 (0.83–0.98)
Youden index (*Y*):	0.48	0.68	0.82
False-negative rate:	0	0.04 (−0.02 to 0.1)	0.09 (0.01–0.17)
Positive predictive value (PPV):	0.62 (0.51–0.73)	0.75 (0.63–0.86)	0.89 (0.81–0.98)
False alarm rate:	0.38 (0.27–0.48)	0.25 (0.14–0.37)	0.11 (0.02–0.19)
Negative predictive value:	1	0.95 (0.89–1.02)	0.92 (0.85–0.99)
Predictive summary index (PSI):	0.62	0.70	0.81
False reassurance rate:	0	0.05 (−0.02 to 0.1)	0.08 (0.01–0.15)
Diagnostic odds ratio (DOR):	□	57.2	102.9
Positive likelihood ratio (LR+):	1.93 (1.49–2.49)	3.44 (2.23–5.32)	9.86 (4.26–22.8)
Negative likelihood ratio (LR−):	0	0.06 (0.04–0.09)	0.09 (0.04–0.22)
Positive utility index (UI+):	0.62 Adequate	0.72 Good	0.81 Excellent
Negative utility index (UI−):	0.48 Poor	0.68 Good	0.84 Excellent

Adapted from [36]

Table 4.4 Summary of results (with 95 % confidence intervals) of ACE-R and MMSE assessments ($n = 243$)

Cutoff	ACE-R ≥ 73/100	MMSE ≥ 24/30
Test accuracy:	0.89 (0.85–0.93)	0.82 (0.77–0.87)
Sensitivity:	0.87 (0.80–0.94)	0.70 (0.60–0.80)
Specificity:	0.91 (0.86–0.95)	0.89 (0.84–0.94)
Youden index (*Y*):	0.78	0.69
Positive predictive value:	0.83 (0.75–0.91)	0.77 (0.67–0.86)
Negative predictive value:	0.93 (0.89–0.97)	0.85 (0.79–0.90)
Predictive summary index:	0.76	0.62
Diagnostic odds ratio:	63.7 (39.1–103.9)	18.4 (11.6–29.0)
Area under ROC curve:	0.94 (0.91–0.97)	0.91 (0.88–0.95)
Positive likelihood ratio:	9.21 (5.65–15.0) Moderate	6.17 (3.91–9.73) Moderate
Negative likelihood ratio:	0.14 (0.09–0.24) Moderate	0.34 (0.21–0.53) Small
Positive utility index (UI+):	0.72 Good	0.54 Adequate
Negative utility index (UI−):	0.85 Excellent	0.76 Good

Adapted from [37]

Other studies of the ACE-R have also found lower cutoffs to be necessary to maximize diagnostic utility. Examining patients preselected by diagnosis, Alexopoulos et al. [20] found the optimal cutoff score for detection of MCI using the German ACE-R to be 86/87, and different cutoffs were optimal for diagnosis of AD and FTD (see Sects. 4.4.2 and 4.4.3, respectively). The ACE-R was found to be no more accurate than the MMSE for identifying MCI. A prospective study of 122 patients referred to a cognitive clinic (dementia prevalence = 67 %) found sensitivity

and specificity for dementia diagnosis of 0.85 and 0.80 at ACE-R cutoff of 84/100. Misclassification was noted in individuals with high levels of education, focal executive dysfunction, significant vascular disease, medical comorbidities, and polypharmacy [38].

A systematic study of English language studies of ACE and ACE-R published up to April 2010 [7] identified nine suitable studies for review [5, 6, 8, 11, 33, 36, 39–41]. ACE and ACE-R were found to be capable of differentiating between those with and without cognitive impairment, but the evidence base on distinguishing dementia subtypes and MCI was lacking [7].

Longitudinal, as opposed to cross sectional, use of the ACE and ACE-R has been relatively little examined. In individuals adjudged by clinical assessment to have "questionable dementia" (some of whom presumably had MCI), ACE was helpful in predicting conversion to AD, based on baseline ACE score (80/100) and measures of episodic and semantic memory (category fluency and naming) [11]. ACE scores have also been reported to help predict conversion of amnestic MCI to dementia [42]: in a small group ($n=44$) of amnestic MCI patients followed up for an average of 4.33 years, significant differences were found in baseline ACE performance between convertors (mean ACE 86.6) and non-convertors (mean ACE 91.3)

A longitudinal study of 23 patients with cognitive complaints who were tested with the ACE on more than one occasion over periods of follow-up ranging from 7 to 36 months found that ACE scores declined in all those who were adjudged to have progressed clinically [35]. Monitoring of change in cognitive function using the ACE and ACE-R has also been documented following immunological treatment in non-paraneoplastic limbic encephalitis associated with antibodies to voltage-gated potassium channels [43] and in patients with intracranial dural arteriovenous malformations treated by endovascular ablation [44].

4.4.2 Alzheimer's Disease

The utility of the VLOM ratio for the diagnosis of AD reported by Mathuranath et al. [5] was largely confirmed in subsequent studies of the ACE in independent patient cohorts. For example, Bier et al. [12], using a French version of the ACE, found VLOM ratio >3.2 to have sensitivity and specificity of 0.72 and 0.69 for detection of AD. Similar findings were reported from a prospective study of ACE in consecutive cognitive clinic attenders [32, 33] (Table 4.5, left hand column).

Using a Spanish translation of the ACE, Garcia-Caballero et al. [16] found a VLOM ratio of >2.80 correctly classified 91 % of AD patients.

Examining patients preselected by diagnosis, Alexopoulos et al. [20] found the optimal cutoff score for detection of AD using the German ACE-R to be 82/83. The ACE-R was found to be no more accurate than the MMSE for identifying AD, but a ratio of the scores for the memory and verbal fluency subtests permitted discrimination between AD and FTLD.

Table 4.5 Summary of results (with 95 % confidence intervals) of ACE VLOM ratios for diagnosis of AD and FTD

VLOM ratio	>3.2 (For diagnosis of AD)	<2.2 (For diagnosis of FTD)
Test accuracy:	0.76 (0.71–0.81)	0.87 (0.83–0.91)
Sensitivity:	0.76 (0.69–0.84)	0.31 (0.09–0.54)
False-positive rate:	0.24 (0.17–0.30)	0.10 (0.06–0.13)
Specificity:	0.76 (0.69–0.84)	0.90 (0.87–0.94)
Youden index (*Y*):	0.52	0.21
False-negative rate:	0.24 (0.16–0.31)	0.69 (0.46–0.91)
Positive predictive value (PPV):	0.69 (0.60–0.77)	0.16 (0.03–0.29)
False alarm rate:	0.31 (0.23–0.40)	0.84 (0.71–0.97)
Negative predictive value:	0.83 (0.77–0.89)	0.96 (0.93–0.98)
Predictive summary index:	0.52	0.12
False reassurance rate:	0.17 (0.11–0.23)	0.04 (0.02–0.07)
Diagnostic odds ratio (DOR):	10.3	4.2
Positive likelihood ratio (LR+):	3.21 (2.40–4.28)	3.20 (1.42–7.21)
Negative likelihood ratio (LR−):	0.31 (0.23–0.42)	0.76 (0.34–1.72)
Positive utility index (UI+):	0.52 Adequate	0.05 Very poor
Negative utility index (UI−):	0.63 Adequate	0.86 Excellent

Adapted from [33]

Data from a national dementia research register in Scotland found that in patients with established AD, most of whom were receiving cognitive enhancing treatment, ACE-R and MMSE scores were highly correlated ($r = 0.92$), and non-MMSE components of ACE-R improved MMSE estimates of cognitive ability by only 16 %. The authors suggested that although ACE-R was more appropriate than MMSE as an estimate of general cognitive function, once MMSE was <24, there was little to be gained by completing the remainder of the ACE-R, since it adds little once AD diagnosis is established [45].

4.4.3 Frontotemporal Lobar Degenerations

The utility of the VLOM ratio for the diagnosis of FTLD reported by Mathuranath et al. [5] was not entirely confirmed in subsequent studies of the ACE in independent patient cohorts. Bier et al. [12] reported that VLOM ratio <2.2 showed good specificity for the diagnosis of FTLD (0.88) but a much lower sensitivity for this diagnosis (0.11), particularly the behavioral variant. These findings were confirmed in a study of consecutive cognitive clinic attenders [32, 33] (Table 4.5, right-hand column). Other instruments with high sensitivity for behavioral variant FTLD may therefore be required if this diagnosis is suspected, such as the Frontal Assessment Battery [46].

Using a Spanish translation of the ACE, Garcia-Caballero et al. [16] found a VLOM ratio of <2.80 correctly classified 77 % of FTD patients.

Examining patients preselected by diagnosis, Alexopoulos et al. [20] found the optimal cutoff score for detection of FTLD using the German ACE-R to be 83/84. Unlike the situation with MCI and AD, ACE-R was found to be more accurate than the MMSE for identifying FTLD (area under the ROC curve 0.97 vs. 0.92). A ratio of the scores for the ACE-R memory and verbal fluency subtests permitted discrimination between AD and FTLD.

It has been reported that linguistic variants of FTLD, either fluent (semantic dementia) or nonfluent (progressive nonfluent aphasia: PNFA), may be detected and tracked using ACE [47]. Mathew et al. [48] found that 82.6 % of a group of PNFA patients were impaired on ACE-R, similar to corticobasal syndrome patients (see Sect. 4.4.4) but with less dysfunction in the visuospatial domain.

A subscore of the ACE, the semantic index (SI), has been reported to differentiate AD from semantic dementia [8], according to the formula:

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

Hence, SI scores ranged from +14 to −15. SI cutoff score of zero was reported to differentiate AD cases (SI = 3.8 ± 3.6) from semantic dementia cases (SI = −6.7 ± 4.7). Individual case studies appear to confirm the utility of the SI [34].

4.4.4 Parkinsonian Syndromes

In a group of 44 patients with Parkinson's disease (PD), ACE was reported to be a valid tool for dementia evaluation [41]. ACE scores correlated with the Mattis Dementia Rating Scale ($r = 0.91$) and the MMSE ($r = 0.84$). Robben et al. [30] used the ACE-R as one component in a three-step diagnostic pathway for dementia in PD. Numbers were small, but in older (>65 years) subjects ($n = 19$, 10 with dementia), an ACE-R cutoff of 75/100 gave only two false-positive results, and in younger (≤65 years) subjects ($n = 22$, 5 with dementia), an ACE-R cutoff of 83/100 gave three false-positive results. ACE-R has also been reported to be of use in the detection of PD-MCI, with a reported sensitivity and specificity of 0.61 and 0.64 at a cutoff of 93/100, influenced largely by the fluency domain score. This cutoff was found to be of particular use in individuals with lower levels of education [49].

Bak et al. [39] reported on the utility of ACE in detecting cognitive impairment in atypical parkinsonian syndromes (i.e. progressive supranuclear palsy, corticobasal degeneration, multiple system atrophy). In a subsequent study of patients with corticobasal syndrome ($n = 21$), ACE-R was reported to have a sensitivity and specificity for cognitive impairment of 0.91 and 0.98 at a cutoff of 88/100 [48].

A subscore derived from the MMSE (see Sect. 3.3.2), which was reported to differentiate AD and dementia with Lewy bodies [50], may also be derived, in a modified form, from the ACE, according to the formula [9]:

$$\text{Attention} - 1/2.(\text{Memory}) + (\text{Construction})$$

Like the original Ala subscore, this modified subscore may range from −5 to +10. In a series of patients with pathologically confirmed AD ($n=27$) or DLB ($n=17$), a subscore of <5 was associated with the diagnosis of DLB with sensitivity of 0.82 and specificity 0.81 in patients with an MMSE ≥ 13/30 [50]. The modified Ala score was evaluated in a prospective study of clinically diagnosed patients seen in a cognitive clinic [9, 34, 51]. Because of the very small number of DLB cases seen, only specificity and false-positive rates (with 95 % CI) could be calculated. The results were similar to those found for the Ala score (see Sect. 3.3.2): specificity 0.47 (0.41–0.53) and false-positive rate 0.53 (0.47–0.59), with a diagnostic odds ratio of 0. These figures did not encourage the view that the modified Ala score might be useful prospectively for the clinical diagnosis of DLB.

4.4.5 Stroke and Vascular Dementia

There have been fewer published studies examining use of ACE/ACE-R in stroke and vascular dementia than in AD and FTLD.

The German version of the ACE was reported to identify patients with mild vascular dementia, the optimal cutoff (85/100) being the same as that for AD, with sensitivity and specificity of 0.93 and 1.00 [19].

Using the Korean version of the ACE-R, Kwak et al. [25] found that although domain scores could be useful in differentiating subcortical ischaemic vascular dementia (SIVD) from AD, test sensitivity and specificity were less accurate than when screening for dementia.

In a post-acute stroke unit, the language component of the ACE-R was found to have satisfactory sensitivity and specificity for the detection of stroke-related aphasia [52].

In a series of acute stroke patients, ACE-R was found to have inadequate diagnostic validity for the detection of overall cognitive impairment, but the ACE-R subscales did predict impairment in specific cognitive domains, namely, visuospatial, fluency, and attention and orientation [53].

4.4.6 Brain Injury

ACE-R has also been evaluated in the setting of brain injury rehabilitation [54]. In a cohort of patients with chronic brain injury with cognitive impairment sufficient to prevent them working or studying, ACE-R had a sensitivity for cognitive

impairment of 0.72 at a cutoff of 88/100, whereas the MMSE sensitivity was only 0.36 at a cutoff of 27/30. The study suggested that ACE-R is a sensitive test for detecting cognitive impairment in chronic brain injury patients.

4.4.7 Depression

ACE scores have been reported to discriminate cognitive decline due to depression from that due to dementia [40]. Examining patients preselected by diagnosis, either dementia (AD and FTLD), "pure affective disorder" (major depression or affective symptoms not meeting criteria for major depression), mixed affective disorder and organic dementia, and healthy controls, ACE scores were lower in all the groups compared to controls. Total ACE scores were significantly lower in the AD and FTLD groups than either of the "pure affective disorder" groups. It was concluded that a score of <88/100 was strongly predictive of underlying organic dementia in suspected dementia patients with affective symptoms. ACE profile was also discriminative, with low scores on memory and letter fluency tasks with normal category fluency being indicative of affective pathology.

Different findings were reported by Roca et al. using the Spanish ACE [17]. Examining patients selected by diagnosis, they found patients with AD and FTLD to score lower than those with major depression and that the scores of the depressed patients did not differ significantly from those of a control group. In an evaluation of the Danish ACE, marked overlap in test scores was noted for demented and depressed patients indicating the need for caution when interpreting scores for the purpose of this differential diagnosis [21].

4.5 ACE and ACE-R in Combination with Other Screening Instruments

The dementia syndrome is a multidimensional construct encompassing not only cognitive but also behavioral, functional and global change [55]. Therefore, combining a cognitive scale such as the ACE with other screening instruments which examine different domains might enhance diagnostic capability. Such combination studies have been reported with the ACE-R and an informant scale, the Informant Questionnaire on Cognitive Decline in the Elderly (IQCODE; [56]; see Chap. 8), and with a functional scale, the Instrumental Activities of Daily Living Scale (IADL; [57]).

In a study of consecutive referrals to two memory clinics, one in a regional neuroscience center and one in an old-age psychiatry unit, patients were administered the ACE-R ($n=114$) at the same time that an informant completed the IQCODE [58]. The correlation between IQCODE and ACE-R scores was highly significant ($r=-0.46$; $t=5.46$, df$=112$, $p<0.001$). Using the test of agreement (kappa statistic) which measures the percentage of agreement beyond chance [59], $\kappa=0.29$ (95 %

confidence interval [CI] = 0.11–0.46), where $\kappa = 1$ is perfect agreement between tests and $\kappa = 0$ is agreement purely due to chance alone; by convention, $\kappa > 0.2$–0.4 is interpreted as fair agreement [60]). Using IQCODE in combination with ACE-R in series or in parallel, as per the method of Flicker et al. [61], showed the expected improvement in diagnostic specificity in the series paradigm ("And" rule: both tests required to be positive before a diagnosis of dementia is made) with some reduction in sensitivity but with improved overall accuracy, while in the parallel paradigm ("Or" rule: either test positive sufficient for a diagnosis of dementia to be made), there was the expected improvement in sensitivity, but with no change in accuracy or specificity [34, 58].

In a similar study of consecutive referrals to two memory clinics [62], some patients were administered the ACE-R ($n = 79$) at the same time that an informant completed the IADL Scale [34, 63]. IADL Scale scores and ACE-R scores were moderately correlated ($r = 0.58$; $t = 6.25$, df = 77, $p < 0.001$), and the test of diagnostic agreement between the two tests was similarly moderate ($\kappa = 0.38$, 95 % CI 0.18–0.58); by convention, $\kappa > 0.2$–0.4 is interpreted as fair agreement [60]. Results of using IADL in combination with ACE-R in series or in parallel, as per the method of Flicker et al. [61], showed the expected improvement in specificity in the series ("And" rule) paradigm but with loss of sensitivity. In the parallel ("Or" rule) paradigm, there was the expected improvement in sensitivity but with loss of specificity. Parallel use of ACE-R and IADL might therefore be of possible advantage for increased sensitivity (case finding) [34, 63].

4.6 Conclusion

The ACE and ACE-R have become widely established since their initial description, largely because of their excellent performance in clinical practice. Systematic review suggests that these instruments are capable of differentiating between those with and without cognitive impairment, but the evidence base on distinguishing dementia subtypes and MCI is currently lacking [7] and hence an appropriate topic for future studies. ACE and ACE-R may identify cognitive impairment of various etiologies (AD, MCI, FTLD, parkinsonian syndromes, stroke and vascular dementia, brain injury, depression). Normative data for ACE and ACE-R are rather scarce [6, 29], so this may also be an area for further data acquisition. Pragmatic studies examining ACE and ACE-R use in day-to-day practice may give more realistic estimates of test screening utility. Slavish adherence to or overreliance on the initially reported test cutoffs may not be justified because of the particular casemix examined in index studies, risking poor specificity [33, 37]. Combination with scales examining functional abilities may improve sensitivity.

Since both ACE and ACE-R incorporate the MMSE, the enforcement of copyright restrictions on the use of the MMSE [64] poses a threat to the future availability of these instruments. Development of a modified ACE omitting the MMSE items, the ACE-III, is planned (J.R. Hodges, 2011, personal communication).

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Chapter 5
Clock Drawing Test

Brian J. Mainland and Kenneth I. Shulman

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Abstract The clock drawing test (CDT) has long been recognized as a useful component for the screening of cognitive disorders. It provides a user-friendly visual representation of cognitive functioning that is simple and rapidly administered, making it appealing to clinicians and patients alike. The ease of use and wide range of cognitive abilities required to complete the CDT successfully have made this test

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an increasingly popular cognitive screening measure in both research and clinical settings. This chapter summarizes and compares the numerous CDT scoring methods that have been described in the literature. Also, psychometric properties are presented for the CDT when used for cognitive screening in a variety of neurologic conditions, including Alzheimer's disease, Parkinson's disease, Huntington's disease, vascular disease, schizophrenia, stroke, and traumatic brain injury. Cultural, ethnic, and educational considerations for the CDT are also discussed.

Keywords Clock drawing test • Cognitive screening • Dementia

5.1 Introduction

The clock drawing test (CDT) is a widely used cognitive screening tool that is simple and quick to administer and has been well accepted by both clinicians and patients [1–3]. Its origins can be traced to neurology textbooks, which reported the usefulness of this test as a measure of attention in hemineglect patients [4]. More recently, it has been used to screen for cognitive impairment, primarily in elderly patients [3] but also in a wide range of other neurological and psychiatric disorders including: Alzheimer's disease [5], Parkinson's disease [6, 7], Huntington's disease [8], vascular disease [9, 10], schizophrenia [11–13], stroke [14], and traumatic brain injury [15].

The CDT is a valuable cognitive screening test for both quantitative and/or qualitative assessments of many cognitive functions, including selective and sustained attention, auditory comprehension, verbal working memory, numerical knowledge, visual memory and reconstruction, visuospatial abilities, on-demand motor execution (praxis), and executive function [2, 16, 17]. The specific abilities falling under the category "executive function" that are assessed by the CDT include abstraction, complex motor sequencing, response inhibition (i.e., the frontal pull of the hands to the "10" in the instruction to set the time at "10 past 11") and frustration tolerance [2]. Interpretation of the CDT necessitates consideration of the broad range of cognitive functions that are assessed by this test [18]. The ease of use and wide range of cognitive abilities required to successfully complete the CDT have made this test an increasingly popular cognitive screening measure among researchers and clinicians. A review of recent literature published on the CDT using the PubMed/MEDLINE database, within the date range of January 2000–December 2011, found a total of 349 peer-reviewed publications when searching for articles containing the keywords "clock drawing test" and 95 articles when searching for articles containing "clock drawing test" in the article title.

5.2 Popularity of CDT

The widespread use of the CDT among clinicians is also evidenced by a number of recent surveys that have investigated the frequency of use of currently available cognitive screening measures among practitioners across a variety of fields. In 2010,

Iracleous and colleagues published a survey of the cognitive screening tools that are currently being used by Canadian family physicians [19]. Of the 249 surveys that were completed and returned by members of the College of Family Physicians of Canada (CFPC), the majority of respondents had been in practice for more than 5 years and devoted 40–60 % of their practice to the care of the elderly. Their findings indicated an overwhelming agreement among practitioners that screening is important within the primary care setting and should not be left to specialists. Furthermore, the most frequently used assessment tools were (i) the MMSE and its variants (76 % of respondents reported using this measure "often" or "routinely"), (ii) the CDT (52 %), (iii) the delayed word recall test (52 %), (iv) alternating sequences (13 %), and (v) the Montreal Cognitive Assessment (MoCA) (5 %). Of note, however, is that the authors did not report the number of respondents who do not incorporate cognitive screening into their practice and, thus, do not use any of the above tools. As a result, the reported percentages reflect the sample of Canadian family physicians as a whole, rather than just those who conduct cognitive screening on a regular basis. Nevertheless, the findings provide strong support that the CDT is a commonly used, and a well-accepted, cognitive screening measure among Canadian family practitioners.

Milne et al. [20] conducted a survey of primary care practices in South East England to determine what, if any, instruments were being used by clinicians to screen for dementia. Each participating practice was asked to mark which measures they used from a list of common screening tools with space provided to report unlisted measures. Data were obtained from a total of 138 practices. Of those, 79 % reported that they routinely used at least one dementia screening instrument, with 21 % not using an instrument at all. Furthermore, of those who used an instrument, 70 % of practices used one, 26 % used two and only 4 % used more than two instruments. The breakdown of the screening instruments most commonly used was as follows: the MMSE and its variants (51 %), the abbreviated mental test (AMT) (11 %), MMSE and AMT (10 %), MMSE and CDT (8 %), MMSE and the 6-item cognitive impairment test (6-CIT) (6 %), and the CDT (5 %). Results from this survey suggest that the CDT is used less often by practitioners in the UK compared to usage rates of Canadian practitioners [19]. However, an earlier survey reported by Reilly, Challis, Burns, and Hughes [21] that sampled only practitioners who were working within old age psychiatry services in England and Northern Ireland found a much higher frequency of usage of the CDT. Their study found that an overwhelming majority (96 %) of the 331 respondents used standardized scales as part of the assessment process for older people with mental health problems in the community. Of the respondents that endorsed the use of standardized scales, the most frequently identified measures were the MMSE (95 %), the Geriatric Depression Scale (52 %), and the CDT (50 %). Thirty-one percent of the respondents used all three of these scales.

Shulman et al. [22] conducted an international survey of geriatric specialists on behalf of the International Psychogeriatric Association (IPA). With the goal of determining which screening tools were routinely used by clinicians with expertise in neuropsychiatric aspects of old age, the survey was mailed to all IPA members as well as members of the American and Canadian Associations of Geriatric Psychiatry.

Of the 334 completed surveys, the majority of respondents were geriatric psychiatrists (58 %), followed by general psychiatrists (14 %) and geriatricians (9 %). Just over 50 % of the respondents were from North America, and 62 % indicated that they devoted more than 75 % of their professional practice to the care of the elderly population. The results revealed that only a small number of tests were used by the vast majority of specialists, including MMSE and its variants (100 %), CDT (72 %), delayed word recall (56 %), the verbal fluency test (35 %), similarities (27 %), and the trail-making test (25 %).

The sequence of instruments reported by Shulman et al. [22] overlaps with that in the primary care setting [23] and suggests that the MMSE is the most frequently used cognitive screening instrument. However, a currently unpublished survey of 155 members of the Canadian Academy of Geriatric Psychiatry (CAGP) and attendees of the 2010 Annual Scientific Meeting suggests that the CDT has increased in popularity in the past few years and may have surpassed the MMSE as the favored screening instrument among Canadian psychogeriatric clinicians (Ismail et al., personal communication, 2012). Preliminary results suggest that the six most frequently identified screening tools used "often" or "routinely" by clinicians were the CDT (92.90 %), the MMSE and its variants (91.40 %), the Montreal Cognitive Assessment (MoCA) (80.20 %), delayed word recall (74.60 %), the trail-making test (43.60 %), and verbal fluency (42.90 %). However, results of this survey have yet to undergo peer review and should be interpreted with caution. The results of these surveys clearly suggest that the CDT is an increasingly popular instrument among practitioners from a variety of clinical settings.

5.3 CDT Administration

The CDT provides a user-friendly visual representation of cognitive functioning that is appealing to busy clinicians. The test takes less than 1 min to conduct (compared to 10 min for the MMSE) and appears to have a high level of acceptability by patients [2]. The scoring systems described in this chapter are not all comparable because of differing emphasis placed on visuospatial, executive, quantitative, and especially qualitative issues [24, 25]. Although each scoring system uses slightly different methodologies and instructions for clock drawing, most studies use a predrawn circle of approximately 4 in. (10 cm) in diameter [25]. However, some authors feel that there is value in observing patients perform free-drawn circles as this can indicate some degree of impairment [26]. The disadvantage of this method is that if the patient begins by drawing a poor-quality circle, at times merely due to age-related issues such as tremor or visual impairment, the remainder of the test may be compromised [27].

Generally, the test instructions presented verbally to the patient are "This circle represents a clock face. Please put in the numbers so that it looks like a clock and then set the time to 10 minutes past 11." This method involves the abstract task of denoting time in symbolic fashion using hands, and thus, the tester should not use

the word "hands" in the instructions [2]. While other times such as 3:00, 8:05, and 2:45 have been used, the 11:10 task is particularly useful because it includes both visual fields and requires that the patient inhibits the "frontal pull" towards the number ten, an error that is common in even mildly impaired patients [25]. The inclusion of copying and time setting or reading tests in addition to clock drawing tests by some authors [28] may help to improve the CDT's predictive validity but also increases its time of administration and complexity, thereby reducing one of the key positive features of the CDT, its speed of completion [27].

5.4 CDT Scoring Systems

Table 5.1 presents the properties of the most common scoring methods as well as several measures that were reported in the studies by the authors that developed these scoring systems and in subsequent studies. Such measures include sensitivity, specificity, inter-rater and test-retest reliability, and correlations with other screening tests. Figures 5.1 and 5.2 provide examples of typical qualitative errors, and Fig. 5.3 indicates the clinical usefulness of clock drawing for demonstrating change in cognitive functioning. Characteristic errors on the CDT include perseveration; right-left confusion; concrete thinking especially the tendency to "pull" the minute hand to "10"; and confusion about the concept of time [2].

In perhaps its first systematic use, Goodglass et al. [29] included the CDT as part of the Boston aphasia battery. Their procedure involved clock setting where the subject was given four pre-drawn clock faces that include short lines marked in the positions of the 12 numbers. The subject was asked to denote four different times: 1:00, 3:00, 9:15, and 7:00. Points were awarded for each correct placement of a hand and one point each for correctly drawing the relative lengths of the minute and hour hands. A total of three points could be achieved for each clock for a maximum of 12 points on the test. The authors reported that age and education appeared to be influential factors only for subjects who scored in the bottom range on the test.

Shulman et al. [30] compared the CDT to the MMSE [31] and the Short Mental Status Questionnaire (SMSQ) [32] in a sample of 75 older adults with a mean age of 75.5 years. Three groups were included in their study, including those with dementia, those with depression, and normal controls. The authors developed a 5-point scale of severity of impairment, based on clinical experience. A score of 1 denoted very minimal error while a score of 5 was assigned when the subject was unable to make any reasonable attempt to draw a clock. In a subsequent study, this scoring was reversed and five points were awarded to a perfectly drawn clock [33]. Shulman's current practice (see Fig. 5.1) is to assign 5 points for a "perfect" clock, 4 points for a clock with minor visuospatial errors, 3 for inaccurate representation of 10 past 11 when the visuospatial organization is done well, 2 for moderate visuospatial disorganization of numbers such that accurate denotation of "ten past eleven" is not possible, 1 for a severe level of visuospatial disorganization, and 0 for inability to make any reasonable representation of a clock [2].

Table 5.1 CDT scoring systems

System	Reference	Screening target	Sensitivity (%)	Specificity (%)	Inter-rater reliability	Test-retest reliability	Correlation with other measures (*r*)
Shulman	Shulman et al. [30, 33]	Dementia	86	72	0.75 0.96	–	MMSE = −0.65; SPMSQ = −0.66; GDS = −0.32
	Beinhoff et al. [65]	Dementia	Cut-off 1 = 86 Cut-off 2 = 71	Cut-off 1 = 60 Cut-off 2 = 95			
Sunderland	Sunderland et al. [34]	Alzheimer's			0.86	–	GDS = −0.56; DRS = 0.59; BDRS = 0.51; SPMSQ = 0.59
	Kirby et al. [35]	Dementia	76	81			
Wolf-Klein	Wolf-Klein et al. [36]	Dementia	75	94	–	–	–
CERAD	Borson et al. [40]	Dementia	82	92	0.97		CASI = −0.80; MMSE = −0.79
Tuokko	Tuokko et al. [42]	Alzheimer's	92	86	0.90–0.95	0.73	–
Rouleau	Rouleau et al. [8]	Alzheimer's			0.92–0.97		–
Death	Death et al. [43]	Cognitively impaired	77	87	–	–	–
Watson	Watson et al. [44]	Cognitively impaired	87	82	0.90	0.82	–
Manos and Wu	Manos and Wu [46]	Mild Alzheimer's	76	78	0.88–0.97	0.94	TMT A = −0.48; MMSE = 0.50; Block Design Test = 0.56
	Manos [47]		71	82			
Shua Haim	Shua Haim et al. [48]	Cognitively impaired	–	–	–	–	MMSE = 0.57

Lin	Lin et al. [49]	Alzheimer's	73	66	0.99	0.90	CASI (Chinese version) = 0.73; MMSE = 0.73
Lessig	Lessig et al. [50]	Dementia	88	71	–	–	
Babins	Babins et al. [51]	Mild cognitive impairment	76	90	–	–	MMSE = 0.48
CLOX	Royal et al. [52]	Executive impairment	–	–	–	–	EXIT25 = −0.78; MMSE = 0.76

SPMSQ Short Portable Mental Status Questionnaire, *GDS* Global Deterioration Scale, *DRS* Dementia Rating Scale, *BDRS* Blessed Dementia Rating Scale, *CASI* Cognitive Abilities Screening Instrument, *TMT A* Trail Making Test Part A, *EXIT25* Executive Interview

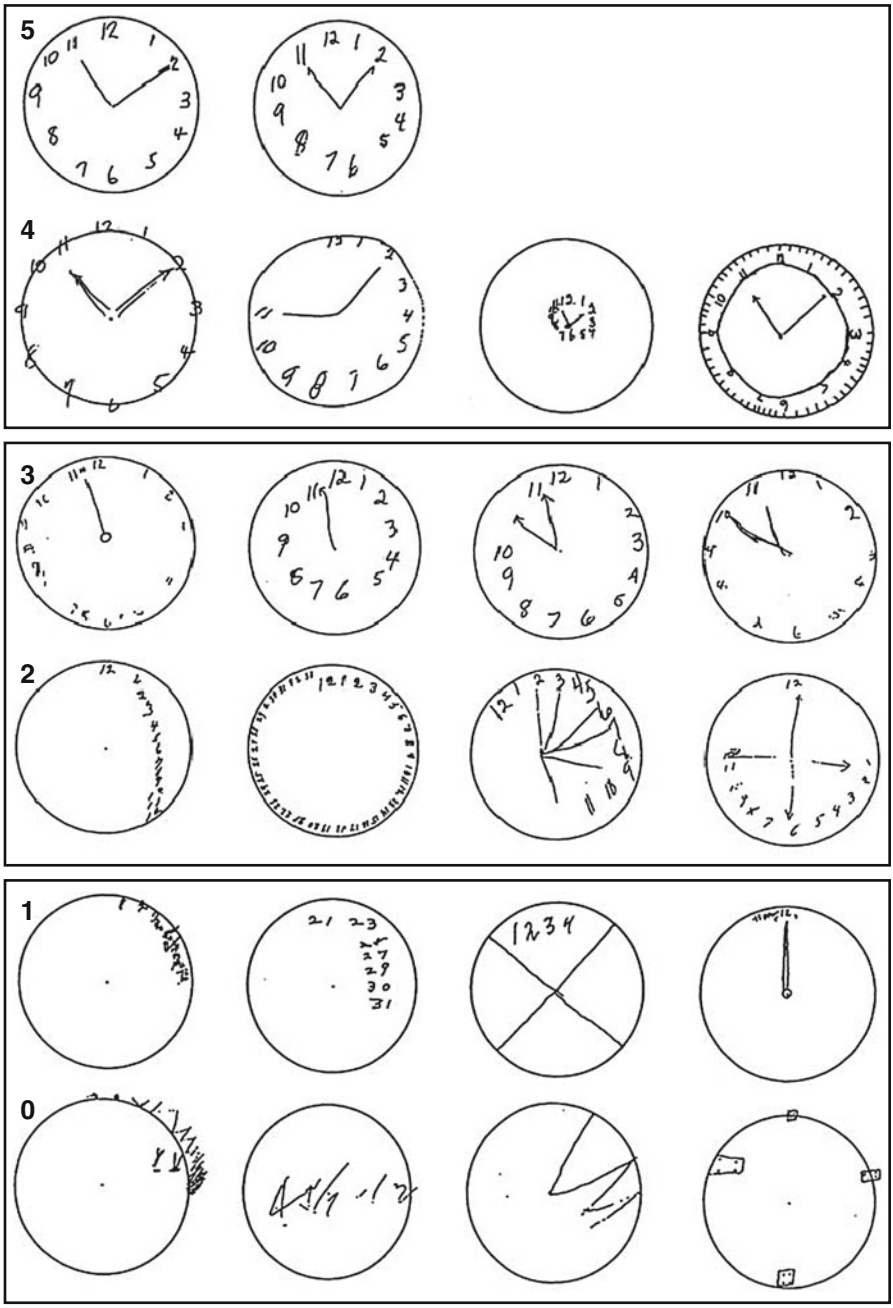

Fig. 5.1 Severity scores from 5 to 0 (Reproduced from Shulman [2], with permission from John Wiley & Sons Ltd.)

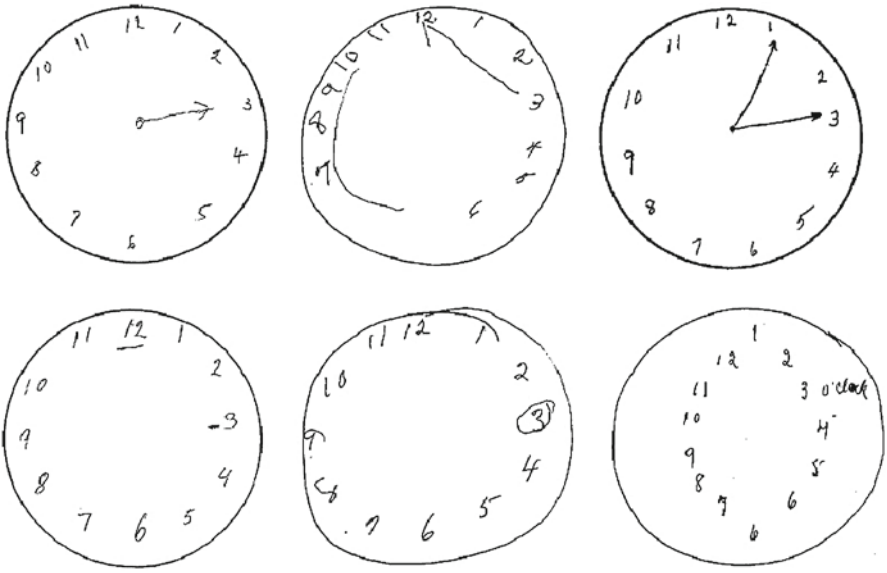

Fig. 5.2 Errors in denoting 3 o'clock (Reproduced from Shulman [2], with permission from John Wiley & Sons Ltd.)

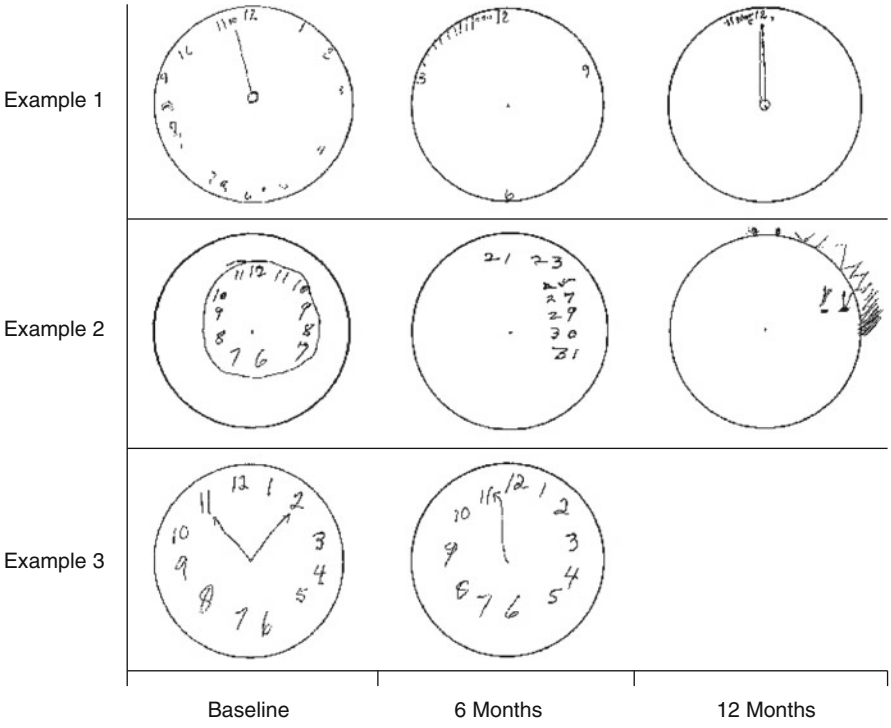

Fig. 5.3 Sensitivity to deterioration in dementia (Reproduced from Shulman [2], with permission from John Wiley & Sons Ltd.)

Sunderland et al. [34] used a priori criteria to develop a 10-point scoring system with 10 as the highest score and 1 as the lowest score. Five points were awarded for drawing a clock face with numbers correctly placed, while 6–10 points were given for accuracy of drawing hands to denote the time 2:45. An arbitrary cut-off score of 6/10 was considered within normal limits. The authors reported that 3 out of 83 controls (3.6 %) scored less than 6, whereas 15 out of 67 patients with Alzheimer's disease (22.4 %) scored more than 6. They also found high inter-rater reliability between clinicians and nonclinicians and high correlation of the CDT with other measures of dementia severity, including the Dementia Rating Scale. A later study by Kirby et al. [35] used this same scoring system while incorporating a more heterogeneous sample of community-dwelling participants. They found that the sensitivity of the CDT in the detection of dementia in the general community was 76 %. The specificities of the CDT against normal elderly and depressed elderly were 81 and 77 %, respectively.

Wolf-Klein et al. [36] compared their clock drawing test to the MMSE [31], Hachinski's scale [37], and the Dementia Rating Scale [38] in a sample of outpatients being screened for cognitive impairment. Their methods included a pre-drawn circle and ten hierarchical clock patterns that were predetermined by a previous pilot study involving over 300 patients. Their patient groups included healthy normals, those with Alzheimer's dementia and multi-infarct dementia, and others. A cut-off score of 7/10 reflected normal performance, and a score of less than 7 was considered "abnormal." With a focus on temporoparietal function, they found that scores of 1–6 were specific for Alzheimer's disease as opposed to multi-infarct dementia or mixed cases.

A simple 4-point scoring system was developed by the Consortium to Establish a Registry for Alzheimer's Disease (CERAD) [39]. In this method, subjects were instructed to draw a clock by first drawing a circle, then adding numbers and then setting the time to show 8:20. The instructions could be repeated, and if necessary, the subject could be instructed to draw a larger circle. In this system, a score of "0" implied an intact clock, 2 = mild impairment, 3 = moderate impairment, 4 = severe impairment. Thus, any score greater than 0 was considered abnormal for the purposes of classification [40]. The CERAD scoring method was later used by Borson et al. [40], who incorporated the CDT into the "Mini-Cog" battery, which also contains a simple three-word delayed recall memory test. The authors found the sensitivity and specificity for probable dementia were 82 and 92 %, respectively, for the CDT compared to 92 and 92 % for the MMSE and 93 and 97 % for the Cognitive Abilities Screening Instrument (CASI) [41]. However, the authors noted that in poorly educated non-English speakers, the CDT detected demented subjects with higher sensitivity than the two longer instruments (sensitivity and specificity 85 and 94 % for the CDT, 46 and 100 % for the MMSE, and 75 and 95 % for the CASI). Furthermore, less information was lost due to non-completion of the CDT than the MMSE or CASI (severe dementia or refusal: CDT 8 %, MMSE 12 % and CASI 16 %).

Tuokko et al. [42] developed a unique procedure involving three empirically derived tasks that involved clock drawing, clock setting, and clock reading. The clock drawing component involved a pre-drawn circle in which the subject was

asked to denote "ten past eleven." Clock setting involved setting five different times, and clock reading involved the same clocks as in clock setting, but in a different order. Errors on clock drawing were classified into the following categories: omissions, perseverations, rotations, misplacements, distortions, substitutions, and additions. Clock setting achieved a maximum of 3 points, as did clock reading. Making more than two errors was considered a positive (abnormal) result for clock drawing, while the cut-off for the clock setting and reading tasks was a score of less than 13. Interestingly, errors from four categories (omissions, distortions, misplacements, and additions) were found to contribute significantly to the difference between normal elderly and Alzheimer's disease patients.

Rouleau et al.'s [8] version of the CDT instructed subjects to "draw a clock, put in all the numbers, and set the hands for ten after eleven." The participants were also asked to copy a pre-drawn clock. This version was designed to identify the quantitative and qualitative aspects of cognitive impairment in patients with Alzheimer's disease. The test was scored is using a 10-point scale, with lower scores indicating greater cognitive impairment.

Death et al. [43] focused on elderly inpatients seen consecutively in surgical and medical wards at three hospitals in Newcastle. Their CDT protocol involved giving the patient a piece of paper with a 10-cm heavy black circle with a dot in the center printed on it. They were asked to "imagine this is a clock face. Please fill in the numbers on the clock face." If, while drawing, a patient spontaneously recognized an error and requested to correct it, he or she was allowed to do so. For scoring, clocks were classified as follows: bizarre (class 1), major spacing abnormality (class 2), minor spacing abnormality or single missing or extra number (class 3), and completely normal (class 4). Clocks class 1 and 2 indicated impairment, and class 3 and 4 indicated no cognitive impairment. The authors found that normal clock drawing ability reasonably excluded cognitive impairment or other causes of an abnormal MMSE in elderly acute medical and surgical hospital admissions where cognitive impairment is often missed.

The clock completion test developed by Watson et al. [44] involved providing patients with a pre-drawn circle and asking them to draw in the numbers on a clock face. Interestingly, in this method, the patients were not asked to draw the hands on the clock, and scoring included only the positioning of the clock numbers. The scoring system divided the pre-drawn circle into four quadrants, assigning greatest weight to the fourth quarter. An error made in quadrants one, two, or three received a score of 1, and any error in quadrant four (containing numbers 9–12) received a score of 4. A score of 0–3 was considered normal, and anything ≥4 was considered abnormal. In the original study, the authors studied a group of patients from a geriatric outpatient assessment clinic and found an excellent comparison with the Blessed Orientation-Memory-Concentration test [45].

Manos and Wu [46] developed a "10-point clock test" that included a scoring system utilizing a transparent circle divided into eighths that was applied to the clock drawn by the patient. A maximum of ten points were awarded for numbers falling into their proper segment and for correctly drawn hands. A difficulty with this method is that some significant errors will not be scored, such as counterclockwise

placement of numbers or numbers that are positioned outside the circle. The authors found that a cut-off score of 7 out of 10 identified 76 % of patients with dementia and 78 % of control patients. A later study using the same test attempted to identify mild AD patients (i.e. those with MMSE > 23) among consecutive ambulatory patients. The authors reported a sensitivity of 71 %, compared to 76 % for the original study that included patients with a mean MMSE score of 20 [47].

A "simple scoring system" (SSS) was developed by Shua Haim et al. [48]. The authors performed a retrospective chart analysis of a sample of elderly patients in an outpatient memory disorders clinic. Their scoring system was based largely on the visuospatial aspects of the task and the correct denotation of time by the hands for a maximum of 6 points. A formula was developed to relate clock scores with the MMSE using simple linear regression in the following way: MMSE = 2.4 × (the clock score) + 12.7. The authors reported that a clock score of zero predicts an MMSE score of <13, whereas a clock score of 6 predicts a MMSE score of ≥27.

Lin et al. [49] examined a comprehensive scoring system of the CDT in screening for Alzheimer's disease in a Chinese population in order to derive a simplified scoring system. In this study, the clocks were first scored based on the systems described by Watson et al. [44], Wolf-Klein et al. [36], and Tuokko et al. [42], which involved first dividing the clocks into quadrants using two reference lines – one line through the center and the numeral 12, and then a second line perpendicular to the first one through the clock center. If a numeral was placed on the reference line, it was included in the quadrant clockwise to the line. Thirteen criteria were then scored as correct or incorrect for a maximum total score of 16 (item 6 received up to four points for correct placement of three numerals in each of the four quadrants). The authors then formulated a simple scoring system of only 3 items (hour hand, number 12, and difference between hands) using a stepwise discriminant analysis to select a minimal set of items from the comprehensive scoring system. The simplified 3-item scoring, with a cut-off score of 2/3, was found to have a sensitivity of 72.9 % and a specificity of 65.6 %. The authors suggest that this simple scoring method can be used as a quick test for AD screening.

Lessig et al. [50] recently analyzed the scoring systems of Shulman et al. [33], Mendez et al. [16] and Wolf-Klein et al. [36], as well as the CDT system used in the Mini-Cog [40] in order to identify an optimal subset of clock errors for dementia screening. The clock drawings of 364 ethnolinguistically and educationally diverse subjects with ≥5 years of education were analyzed. An algorithm using the six most commonly made errors of inaccurate time setting, no hands, missing numbers, number substitutions or repetitions, and failure to attempt clock drawing detected dementia with 88 % sensitivity and 71 % sensitivity. A stepwise logistic regression found the simplified scoring system to be more strongly predictive of dementia than the three other CDT scoring systems. Also, substituting the new CDT algorithm for that used in the original version of the Mini-Cog improved the test's specificity from 89 % to 93 % with minimal change in sensitivity.

Babins et al. [51] developed "the 18-point clock-drawing scoring system" based on clinical intuition as well as a literature review. The goal of their system was to enhance the utility of the CDT for recognition and prognostication in mild cognitive

impairment (MCI). In this system, errors were grouped into four major categories: stimulus-bound errors, conceptual deficits, perseverations, visuospatial organization, and planning deficits. Using this scoring system with a sample of 123 retrospectively assessed individuals from a memory clinic in Montreal, the authors found that there were three significant hand items that appeared to be possible early markers of progression to dementia. The items "clock has two hands," "hour hand is towards correct number" and "size difference of hands is respected" all showed significant differences between progressors and non-progressors. The authors suggest that the 18-point clock drawing scoring system may have advantages in identifying MCI individuals who are more likely to progress to dementia.

In an interesting twist on the standard administration and scoring of the CDT, Royall and colleagues [17] developed a variant of the clock drawing test (CLOX) designed to detect executive impairment and differentiate it from nonexecutive visuo-spatial failure. This version of the test is divided into two parts to distinguish the executive control of clock drawing from the constructional/visuospatial ability. For the first part of the test (CLOX 1), the subject is asked to "draw me a clock that says 1:45. Set the hands and numbers on the face so that a child could read them." The notion underlying the method for CLOX 1 is that it reflects performance in a novel and ambiguous situation eliciting the executive skills of goal setting, planning, motor sequencing, selective attention and self-monitoring of a subject's current action plan. Some of the CLOX 1 instructions are deliberately designed to distract the subject. For example, use of the terms "hand" and "face" has the potential to elicit semantic intrusions because they are more commonly associated with body parts than with elements of a clock. The maximum score for CLOX 1 test is 15. The second portion of the task (CLOX 2) involves a simple copying task of a pre-drawn clock already set at 1:45. Differences in scores on CLOX 1 and 2 are hypothesized to reflect executive contribution to the clock drawing test versus visuospatial and constructional ability. The participant's performance is rated on a 15-point scale (lower scores indicate impairment) on both CLOX 1 and 2. Cut points of 10/15 (CLOX 1) and 12/15 (CLOX 2) represent the fifth percentile for young adult controls. A later study by the same authors found the CLOX test explained more variance in executive control function than other clock drawing tests [52].

5.5 Comparing CDT Scoring Systems

Scanlan et al. [53] examined 80 clock drawings by subject with known dementia status from four categories (i.e. normal, mild, moderate, and severe abnormality) as defined by the Consortium to Establish a Registry for Alzheimer's Disease (CERAD). In order to compare dementia detection across scoring systems, an expert rater scored all clocks using published criteria for seven systems, including Shulman et al. [30], Morris et al. [39], Sunderland et al. [34], Wolf-Klein et al. [36], Mendez et al. [16], Manos et al. [46], and Lam et al. [28]. Additionally, 20 naïve raters with no formal instruction judged each clock as either normal or abnormal. The authors

found that when using categorical cut-off points published for each CDT scoring system, the overall concordance between the naïve scores and the different CDT systems was high (86–89 %), with the exception of the Sunderland (73 %) and Wolf-Klein (66 %) systems. When CDT classifications were compared against independent clinical dementia diagnoses, the Mendez system most accurately distinguished demented from non-demented individuals, followed closely by the CERAD system. Naïve raters did not differ from the Manos or Shulman systems but were significantly better than the Lam, Sunderland, and Wolf-Klein systems. The CERAD and Mendez systems were found to be most sensitive in detecting mild and moderate dementia, while the Wolf-Klein system failed to detect 100 % of even severely demented subjects. Of note is that the Wolf-Klein system requires no time setting and mild to moderate number spacing errors are disregarded, both factors that likely contributed to poor performance of this system. Interestingly, the authors reported that detection of both MCI and mildly demented subjects was minimally two to three times greater than physician recognition for all systems except the Sunderland and Wolf-Klein systems [53].

Van der Burg et al. [54] compared the dementia screening performance of two scoring systems, the CERAD system [39, 40] and the Shulman et al. [33] system, to determine whether a somewhat more complex system has clear advantages over a simpler and less time-consuming scoring system. The authors selected the simple four-item CERAD method because of its user-friendly qualities and the Shulman six-item system because of its proven diagnostic qualities. A selection of 473 drawings was selected from a larger sample of 1,199 elderly subjects for whom the presence or absence of dementia was known. Results showed that both scoring systems had good inter-system and inter-rater reliabilities and both correlated equally well with the true diagnosis of dementia. These findings are similar to earlier studies by Scanlan et al. [53] and Lin et al. [49], which also concluded that simpler systems were found to be accurate when compared to more complex systems. The authors concluded that primary care physicians and other health-care providers should be encouraged to use the simpler four-item scoring checklist as it is easier to administer and requires less time than the six-item method [54].

Matsuoka et al. [55] identified brain regions associated with performance on various measures of the CDT using magnetic resonance imaging (MRI) in 36 patients with Alzheimer's disease, 8 with mild cognitive impairment and 4 healthy controls. Multiple regression analyses were used to identify relationships between each CDT scoring system (Shulman [2], Rouleau [8] and CLOX 1 [17]), and regional gray matter volume. The authors reported that the CDT scores of the three scoring systems were positively correlated with gray matter volume in various regions in the brain. Furthermore, some brain regions overlapped with the three different scoring systems, whereas other regions showed differences between tests. All three CDT scoring systems were positively correlated with gray matter volume in the right parietal lobe. Furthermore, the Shulman system was positively correlated with gray matter volume in the bilateral posterior temporal lobes, leading the authors to speculate that the Shulman CDT might be useful in detecting the impairment of semantic knowledge and comprehension. The Rouleau CDT score was positively

correlated with gray matter volume in the right parietal lobe, right posterior inferior temporal lobe and right precuneus, suggesting that the Rouleau CDT may detect impairment of visuospatial ability and the retrieval of visual knowledge. Finally, the CLOX 1 score was positively correlated with gray matter volume in the right parietal lobe and right posterior superior temporal lobe, suggesting that the CLOX 1 system may detect impairment in visuospatial ability and sentence comprehension. The authors concluded that distinct brain regions might be associated with CDT performance using different scoring systems and that different scoring and administration systems require different cognitive functions. Thus, rather than using only one scoring system, a combination of CDT scoring systems may cover a wider range of brain functions in dementia screening [55].

5.6 Predictive Validity of CDT

5.6.1 Normal Aging

Bozikas et al. [56] administered Freedman et al.'s [26] version of the CDT to 223 healthy community-dwelling adults in order to develop norms for the Greek population and to explore the influence of demographic factors (i.e. sex, age, and level of education) on the performance of healthy individuals. The authors found no sex differences in performance but did find that age and level of education contributed to CDT scores. More specifically, they found that greater years of education were associated with better performance, while age had a negative contribution. Analysis revealed that the influence of age was due exclusively to the elderly group; for those patients under the age of 60 years, age did not influence CDT performance. However, there was a marked decline after 60 and another decline after 70 years of age. The authors suggest that performance on the CDT is resistant to the aging process, at least in the non-elderly. However, the authors note that future research should establish more reliable norms for the elderly by including more extensive sampling of elderly patients with varying levels of education.

Hershkovitz et al. [57] assessed the relationship between the CDT and rehabilitation outcome in 142 elderly hip fracture patients who scored within the normal range of the MMSE (>23). This retrospective study was performed in a post-acute geriatric rehabilitation center, and patients were divided into two groups according to CDT performance (impaired versus intact) scored using the Watson method [44]. The differences between the two groups in relation to age, gender, education level, living arrangement, pre-fracture functional level, and outcome measurements were compared. The patients' functional status was assessed using the Functional Independent Measure (FIM) and the motor FIM [58]. The FIM is comprised of 18 parameters, each assessed on a scale of 1–7 according to the degree of assistance the patient requires to perform a specific activity in three domains: basic activity of daily living, mobility level, and cognitive functioning. Patients' rate of in-hospital improvement was calculated by comparing admission and discharge FIM scores.

Discharge FIM scores were significantly lower for the impaired CDT group (89 vs. 94.9, $p=0.007$). Also, length of hospital stay was significantly longer (28.2 vs. 25.3 days, $p=0.033$), and rate of improvement in FIM was significantly slower (0.62 vs. 0.77, $p=0.036$) for the impaired CDT group. The authors concluded that the CDT may assist the multidisciplinary team in identifying hip fracture patients whose MMSE scores are within the normal range but require a longer training period in order to extract their rehabilitation potential.

5.6.2 Mild Cognitive Impairment

Research examining the CDT's ability to differentiate between subjects with and without mild cognitive impairment (MCI) is inconsistent [9, 27, 59]. For example, Yamamoto et al. [60] found that the CDT had positive utility for MCI screening, whereas Lee et al. [61] did not recommend the use of the CDT as a screening instrument for MCI. Ehreke et al. [62] speculated that the inconsistent results might be due to the variety of versions of CDT administration and scoring, and thus they compared the utility of different CDT scoring systems for screening for MCI using a sample of German subjects aged 75 years and older. Diagnosis of MCI was established according to the criteria proposed by the International Working Group on MCI [63]. These criteria include (a) absence of dementia according to DSM-IV or ICD-10; (b) evidence of cognitive decline: subjective cognitive impairment (measured by self-rating or informant report) and impairment on objective cognitive tasks, and/or evidence of decline over time on objective cognitive tasks; and (c) preserved baseline activities of daily living or only minimal impairment in complex instrumental functions. The CDT scoring systems that were examined included Sunderland et al. [34], Shulman et al. [33], Mendez et al. [16], Rouleau et al. [8], Babins et al. [51], and Lin et al. [49]. The authors reported significant differences in CDT scores between participants with and without MCI for all scoring systems applied. Furthermore, receiver operating characteristics (ROC) analysis revealed a significant probability of correctly differentiating between subjects with and without MCI for all scoring systems (a 64–69 % probability of MCI subjects achieving a different CDT score from subjects without MCI). However, an examination of screening utility indicators (sensitivity and specificity) showed that none of the scoring systems were able to screen reliably for MCI, as evidenced by the fact that no cut-off point in any system produced values of sensitivity higher than 80 % and values of specificity higher than 60 % (recommended values of sensitivity/specificity outline by Blake et al. [64]). The scoring system that came closest to these recommended values was that of Shulman et al., which produced 76 % sensitivity and 58 % specificity. The sensitivity and specificity values for the other systems were as follows: Sunderland et al. = 69 and 63 %; Rouleau et al. = 48 and 79 %; Babins et al. = 60 and 70 %; Mendez et al. = 64 and 70 %; Lin et al. = 76 and 49 %. The authors concluded that the CDT, as currently administered, is not a good screening instrument for MCI. However, they

suggest that the CDT's clinical utility in this population could be improved by being semi-quantitative, having a wider score range and focusing on the clock's hands and numbers in more detail.

Similarly, Beinhoff et al. [65] employed the Shulman [2] scoring system to examine its usefulness in a sample of 232 patients with various degrees of dementia in an outpatient memory clinic in Germany. Using a cut-off point of >1, 86 % of AD patients and 40 % of MCI patients were detected. These authors also concluded that the CDT was useful for the detection of AD, but not for MCI.

Forti et al. [66] examined whether the CLOX [17], both alone and in combination with the MMSE, could be useful as a screening tool for MCI in a sample of 196 elderly individuals seeking medical help for cognitive complaints. The CLOX is a CDT protocol that has been reported to be more sensitive to executive functioning impairment than either the MMSE or several other CDT tasks [52]. Forti et al. employed an extensive screening process in order to subdivide their MCI participants into the following subtypes: amnestic MCI (aMCI), if there was impairment in memory alone; multiple-domain MCI with memory impairment (mMCI), if there was impairment in memory and at least one other cognitive domain; non-amnestic MCI (naMCI), if there was impairment in one or more non-memory cognitive domains. The study found that, at standard cut-offs, both CLOX subtests had reasonable specificity (CLOX 1 = 72 %, CLOX2 = 92 %) but unacceptably low values of sensitivity (CLOX 1 = 54 %, CLOX 2 = 28 %), as well as likelihood ratio (CLOX 1 = 1.91, CLOX 2 = 3.59) for MCI. Furthermore, using different cut-off scores or combining the CLOX with the MMSE did not result in a statistically significant increase in diagnostic efficiency. Scores for both CLOX subtests were lower in subjects with MCI than in controls, but neither subtest achieved efficacy enough to merit recommendation as a screening tool. As expected, the lowest CLOX scores were found for patients diagnosed with the mMCI subtype, which support previous findings that, independent of the scoring system used, the greater the severity of cognitive impairment, the better the ability of a CDT task to detect it [27, 67]. The authors concluded that the CLOX, either alone or used in conjunction with the MMSE, is not a useful screening tool for MCI in a clinical setting.

A recent study by Parsey and Schmitter-Edgecombe [68] used both an established quantitative scoring system and a revised qualitative scoring method based on error criteria developed by Rouleau et al. [8] to demonstrate the sensitivity of the CDT to MCI. For the qualitative component, the authors converted the qualitative errors examined by Rouleau et al. [8] into a quantitative system to increase the speed and practicality of its use while maintaining the entirety of the scoring criteria. The authors hypothesized that by maintaining a greater number of qualitative errors and incorporating an efficient quantitative total score component, the modified scoring system would be both sensitive to MCI and practical for use in both clinical and research settings. The study found that MCI participants scored significantly different than non-demented controls in terms of overall total score using the Modified Rouleau method, but not the original 10-point Rouleau system. Furthermore, sensitivity and specificity analyses revealed that the Modified Rouleau CDT scoring method demonstrated a moderate ability to detect

early signs of cognitive impairment. However, the Modified Rouleau system still exhibited significant numbers of false-negative identifications. When compared to the original Rouleau scoring system, the modified version was more sensitive to MCI, which supports previous studies demonstrating that more complex scoring systems are more sensitive to the earliest stages of dementia [51, 53, 61]. The authors concluded that qualitative observations of clock drawing errors can help increase sensitivity of the CDT to MCI and that using a more detailed scoring system is necessary to differentiate individuals with MCI from cognitively health older adults.

5.7 CDT and Specific Neurologic Conditions

The value of the CDT has been assessed in a wide variety of neurologic conditions including dementia, delirium, Huntington's disease, Parkinson's disease, stroke, traumatic brain injury, and schizophrenia.

5.7.1 Vascular Dementia and Alzheimer's Disease

An interesting observation on CDT strategy was reported by Meier [69], who observed that patients with vascular dementia commonly begin the task by dividing the circle with radial lines into segments. When comparing the frequency of segmentation patterns in clock drawings of patients with Alzheimer's disease compared to those with vascular dementia, the vascular patients used the strategy at twice the rate. Specifically, almost half of all impaired drawings of patients with vascular dementia showed segmentation compared with only one-quarter of the impaired drawings of Alzheimer's patients. Moreover, patients using segmentation had a higher score on the MMSE than patients with other strategies.

Kitabayashi et al. [70] used quantitative analyses of clock drawings to demonstrate differences in the neuropsychological profiles of Alzheimer's disease compared to vascular dementia. Using Rouleau et al.'s [8] CDT protocol, the authors found that Alzheimer's disease patients' error patterns tended to be stable and independent of disease severity. However, patients with vascular dementia showed increased frequency of graphic difficulties and conceptual deficits with increasing severity of the disease. However, the frequency of visuospatial or planning deficits decreased with dementia severity. In mild dementia groups, the frequency of spatial and/or planning deficit was higher in vascular dementia. In moderate dementia groups, the frequency of graphic difficulties was significantly higher in vascular dementia and the difference in the frequency of spatial and/or planning deficit that was seen in mild dementia disappeared [70].

The finding of increased spatial and planning deficits in mild vascular dementia suggests that frontal-subcortical disturbances are operative. However, at the moderate stage, patients experience conceptual deficits and graphic difficulties more prominently, while the spatial and conceptual deficits decrease. This suggests that the impairment of memory and motor function masks the frontal executive dysfunction as dementia severity increases [70]. The authors concluded that the cognitive profiles of patients are significantly different between Alzheimer's disease and vascular dementia at the mild and moderate levels and it may be possible to discriminate between these profiles using qualitative analyses of clock drawings [70].

Wiechmann et al. [71] examined the sensitivity and specificity of Borson et al.'s [40] 4-point scoring system for the CDT in discriminating Alzheimer's disease and vascular dementia. Receiver operating characteristic (ROC) analysis revealed that the CDT was able to distinguish between normal elderly control participants and those with a dementia diagnosis (Alzheimer's disease and vascular dementia combined). The authors reported that the optimal cut-off score for normal controls was 4, which produced 100 % sensitivity and 70 % specificity. The cut-off score for differentiating Alzheimer's disease from vascular dementia was 3, which produced a sensitivity of 55 % and a specificity of 22 %. Similarly, the cut-off score for discriminating vascular disease from vascular dementia was 3, which produced a sensitivity of 69 % and a specificity of 33 %. Thus, since the optimal cut-off scores for both Alzheimer's disease and vascular dementia were the same, it was impossible to predict one diagnosis from the other solely based on the four-point total score. Wiechmann et al. concluded that Borson et al.'s [40] 4-point system demonstrated good sensitivity and specificity for identifying cognitive dysfunction associated with dementia, but the system did not adequately discriminate between Alzheimer's disease and vascular dementia [71].

Cacho et al. [5] examined the effect of presenting the CDT instructions with a verbal command versus asking participants to copy a clock model presented visually. Their sample included patients with early Alzheimer's disease against a control group of healthy control subjects. Patients in the early Alzheimer's disease group obtained significantly higher scores on the copy command version of the task compared to the verbal command version ($z = -7.129$, $p < 0.001$), whereas no statistically significant differences were found for the healthy control group ($z = -2.001$, $p < 0.080$). In other words, early Alzheimer's disease patients showed a significantly better performance and score on the CDT when copying a clock model than when the clock was drawn in response to verbal command. The authors referred to this difference in performance as the "performance pattern." This is similar to the pattern of response seen in the CLOX test for executive function [52]. Thus, the study found that patients with early Alzheimer's disease showed an improvement pattern in the execution of the CDT copy command in comparison with the execution of the CDT verbal command that is not seen in healthy controls. Such results may be associated with a greater deterioration of memory functions compared to visual-construction functions in patients with early Alzheimer's disease [5].

5.7.2 *Delirium*

Fisher and Flowerdew [72] examined older patients who were undergoing elective orthopedic surgery to assess whether the CDT could predict postoperative delirium. The authors suggested that identifying high-risk patients for delirium may assist clinicians in decreasing the morbidity associated with delirium by providing timely interventions. In their study, patients undergoing elective hip and knee surgery were examined pre- and postoperatively, using a modified Confusion Assessment Method (CAM) questionnaire [73]. Using a stepwise multiple logistic regression, the authors identified two significant risk factors for postoperative delirium. The first risk factor was male gender, and the second was a CDT score of ≤6 based on the modified clock drawing scoring system of Sunderland et al. [34] and Wolf-Klein et al. [36]. Interestingly, abnormal MMSE scores did not predict delirium in the authors' model. Thus, the authors speculated that the CDT measures nondominant parietal functions better than the MMSE and therefore may be indirectly detecting an increased predisposition to the development of delirium.

Manos [74] reported a case of an 80-year-old man who underwent a decompression lumbar laminectomy and later developed a wound infection and other complications, necessitating a second surgery. He developed a delirium the night after his second operation. The CDT was used to document recovery from the delirium up to 14 days postoperatively. By postoperative day 10, the delirium had cleared from a clinical perspective, but cognitive impairment was still evident on the CDT, with minor impairment lasting until day 14. This case study provided further evidence of the usefulness of the CDT in the monitoring of delirium.

Recently, Bryson et al. [75] evaluated the accuracy of the CDT in a sample of patients undergoing surgery for aortic repair. Their study was a subcomponent of a trial whose primary purpose was to explore the relationships among delirium, postoperative cognitive dysfunction, and the apolipoprotein ε (epsilon) 4 genotype. Delirium was assessed using the Confusion Assessment Method [73] on postoperative days 2 and 4 and at discharge. Cognitive functioning was assessed with neuropsychometric tests before surgery and at discharge. Postoperative cognitive dysfunction was determined using the reliable change index method [76], and the CDT was administered at all time points. Delirium was noted in 36 % of patients during their hospital stay, while postoperative cognitive dysfunction was noted in 60 % of patients at discharge. Agreement between the CDT and the test for delirium or postoperative cognitive dementia was assessed with Cohen's kappa statistic. The authors found that agreement between the CDT and Confusion Assessment Method was poor at 2 and 4 days postoperatively, as well as at discharge, with kappa consistently <0.3. For the purpose of their study, the authors assumed that the Confusion Assessment Method is diagnostic of delirium and reported the sensitivity of the CDT in identifying delirium ranges from 0.33 at discharge to 0.59 at the day 4 assessment. Specificity ranged from 0.65 at 2 days postoperatively to 0.83 at discharge. The results of this study suggested that the sensitivity of the CDT for delirium and postoperative cognitive dysfunction was poor, and thus the CDT is not recommended for bedside screening of delirium or postoperative cognitive dysfunction. However, the

authors acknowledge that their study was limited by the absence of an agreed standard of reference on which to base their diagnoses of delirium and postoperative cognitive dysfunction, as well as by a highly selected patient sample that does not reflect the variety of patients presenting for elective noncardiac surgery [75].

5.7.3 Huntington's Disease

Rouleau et al. [8] applied both quantitative and qualitative analyses of the CDT to distinguish characteristics associated with Huntington's disease and Alzheimer's disease. The authors used a CDT protocol adapted from the Boston Parietal Lobe Battery [29] with added qualitative analysis assessing (a) graphic difficulties to stimulus-bound responses, e.g. for 11:10, hand pointing to "10" rather than "2"; (b) conceptual deficits; (c) spatial or planning deficits; (d) perseveration. The study also included a copy task in which Alzheimer's disease patients showed significant improvement compared to Huntington's disease patients. The authors suggested that the primary cause of drawing problems is not graphic, motor, or visual perceptual difficulties, but rather they are due to the loss of semantic associations with the word "clock." Huntington's versus Alzheimer's patients demonstrated moderate to severe graphic and planning deficits. Such planning difficulties may be related to frontostriatal dysfunction associated with Huntington's disease. Moreover, since cognitive impairment was equal between Alzheimer's and Huntington's patients, qualitative differences between groups appear to be due to differential involvement of the limbic cortical regions in Alzheimer's disease compared to the basal ganglia and corticostriatal dysfunction associated with Huntington's disease.

5.7.4 Parkinson's Disease

Saka and Elibol [77] examined the utility of practical neuropsychological tests, including the CDT, in differentiating Parkinson's disease with dementia (PD-D) and Alzheimer's disease, as well as Parkinson's disease with mild cognitive impairment (PD-MCI) and amnestic MCI (aMCI). The authors evaluated consecutive cases with mild to moderate Alzheimer's disease ($n=32$) and PD-D ($n=26$), as well as aMCI ($n=34$) and PD-MCI ($n=19$). The study found that the CDT was more impaired in patients with PD-D than Alzheimer's disease. For differentiation of PD-D from Alzheimer's disease, the CDT was found to be valuable with moderately high sensitivity (85.7 %) and specificity (69.6 %). In differentiation to aMCI and PD-MCI, the CDT was again found to be helpful with a sensitivity of 75.0 % and a specificity of 62.5 %. By applying stepwise linear discrimination function analysis, the authors found that a combination of the CDT with an enhanced cued recall task correctly classified 70.7 % of the overall study population; specifically, 71.4 % of Alzheimer's disease, 71.9 % of aMCI, 69.6 % of PD-D, and 68.8 % of PD-MCI patients were

correctly identified. These results suggest that the CDT can supplement clinical diagnostic criteria in differentiation of dementia or MCI associated with Parkinson's disease from Alzheimer's disease and aMCI. The authors note, however, that while the CDT measures visuospatial impairment, it also involves frontal lobe functions such as planning, which is more impaired in PD-D than Alzheimer's disease. Moreover, impairment of visuospatial function occurred more frequently in PD-MCI than aMCI cases, and thus, it may predict the developing state of PD-D.

5.7.5 Stroke

The utility of the CDT for localizing vascular brain lesions was explored by Suhr et al. [78] in a sample of 76 stroke patients and 71 normal controls. In addition to comparing six quantitative scoring systems, the study also assessed the discriminative ability of a number of qualitative aspects of CDT performance using Rouleau et al.'s scoring protocol [8]. The authors hypothesized that the qualitative aspects of the CDT would be more useful than quantitative scores in discriminating among patients with respect to lesion location. The results found that, indeed, no significant differences emerged between various lesion groups when using quantitative scoring techniques in assessing localization of function. However, qualitative features of the CDT were found to discriminate between lesion locations. Specifically, right-hemisphere stroke patients displayed more graphic errors and impaired spatial planning compared to left-hemisphere stroke patients. This pattern of performance is consistent with the impaired visuospatial/visuoconstructional difficulties seen after right-hemisphere strokes. Also, subcortical patients showed more graphic errors compared to cortical patients, while cortical patients demonstrated more perseveration on qualitative assessments. This pattern of performance is similar to the findings of Rouleau et al. [8], who found graphic difficulties were more common in the subcortical dementias associated with Huntington's disease. The authors concluded that scoring the CDT qualitatively might provide useful additional information about the location of brain dysfunction, while adding little time and effort to the evaluation process.

Cooke et al. [79] explored the relationships between CDT performance following stroke and key clinical variables, including cognition, lateralization, and type of stroke. Their sample included 197 patients with stroke from 12 hospital and rehabilitation facilities. The results showed that MMSE [31] performance was strongly associated with performance on the CDT. The authors suggested that this relationship provided further corroboration of the validity and sensitivity of the CDT as a quick screening tool of cognitive impairment in the stroke population. As hypothesized by the authors, the location of the stroke (left or right cerebral hemisphere) demonstrated a significant relationship with the CDT. Approximately half of the patients with a right-hemisphere stroke had impaired clock drawings (54 %), whereas less than half of those with left-hemisphere stroke had impaired clock drawings (35.6 %). The right hemisphere controls the majority of cognitive and

perceptual functions that are responsible for executing the CDT [80], and visuospatial and visuoconstructional skills are predominantly affected following lesion to the right hemisphere [25]. Thus, it is expected that those with right-hemisphere stroke would have impaired CDT performance [79].

Freedman et al. [26] describe how the CDT can be used to assess and diagnose perceptual and cognitive impairments post-stroke due to the organization of the brain. For example, if all elements of the clock (circle, hands, and numbers) are present but distorted, then the lesion is more likely to be found in the right hemisphere and may be further localized to the posterior area of the right hemisphere where spatial organization skills are located. In contrast, a lesion in the left hemisphere may be indicated by sequential errors, such as writing the numbers in the correct sequence but in the counterclockwise direction [26].

5.7.6 Traumatic Brain Injury

De Guise et al. [15] examined the neuroanatomical correlates of the CDT in patients with different types and sites of injury sustained after traumatic brain injury (TBI). Patients were assessed in the context of a level 1 trauma center, and different types of injuries (epidural haematoma, subdural haematoma, subarachnoid hemorrhage, intraparenchymal haematoma, and brain edema) in different sites (frontal, temporal, parietal, occipital lobes, bilateral, and right or left hemisphere) were included. The authors anticipated that more impaired performance on the CDT would be associated with parietal injuries. The results showed that patients who sustained a traumatic subarachnoid hemorrhage, brain edema, and bilateral injury showed more deficits on the CDT. Errors made by these patients included difficulty producing the clock face and correctly placing the hands and in numbering the clock accurately. The authors found that traumatic subarachnoid hemorrhage, brain edema, and bilateral injuries interfere with CDT performance, likely because they are more diffuse and involve a combination of cerebral areas. Further analyses based on the sites of lesions confirmed the involvement of the parietal lobe in performance on the CDT. Specifically, a higher percentage of patients who sustained parietal lesions presented with more deficits in the drawing of the clock and in accurately producing numbers and hands. The authors concluded that the CDT can be used as a sensitive and reliable screening tool for detecting cognitive impairment in patients with TBI.

In response to the study by De Guise et al. [15], Frey and Arciniegas [18] noted that most (72.9 %) of the subjects in the De Guise study had frontal injuries. As a result, it is likely that performance problems in their sample are at least partially reflective of the effects of injury to the frontal and/or frontal white matter elements of CDT-relevant frontoparietal networks. Frey and Arciniegas suggested that, while parietal lesions might exert an additional adverse effect on the function of those networks, confirming the presence of such an effect necessitates controlling for the effects of frontal and/or white matter lesions on CDT performance. After reanalyzing the data presented by De Guise et al. using one-tailed hypothesis testing, Frey

and Arciniegas demonstrated that significant effects on CDT performance are not limited to parietal injuries. Moreover, Frey and Arciniegas stressed that any predictive model of CDT total score using neuroanatomical variables requires the inclusion of frontal, temporal, and parietal lesions [18]. Thus, while it is clear that the CDT may be a viable tool for discriminating between lesion locations in TBI patients, there remains a need for additional research with greater refinement of the concepts and methods employed.

The executive clock drawing tasks (CLOX 1 and 2) were examined by Writer et al. [81] for their ability to predict functional impairment in a sample of patients with combat-related mild traumatic brain injury and comorbid post-traumatic stress disorder (PTSD). Functional impairment was assessed using the structured assessment of independent living skills (SAILS). The SAILS assesses instrumental activities of daily living and measures both competency (performance ability and accuracy) and efficiency (time to completion) [82]. Pilot findings reported by the authors found CLOX 1-defined executive functioning correlated well with SAILS-defined functional competency and efficiency. Moreover, CLOX 1 performance contributed variance independent of comorbid PTSD anxiety symptom burden or other potentially confounding subject and injury characteristics. These findings suggest that the CLOX can discriminate between those with high versus low performance-based functional status scores in patients with mild TBI. However, the authors acknowledge that these results need to be interpreted with caution due to the low sample size used ($n = 15$) [81].

5.7.7 Schizophrenia

Herrmann et al. [83] compared 24 patients with schizophrenia to 24 healthy, age-matched controls on clock drawing, copying, and reading. Patients all met DSM-IV [84] criteria for schizophrenia with diagnoses made by a psychiatrist. Participants' cognition was assessed using the MMSE [31], and symptom severity was documented with the Brief Psychiatric Rating Scale (BPRS) [85]. Clock tasks were scored according to the method described by Freedman et al. [26]. The authors found that schizophrenic patients performed worse than controls on clock drawing and copying, but showed no differences on the reading task, even though both groups had similar scores on the MMSE. They speculated that the CDT may be more sensitive to cognitive impairment in schizophrenics than the MMSE, given the latter's lack of sensitivity to frontal system dysfunction. Furthermore, since performance on the CDT was significantly affected by scores on the BPRS, it has been suggested that the clock tasks might be measuring state-associated impairment (related to symptom severity) rather than trait-associated changes (related to the inherent neurocognitive deficit of the illness per se) [83]. The authors also suggested that the examination of specific errors made on the CDT may shed some light on the deficits displayed. Specifically, compared with controls, the patients with schizophrenia made most errors on placing and spacing the numbers on the free-drawn

and pre-drawn clocks. These errors may reflect impairment in frontal visual-spatial function as these errors may be related to attention and strategy formation rather than to vision and topography. The relatively normal clock reading in schizophrenic patients may reflect sparing of the posterior regions that mediate reading in general [86]. The authors concluded that, while the role of clock drawing and copying in schizophrenia requires further study, the easily administered CDT may prove useful in monitoring changes in cognition, possibly associated with symptom severity. The CDT may also help to document positive or negative changes in cognition associated with the use of antipsychotic medications.

5.8 Cultural, Ethnic, and Educational Considerations

As with any cognitive screening tool, the characteristics of the subject population (i.e. language, cultural background, level of education) can influence the validity of the CDT. Numerous studies have examined the effect of such variables, with particular attention being paid to the influence of level of education. To date, the results have been contradictory, with some studies finding a link between such variables and CDT performance and others finding no correlation.

Sugawara et al. [3] sought to develop normative data for the CDT for the Japanese community-dwelling population using Freedman's scoring protocol [26]. The CDT and MMSE were administered to 873 volunteers aged 30–79 years old (36.8 % males) who participated in the Iwaki Health Promotion Project in 2008. The authors found gender differences in the free-drawn condition in both nonparametric and multiple regression analyses. Specifically, female CDT scores were higher than those of males. The authors noted, however, that the results of previous research examining gender differences in CDT performance were controversial, with some supporting an influence of gender [87, 88] and others finding no differences [56]. In all conditions that were tested in this study, subjects 60 years of age and older showed either significant decreases in CDT scores or a decreasing trend in performance. Interestingly, the authors only found an influence of education on CDT scores in females 60 years of age and older in the free-drawn condition. This finding is in contrast to results published by Yamamoto et al. [60], who also studied CDT performance in the Japanese population but found CDT scores to be independent of years of education. The authors noted, however, that most participants included in the study (96.8 %) had received 9 or more years of education. Thus, it is possible that the high level of literacy in their subjects may have precluded their study from finding strong educational differences in CDT scores [3].

Kim and Chey [1] investigated CDT performance of 240 non-demented elderly Korean individuals with a wide range of education levels and 28 patients with mild dementia of the Alzheimer's type (DAT). They found that literacy and education of patients significantly influenced the CDT performance in the sample, in that older people with lower education had lower CDT scores and wider range of performance. These effects were most dramatic in the illiterate individuals. Moreover, illiterate

and/or uneducated older persons made conceptual errors similar to those of the DAT patients. Conceptual deficits observed in the DAT patients have been interpreted as stemming from the loss of semantic association evoked by the word "clock" and the graphic representation of a clock [8]. However, Kim and Chey [1] found that misrepresentation of the clock was mostly observed in the uneducated participants from both the normative groups and the DAT group. The authors speculated that the conceptual errors made by an uneducated normal individual are likely to be due to poor development of the representation of a clock or time on a clock face, which are based on numeracy and abstract thinking. Thus, even though semantic association or representation may be intact, the necessary constructional skills may be poorly developed in uneducated people as well. The authors concluded that the CDT performance in older people who are either illiterate or with 6 or less years of education should be interpreted with caution [1].

The correlation of the MMSE and the CDT was explored by Fuzikawa et al. [89] using Shulman's method [2] in a sample of elderly Brazilian adults with very low levels of formal education. Participants were recruited from Bambui, a town of 15,000 inhabitants in southeast Brazil. The median schooling level of the sample was 2 years. The authors found that the correlation between the MMSE and CDT was moderate (ρ (rho) = 0.64) in the sample of older adults with very low formal education, and no differences were found according to gender, age, or schooling level. Specifically, higher CDT scores were associated with higher MMSE scores, whereas lower CDT scores corresponded to a wider range of MMSE scores. Thus, it appears that in this population with very low education, the majority of subjects who perform well on the CDT could be expected to obtain a high MMSE score. Therefore, if an individual was able to draw a good clock despite having a low level of education, this could indicate adequate cognitive function that is reflected by high scores on the MMSE. In contrast, a low CDT score in this population would not allow suppositions about the MMSE score but would suggest the need for further assessment and/or investigations. The results of this study suggest that the CDT may be very practical in developing counties, where resources are limited and low education among the elderly is common.

Borson et al. [90] proposed that telling time by clock face is familiar across all major cultures and civilizations, whereas the more abstract figure copying seen in the MMSE intersecting pentagons task is a skill that is more familiar to those educated in developed countries. They argued that the task of drawing a clock "from scratch" requires the use of multiple cognitive abilities from a wide range of cerebral regions. While this feature is ideal for a cognitive screening instrument, it is not common across all screening and visuospatial copying tasks. The "diffuse" CDT task is thus ideal for cognitive screening purposes as it elicits a number of cognitive abilities, including long-term memory and information retrieval, auditory comprehension, visuospatial representation, visual perceptive and visual motor skills, global and hemispheric attention, simultaneous processing, and executive functions [40].

In an earlier study, Silverstone et al. [91] described the usefulness of the CDT in a sample of 18 Russian immigrants who were unable to speak English. CDT screening identified abnormal scores in four of the participants, and follow-up with these

patients' families confirmed a diagnosis of progressive cognitive loss and dementia. The authors suggested that the CDT is a useful screening tool when language is a serious barrier to cognitive testing.

5.9 Conclusion

In this chapter, a wide range of CDT scoring and administration methods were presented, and it appears as though the simpler the scoring system, the better for most clinical settings as the more complicated and lengthy scoring systems do not appear to add significant value to the clinical utility of the test. In terms of simplicity, the four-point system used by the Consortium to Establish a Registry for Alzheimer's Disease (CERAD) seems optimal [90]. However, when examining the utility of the CDT scoring systems for screening for MCI, Ehreke et al. [62] found that while significant differences were observed between MCI subjects and normal controls, no scoring method produced sensitivity and specificity values high enough to conclude that the CDT, as currently administered, is a good screening instrument for MCI. However, they suggested that the clinical utility could be improved by including a semi-quantitative and wider scoring range that places more focus on the clock's hands and number placement. Thus, it appears that in some situations, an overly simplified scoring system may limit the utility of the CDT. With this in mind, it falls to the clinician to decide what level of detail they wish to extract when deciding which scoring protocol to apply.

The CDT appears to have achieved widespread clinical utilization, albeit with inconsistent approaches to scoring and interpretation. The CDT is well accepted by clinicians and patients due to its ease of use and short administration time. The recent literature reflects increasing interest and focus on this test as a quick screening tool for cognitive impairment. Moreover, conclusions from studies examining its utility in various populations of patients are predominantly positive. As a screening instrument, it can also provide an easy to administer and valuable baseline from which to monitor cognition over time. Available evidence suggests that the CDT, used in conjunction with other brief validated cognitive tests and informant reports, should provide a significant advance in the early detection of dementia [2].

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Chapter 6
Montreal Cognitive Assessment (MoCA): Concept and Clinical Review

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Abstract The Montreal Cognitive Assessment (MoCA) is a cognitive screening instrument developed to detect mild cognitive impairment (MCI). It is a simple 10 minute paper and pencil test that assesses multiple cognitive domains including memory, language, executive functions, visuospatial skills, calculation, abstraction, attention, concentration, and orientation. Its validity has been established to detect mild cognitive impairment in patients with Alzheimer's disease and other pathologies in cognitively impaired subjects who scored in the normal range on the MMSE. MoCA's sensitivity and specificity to detect subjects with MCI due to Alzheimer's disease and distinguish them from healthy controls are excellent. MoCA is also sensitive to detect cognitive impairment in cerebrovascular disease and Parkinson's disease, Huntington's disease, brain tumors, systemic lupus erythematosus, substance use disorders, idiopathic rapid eye movement sleep behaviour disorder, obstructive sleep apnoea, risk of falling, rehabilitation outcome, and epilepsy. There are several features in MoCA's design that likely explain its superior sensitivity for detecting MCI. The MoCA's memory testing involves more words, fewer learning trials, and a longer delay before recall than the MMSE. Executive functions, higher-level language abilities, and complex visuospatial processing can also be mildly impaired in MCI participants of various etiologies and are assessed by the MoCA

with more numerous and demanding tasks than the MMSE. MoCA was developed in a memory clinic setting and normed in a highly educated population. Norms in lesser educated, community based, multi-cultural samples will hopefully be available to help first line healthcare providers better assess subjects presenting with cognitive complaints. The MoCA is freely accessible for clinical and educational purposes (www.mocatest.org), and is available in 36 languages and dialects.

Keywords Montreal Cognitive Assessment (MoCA) • Alzheimer's disease • Mild cognitive impairment • Vascular cognitive impairment • Dementia

6.1 Introduction

The Montreal Cognitive Assessment (MoCA) was developed as a brief screening instrument to detect Mild Cognitive Impairment [1]. It is a paper-and-pencil tool that requires approximately 10 minutes to administer, and is scored out of 30 points. The MoCA assesses multiple cognitive domains including attention, concentration, executive functions, memory, language, visuospatial skills, abstraction, calculation and orientation. It is widely used around the world and is translated to 36 languages and dialects. The test and instructions are freely available on the MoCA official website at www.mocatest.org. No permission is required for clinical or educational use.

This chapter will describe how each MoCA sub-test/domain, assesses various neuro-anatomical areas, and often overlapping cognitive functions. A comprehensive review of studies using the MoCA in multiple clinical settings and populations is provided. An algorithm for using the MoCA in clinical practice is suggested. In conclusion, MoCA limitations, future research and developments are discussed.

6.2 Cognitive Domains Assessed by the MoCA

6.2.1 Visuospatial/Executive

6.2.1.1 Modified Trail Making Test

Beside visuomotor and visuoperceptual skills, the trail making test–B (TMT-B) requires mental flexibility to shift between numbers and letters which mainly rely on frontal lobe function [2–5]. In functional Magnetic Resonance Imaging (fMRI) studies, shifting ability in the TMT-B revealed greater activation relative to the trail making test A in the left dorsolateral and medial frontal cortices, right inferior and

middle frontal cortices, right precentral gyrus, left angular and middle temporal gyri, and bilateral intraparietal sulci [6–8]. A study of patients with frontal and non-frontal lobe lesions reported that all patients who had more than one error in the TMT-B had frontal lobe lesions. Specifically, patients with damage in the dorsolateral frontal area were mostly impaired [9]. Left frontal damage tended to cause more impairment than controls and right frontal damage groups, either for execution time or number of errors [10]. Nonetheless, specificity of the TMT-B to frontal lobe lesions is debated as one study reported comparable performance between frontal and non-frontal stroke patients [11].

6.2.1.2 Copy of the Cube

To copy a cube, subjects have to initially convert a two-dimensional contour to a three-dimensional cube. This ability is enhanced by learning experiences [12, 13]. After spatial planning, visuomotor coordination also plays a role in copying the cube. Various brain areas are involved; visual perception in the parieto-occipital lobe, planning in the frontal lobe, and integration of visual and fine motor sequences in the fronto-parieto-occipital cortices.

The cognitive mechanisms underlying performance in copying a figure are different according to the underlying disease. Alzheimer's disease (AD) patients with spatial perception/attention impairment had significant atrophy in the right parietal cortex. Complex two-dimensional figure copy was negatively associated with degree of right inferior temporal atrophy and reduction of cerebral blood flow in the right parietal cortex [14, 15]. Patients with behavioral variant fronto-temporal dementia with spatial planning and working memory dysfunction had significant atrophy in the right dorsolateral prefrontal cortex [16]. A correlation between neuro-imaging and cube copying specifically has not yet been reported.

Even though a high proportion of either normal subjects (40 %) or Alzheimer patients (76 %) performed poorly on cube drawing on verbal command, persistent failure to copy a cube from a previously drawn cube is highly discriminative to detect patients with Alzheimer's disease [17]. Less educated, older age, female and depressed subjects performed poorly in drawing-to-command and copying conditions.

6.2.1.3 The Clock Drawing Test

The Clock Drawing Test (CDT) has been widely used and studied for detection of dementia and mild cognitive impairment (see Chap. 5). Planning, conceptualization, and symbolic representation are involved in drawing a clock's face and in placing all the numbers correctly [18, 19]. Inhibitory response is required when placing each hand to tell the time of "ten past eleven". Self-initiated-clock-drawing also requires intact visuoconstructive skills which are mainly represented in the parietal lobe.

In volunteers, fMRI demonstrated bilateral activation of the posterior parietal cortex and the dorsal premotor area during task performance suggesting the contribution of the parieto-frontal cortical networks to integrate visuospatial elements and motor control in self-initiated clock drawing [20].

In AD patients, errors in CDT were mainly conceptual and due to semantic memory impairment [21–23]. This was supported by various neuroimaging studies that found negative correlation between CDT performance and atrophy of the right/left temporal cortices [24, 25], atrophy of the medial temporal lobe [23], reduction in the activation of the left superior parietal lobe [26], and hypometabolism of the right parietal cortex [27] in patients with cognitive impairment caused by AD pathology.

White matter hyperintensities (WMH) are also related to performance on CDT [23]. Patients with severe WMH and patients with Parkinson's disease (PD) performed poorly and similarly on all subscales of CDT [28]. Even though both groups were different in terms of neuropathology, they both have disrupted subcortico-frontal pathways. PD affects the subcortical dopaminergic pathway projecting to the prefrontal cortex [28, 29].

The scoring criteria for the CDT in the MoCA have been simplified to decrease scoring complexity, scoring time, and minimize inter rater variability.

Despite the simpler scoring instructions, suboptimal inter and intra-rater reliability for MoCA's CDT were recently reported [30]. CDT may be influenced by literacy status and education level [21, 31, 32].

6.2.2 Naming

The three animals in the MoCA (Lion, Rhinoceros and Camel) are infrequently seen in Western and even in Asian countries. The failure to name these animals may point to various types of cognitive impairment. If subjects cannot name but can give contextual information about the animal, for example, "It lives in the desert (Camel)", this could suggest either word finding difficulty or semantic memory impairment. If subjects cannot tell both the name and the context, they may have impaired visuoperceptual skills with inability to recognize the animal (failure in the cube copy and the CDT can support this possibility). They may also be impaired in both visuoperception and semantic memory such as in moderate to severe AD or advanced PD with dementia. Low education or cultural exposition to such animals can also be responsible.

In AD, impairment tends to reflect a breakdown in semantic processes which is different from visuoperceptual deficits caused by subcortical dementia such as Huntington's disease (HD) [33, 34]. Some studies have shown that semantic dysfunction is the primary cause of misnaming in both cortical or subcortical dementia [35, 36].

The neuronal network involved in naming is category-dependent [37–41]. In healthy subjects, the commonly activated regions were bilateral occipital lobes including the fusiform gyri, and pars triangularis of the left inferior frontal gyrus [38–40]. This activation pattern may be explained by processing of visual features and shape analysis in the primary visual cortex and fusiform gyri, and the subsequent retrieval process from semantic and conceptual knowledge of animals mediated by the pars triangularis of the left inferior frontal gyrus [40, 42]. Interestingly, animal naming was also associated with activation of the frontal regions linked to the limbic emotional system, namely the left supplementary motor area and the anterior cingulate gyrus [38, 39]. It has also been shown that animal naming is more associated with primary visual cortex activation than naming of tools which is associated with frontal and parietal lobe activation (premotor cortex and postcentral parietal cortex) [38].

6.2.3 Attention

6.2.3.1 The Digit Span

Digit Span Forward (DSF) measures retention of auditory stimuli and articulatory rehearsal. Digit span backward (DSB) requires working memory, and a more demanding ability in transforming digits into a reversed order before articulating. This extra-step requires central executive processing [43].

Neuronal networks involved in digit span processing have been shown in many neuroimaging studies. In healthy subjects, using near-infrared spectroscopy (NIRS) a relationship between activation of the right dorsolateral prefrontal cortex and performance on DSB was observed [44]. Other studies have shown greater activation of the bilateral dorsolateral prefrontal cortices, prefrontal cortex and left occipital visual regions for DSB compared to DSF [43–46]. These findings confirm the need for executive function to complete the DSB task. Activation of the visual cortex during DSB supports the hypothesis that visuospatial processing may be involved during mental reversal imaging of digit sequences [44, 45].

Amnestic Mild Cognitive Impairment (MCI) and AD patients performed poorly on both tasks compared with normal controls [47–49]. PD patients with amnestic MCI had some impairment in DSB, but not DSF [50]. Early impairment of executive function caused by subcortico-frontal dopaminergic dysfunction explains the isolated poor performance on DSB among PD patients. At the cutoff <3 digits, the sensitivity and specificity of DSB in detection of major cognitive disorders (including dementia, delirium and cognitive impairment not otherwise specified) are 77 and 78 %, respectively [51]. With the same cutoff, DSB can detect 81 % of the delirium patients, however, with false positive rate of 37 % [51]. Moreover, impaired digit span in elderly subjects with subjective memory complaints is a predictor for the conversion from subjective memory complaints to mild cognitive impairment [52].

6.2.3.2 Concentration and Calculation: Letter A Tapping Test

In this test the subject listens and taps when the letter A is read out among a series of other letters. Concentration, which is defined as sustained and focused attention, is the primary function required for proper identification of the letter A and inhibition of inappropriate non-letter A tapping. It has good sensitivity to detect cognitive impairment in mild traumatic brain injury and persistent post-concussion syndrome [53, 54]. Speed of response to externally-paced stimuli accounts for this test's sensitivity [54]. This task has not been well studied in neurodegenerative diseases. In the MoCA validation study, MCI subjects and Normal Controls had comparable normal performance, however, AD subjects were significantly more impaired on this task [1].

6.2.3.3 Concentration and Calculation: Serial 7 Subtractions

Calculation is an essential part of everyday social and living activities. In normal subjects, bilateral parietal and prefrontal cortices have been reported to be consistently activated during mental calculation, along with left inferior frontal lobe and angular gyrus activation [55–59]. Some studies suggest that the linguistic representation and visuospatial imagery also play a role in mental calculation [56, 60]. Specific to serial 7 subtraction, fMRI studies have reported similar greater activation in the bilateral premotor, the posterior parietal and the prefrontal cortices when normal participants performed this task compared with the control condition [61]. The prefrontal cortex activation is associated with working memory which is required to maintain the previous answer in a loop for further subtractions.

In AD patients, a reduction of fMRI activation or PET glucose metabolism in the inferior parietal cortex was observed during mental calculation [55, 62]. Some studies also reported a reduction in activation in the bilateral lateral prefrontal cortices [55], and the left inferior temporal gyrus [62]. These hypofunctional areas are the same as the ones reported being significantly activated in normal subjects.

6.2.4 Language

6.2.4.1 Sentence Repetition

Sentence repetition assesses language skills which are supported by left temporo-parieto-frontal circuit. Repeating complex sentences also requires attention and concentration to memorize the words which are supported by working memory systems in the frontal lobes [63]. AD patients had lower scores on this task compared with normal subjects [1, 63, 64]. Education also plays a role in sentence repetition, and interpretation of the results should take into consideration subjects' education level [65].

6.2.4.2 Letter F Fluency

Verbal fluency is divided into phonemic (letter) and semantic (category) fluency. Letter F fluency in the MoCA mainly depends on frontal lobe function compared with semantic fluency, which is sustained by both temporal and frontal lobes. Letter F fluency requires coordination of lexico-semantic knowledge, shifting from word to word, working memory, searching strategy and inhibition of irrelevant words which all highly depend on frontal lobe function and to a lesser extent the temporal lobe.

Patients with frontal lesions produced fewer words than healthy controls [66–69]. Left frontal lesions play a greater role in letter fluency impairment than right frontal lesions [66, 69, 70]. However, specificity of the frontal lobe dysfunction to letter fluency impairment is still debated as patients with non-frontal left hemisphere lesions also performed worse than patients with right hemisphere frontal and non-frontal lesions [69].

Neuroimaging studies indicate that letter fluency activates a variety of frontal (left dorsolateral prefrontal cortex, left inferior frontal gyrus, supplementary motor area) and non-frontal areas (anterior cingulate cortex, bilateral temporal and parietal lobes) [71–73]. Both lesional and neuroimaging studies suggest high sensitivity of the test, but low specificity, to detect frontal lobe dysfunction [74]. Low specificity may partly depend on education level and literacy status, as this task requires grapheme-phoneme correspondence. Lower educated and illiterate subjects generate fewer words than subjects with higher education [75–77]. Since letters do not exist in certain languages, letter fluency was replaced by semantic fluency (animal naming) for languages such as Chinese, Korean, in the MoCA test [78, 79].

As phonemic fluency is highly associated with frontal executive function, pathologies affecting frontal lobe or fronto-subcortical circuits, such as in PD and HD patients, frequently impair this function more than lesions of the temporo-parietal lobe which are associated with storage of lexicosemantic knowledge [50, 80–82]. In contrast, patients with Alzheimer's pathology will more likely have semantic fluency impairment early in the course of their disease [83]. Patients with depression have also impaired phonemic fluency as a result of probable overall global cognitive slowing [84].

6.2.5 Abstraction

Similarity between objects requires semantic knowledge and conceptual thinking. In right-handed subjects, the left perisylvian glucose metabolism was closely associated with performance on the Wechsler Similarities Test (WST) [59]. On PET imaging, the metabolic reduction in the left temporal lobe and left angular gyrus of Alzheimer's disease patients correlates with impairment on test for similarities [85]. Frontal executive function and the parieto-temporal semantic knowledge may be

involved in this task for more difficult and demanding word pairs [85]. AD and Huntington's disease patients performed poorly on the WST compared to normal controls. Patients with frontotemporal dementia have more deficits than AD patients in the similarities subtest of the Frontal Assessment Battery when controlled for MMSE level [86]. Moreover, performance decline in the WST is predictive of AD conversion in non-demented participants [87].

6.2.6 *Delayed Recall*

More words to recall (5 versus 3), less learning trials (2 versus up to 6), and more time between immediate recall and delayed recall (5 versus 2 min) probably explains MoCA's superior sensitivity for amnestic MCI detection compared to the MMSE. In the first MoCA validation study, MCI patients recalled on average 1.17 words out of 5, while normal controls recalled 3.73 words [1].

Category and multiple choice cues provide useful information to distinguish encoding memory impairment, which does not improve with cueing, from retrieval memory impairment that does improve with cueing.

Retrieval memory impairment may be associated with medial parietal and frontal white matter loss [88], posterior cingulate hypometabolism [89], pathologies affecting subcortical structures [90] and the hippocampo-parieto-frontal network [88]. Retrieval memory deficits are seen in pathologies affecting sub-cortical structures such as Vascular Cognitive Impairment [91, 92], Parkinson's disease [93], and Huntington's disease [94, 95]. However, the retrieval deficit hypothesis of PD-related memory impairment has been debated, as some studies have shown that even given cues, PD patients still had impairment in recognition [96, 97]. Retrieval memory deficits can also be seen in depression [98, 99], frontotemporal dementia [100, 101], normal pressure hydrocephalus [102], and HIV cognitive impairment [103, 104].

Encoding memory impairment correlates with hippocampal atrophy and hypometabolism [88, 89, 105]. AD patients typically perform poorly on delayed free recall without improvement after cueing, and also have higher rates of intrusion compared with PD and HD patients [106]. Encoding memory deficits are also seen in Wernicke and Korsakoff syndromes, strategically located ischemic or hemorrhagic strokes or tumors that affect the Papez circuit (hippocampus, fornix, mamillary bodies, thalamus, and cingulate cortex), and post surgical excision of the medial temporal lobes for epilepsy control, as first described in patient HM by Milner [107–109].

6.2.7 *Orientation*

Impairment in orientation has been shown to be the single best independent predictor of daily functions in patients with dementia, and is also associated with caregiver

burden and psychological distress [110, 111]. Temporal orientation yields high sensitivity in detection of dementia and patients with delirium. Errors in identifying the date has the highest sensitivity (95 %), but also lowest specificity (38 %) [112]. Identification of the year or month was suggested to detect cognitively impaired subjects with optimal validity [112]. However, orientation is not a good indicator to detect milder stages of cognitive impairment [1]. Temporal orientation can also predict overall cognitive decline over time [113]. Moreover, patients with temporal disorientation tend to be impaired on verbal memory as well [114]. Orientation to place is not discriminative in milder stages of cognitive impairment and dementia, but may be able to detect very severe cognitive impairment which is also obvious without cognitive screening.

6.3 MoCA Development and Validation

The MoCA (Copyright: Z. Nasreddine M.D.) was developed based on the clinical intuition of one of the authors of the validation study (ZN) regarding domains of impairment commonly encountered in MCI and best adapted to a screening test [1]. An initial version covered ten cognitive domains using rapid, sensitive, and easy-to-administer cognitive tasks. Iterative modification of the MoCA took place over 5 years of clinical use. An initial test version was administered to 46 consecutive patients (mostly diagnosed with MCI or AD) presenting to the Neuro Rive-Sud (NRS) community memory clinic with cognitive complaints, a MMSE score of 24 or higher, and impaired neuropsychological assessment. They were compared with 46 healthy controls from the same community with normal neuropsychological performance. Five items did not discriminate well and were replaced. Scoring was then adjusted, giving increased weight to the most discriminant items. The final revised version of the MoCA (version 7.1) covers eight cognitive domains and underwent a validation study at the Neuro Rive-Sud (NRS) community memory clinic on the south-shore of Montreal and the Jewish General Hospital memory clinic in Montreal [1]. Participants were both English and French speaking subjects divided into three groups based on cognitive status; normal control ($n=90$), Mild Cognitive Impairment ($n=94$), and mild Alzheimer's disease ($n=93$). MoCA was administered to all groups, and its sensitivity and specificity were compared with those of the MMSE for detection of MCI and mild AD.

6.3.1 Optimal Cutoff Scores

Sensitivity was calculated separately for the MCI and AD groups. One point was added to the total MoCA score to correct for education effect for subjects with 12 years or less education. The MoCA exhibited excellent sensitivity in identifying MCI and AD (90 and 100 %, respectively). In contrast, the sensitivity of the MMSE

was poor (18 and 78 %, respectively). Specificity was defined as the percentage of NCs that scored at or above the cutoff score of 26. The MMSE had excellent specificity, correctly identifying 100 % of the NCs. The MoCA had very good to excellent specificity (87 %). When MMSE and MoCA scores were plotted together (Fig. 6.1), the large majority of NC participants scored in the normal range, and the large majority of AD patients scored in the abnormal range on both MMSE and MoCA. In contrast, 73 % of MCI participants scored in the abnormal range on the MoCA but in the normal range on the MMSE [1].

The test-retest reliability was 0.92. The internal consistency of the MoCA was good with a Cronbach alpha on the standardized items of 0.83 [1]. In addition, the positive and negative predictive values for the MoCA were excellent for MCI (89 and 91 %, respectively) and mild AD (89 and 100 %, respectively).

6.3.2 Recommendations

The Third Canadian Consensus Conference on the Diagnosis and Treatment of Dementia (CCCDTD3) recommended administering the MoCA to subjects suspected to be cognitively impaired who perform in the normal range on the MMSE [115]. Immediate and Delayed recall, Orientation, and letter F fluency subtest of the MoCA have been proposed by the National Institute for Neurological Disorders and Stroke (NINDS) and the Canadian Stroke Network (CSN) to be a 5-minute Vascular

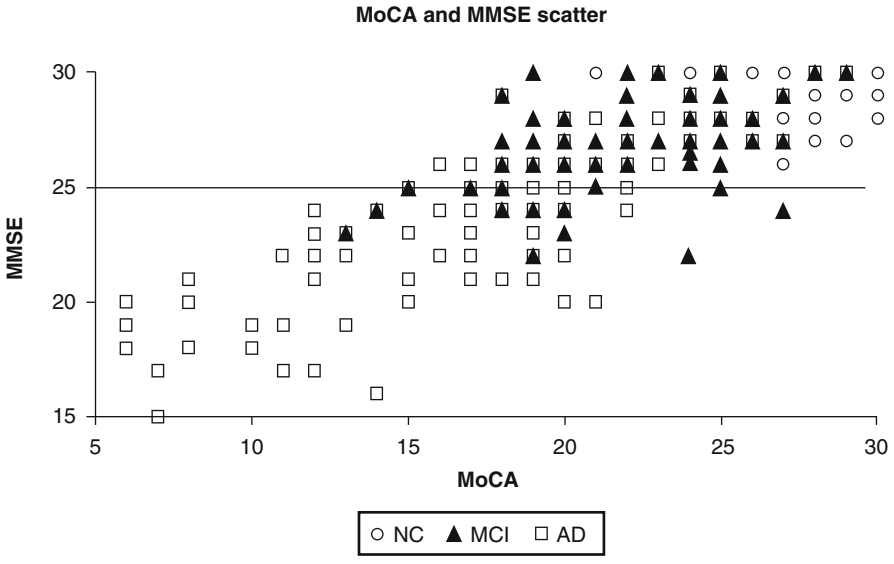

Fig. 6.1 Scatter plot of the Montreal Cognitive Assessment (*MoCA*) and the Mini-mental State Examination (*MMSE*) scores for normal controls (*NC*) and subjects with Mild Cognitive Impairment (*MCI*) and mild Alzheimer's disease (*AD*) (Reproduced with permission [1])

Cognitive Impairment screening test administrable by telephone [116]. The MoCA has also been recommended for MCI or dementia screening in review articles [117–119].

6.3.3 Practical Approach

It is important to emphasize that MoCA is a cognitive screening instrument and not a diagnostic tool, hence clinical judgment, based on thorough clinical evaluation, is important in interpreting MoCA test results and correctly diagnosing patients who present with cognitive complaints. Figure 6.2 illustrates a practical approach to evaluate patients with cognitive complaints. Patients presenting with cognitive complaints and no functional impairment in their activities of daily living (ADL) would be better assessed by the MoCA as first cognitive screening test. Subjects presenting with cognitive complaints and ADL impairment would probably be better assessed by the MMSE first, then the MoCA if the MMSE is in the normal range.

6.4 Demographic Effect on MoCA Performance

Originally a highly educated normative group was used, suggesting a correction of one added point for education of 12 years or less [1]. Subsequent studies locally in Montreal suggest to better adjust the MoCA for lower educated subjects, 2 points should be added to the total MoCA© score for subjects with 4–9 years of education, 1 point for 10–12 years of education [120]. Education has been consistently reported around the world affecting total MoCA scores [1, 78, 121–126]. Trail making test and digit span of the Japanese version of the MoCA significantly correlate with years of schooling [127]. The cube copy, semantic fluency (substitution of letter F fluency), abstraction, serial-7 subtraction and naming in the Korean version of the MoCA positively correlated with education [79]. There are many cutoff scores reported according to the level of education of the studied population. In general, studies recruiting a higher proportion of low educated subjects recommend lower cutoff scores for the education correction.

The MoCA has been shown to be age [78, 122, 124, 125] and gender independent [78, 122, 124–126]. However, in a large normative study in the USA, age negatively correlated with MoCA scores. Upon further analysis, age was a significant factor in MoCA scores mostly for less educated subjects [126] which could be explained by low cognitive reserve among less educated individuals which may result in lessened ability to recruit neuronal networks and compensate age-related cognitive changes. Moreover, lower educated subjects are known to have more vascular risk factors that could also impair their cognition [128].

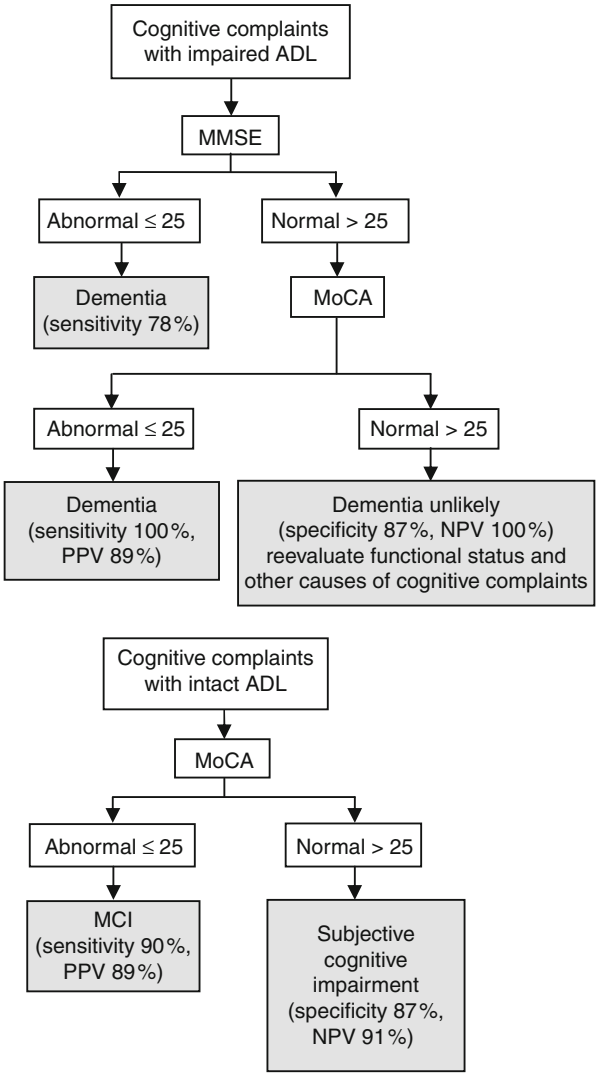

Fig. 6.2 Practical approach to evaluate patients who present with cognitive complaints. *ADL* Activities of Daily Living. *NPV* Negative Predictive Value, *PPV* Positive Predictive Value, *MCI* Mild Cognitive Impairment (Adapted from Nasreddine et al. [1])

6.5 Mild Cognitive Impairment (MCI) and Alzheimer's Disease (AD)

The MoCA has been extensively studied as a screening tool for detection of MCI and Alzheimer Disease (see Table 6.1; [1, 79, 121–123, 127, 129–137]). Sensitivity for MCI detection has been on average 86 % (range 77–96 %). Sensitivity to detect AD has been on average 97 % (range 88–100 %). Specificity, defined as correctly identifying normal controls, was on average 88 % (range 50–98 %). Table 6.1

Table 6.1 MoCA studies in MCI and AD

Author (year)	Language	Subjects (*n*)	Education (years)	Condition to be screened	Cutoff point	Sn	Sp	PPV	NPV
Nasreddine et al. (2005) [1]	English and French	277 NC 90, aMCI 94, AD 93	11.86	aMCI vs NC AD vs NC	25/26[a] 25/26[a]	0.90 1.00	0.87	0.89 0.89	0.91 1.00
Smith et al. (2007) [129]	English	67 MCC 12, MCI 23, Dem (AD 18, VaD 13, PDD 1)	12.1	MCI vs MCC Dem vs MCC	25/26[a]	0.83 0.94	0.50 0.50	–	–
Ng Hoi Yee (2008) [123]	Cantonese-Hong Kong	158 NC 74, aMCI 54, AD 30	5.37	aMCI vs NC	23/24[a]	0.79	0.75	0.70	0.83
Lee et al. (2008) [79]	Korean	196 NC 115, MCI 37, AD 44	8.03	MCI vs NC AD vs NC	22/23[a] 22/23[a]	0.89 0.98	0.84 0.84	0.65 0.70	0.96 0.99
Luis et al. (2009) [122]	English	118 NC 74, aMCI 24, AD 20	14.00	aMCI vs NC	23/24[a]	0.96	0.95	–	–
Rahman et al. (2009) [130]	Arabic	184 NC 90, MCI 94	High school (49 %)	MCI vs NC	25/26[a]	0.92	0.86	–	–
Tangwongchai et al. (2009) [131]	Thai	120 NC 40, MCI 40, AD 40	10.59	MCI vs NC AD vs NC	24/25[b] 21/22[b]	0.80 1.00	0.80 0.98	0.80 0.98	0.80 1.00
Duro et al. (2010) [132]	Portuguese	212 MCI 82, AD 70, ODD 60	≤4 ($n=117$)	MCI Dementia	25/26[a] 25/26[a]	Correctly identified 84.1 %[c] Correctly identified 100 %[c]			

Fujiwara et al. (2010) [127]	Japanese	96 NC 36, aMCI 30, AD 30	11.98	aMCI vs NC AD vs NC	25/26[a] 25/26[a]	0.93 1.00	0.89 0.89	0.88 0.88	0.94 1.00
Selekler et al. (2010) [133]	Turkish	205 NC 165, MCI 20, AD 20	11.59	MCI/AD vs NC	21/22[a]	0.81	0.78	0.46	0.95
Larner (2012) [134]	English	150 NC 85, MCI 29, Dem 36	–	MCI/Dem vs NC	25/26[a]	0.97	0.60	0.65	0.96
Zhao et al. (2011) [121]	Chinese	300 NC 150, aMCI 150	5–12 years (97 %)	aMCI vs NC	23/24[a]	0.77	0.90	–	–
Karunaratne et al. (2011) [135]	Sinhala	98 NC 49, AD 49	10.34	AD vs NC	23/24[a]	0.98	0.80	–	–
Damian et al. (2011) [136]	English	135 Cognitively normal 89, Cognitively impaired 46	15.30	Normal vs impaired	23/24[a]	0.87	0.75	0.38–0.54	0.95–0.97
Freitas et al. (2012) [137]	Portuguese	360 NC 180, MCI 90, AD 90	6.38	MCI vs NC AD vs NC	21/22[a] 16/17[a]	0.81 0.88	0.77 0.98	– –	– –

AD Alzheimer's disease, *aMCI* amnestic mild cognitive impairment, *Dem* dementia, *MCC* Memory Clinic Controls with other diagnosis than dementia, *NC* normal controls, *ODD* other dementia diseases, *Sn* sensitivity, *Sp* specificity, *PPV* positive predictive value, *NPV* negative predictive value

[a]One additional point for subjects who have ≤12 years of education

[b]One additional point for subjects who have ≤6 years of education

[c]Validity cannot be fully assessed due to lack of normal control group

summarizes the MoCA validation in MCI and AD in diverse populations and languages. Variability in sensitivity and specificity is explainable by differences in selection criteria for normal controls, diagnostic criteria for MCI and AD, community or memory clinic setting, confirmation with neuropsychological battery, age and education levels, and possibly linguistic and cultural factors.

6.6 Vascular Cognitive Impairment (VCI)

Multiple studies have addressed the usefulness of the MoCA in Vascular Cognitive Impairment (See Table 6.2; [78, 124, 138–149]).

6.6.1 Asymptomatic Cerebrovascular Disease Patients with Vascular Risk Factors

The MoCA has been shown to detect cognitive decline in asymptomatic subjects with hypertension alone, or thickening of the carotid artery wall, or multiple vascular risk factors [138, 139]. Cognitive decline was also detected in subjects with transient ischaemic attack (TIA) or first ever stroke if they had more than two vascular risk factors or low cerebral perfusion on transcranial Doppler ultrasound [138, 139]. MoCA also correlated with the Framingham coronary and stroke risk scores [150].

Advanced internal carotid artery stenosis (>70 %) occlusion is also negatively correlated with MoCA but not MMSE scores in asymptomatic subjects [141, 142].

Subtle cognitive impairment among subjects from cardiac and diabetic/endocrine outpatient clinics of a tertiary-referral hospital were detected using the MoCA with sensitivity of 83–100 %, but with lower specificity of 50–52 % [148].

6.6.2 Symptomatic Cerebrovascular Disease

6.6.2.1 Cognitive Impairment Post-stroke or TIA

The MoCA has been shown to detect cognitive impairment in 65 % of subjects 3 months post-stroke [145]. Also 30–58 % of subjects with TIA or stroke who were considered normal on the MMSE scored below the normal cut-off on the MoCA ranging from 14 days to up to 5 years after the event [143, 144]. Table 6.2 summarises studies of the MoCA for vascular cognitive impairment. Another study, using neuropsychological assessment as gold standard, found that MoCA had a sensitivity of 67 %, and a specificity of 90 % for detection of cognitive impairment post acute stroke [147]. In this study, the neuropsychological battery was not

Table 6.2 MoCA studies in vascular cognitive impairment

Author (year) MoCA language	Objective of study	Subject (*n*) Measurement	Results
Martinić-Popović (2006, [138]; 2007, [139]) Croatian	To assess subtle cognitive decline in patients with first ever cerebrovascular disease (CVD) and in subjects without CVD symptoms but with CVD risk factors (CV-RF)	CVD ($n=81$ [138] and 110 [139]) CV-RF ($n=45$) MoCA and MMSE	The MoCA provided superior sensitivity than the MMSE in detection of MCI in CVD and CV-RF patients
Wong et al. (2008) [140] Cantonese-Hong Kong	To assess the validity of the MoCA in detection of white matter lesions (WML)	NC 33, WML 33 MoCA	At the cutoff 21/22, the sensitivity and specificity to detect WML are 0.82 and 0.73, respectively. The PPV and NPV are 0.80 and 0.75, respectively
Wong et al. (2009) [78] Cantonese-Hong Kong	To assess the validity of the MoCA in detection of small vessel disease (SVD)	NC 40, SVD 40 MoCA	At the cutoff 21/22[a], the sensitivity and specificity to detect SVD are 0.73 and 0.75, respectively. The PPV and NPV are 0.74 and 0.73, respectively
Martinić-Popović (2009 [141]; 2011 [142]) Croatian	To assess MCI in patients with asymptomatic advanced internal carotid artery stenosis (ICS)	asymptomatic ICS ($n=26$ [141] and 70 [142]) MoCA and MMSE	The MoCA proved to be a more sensitive tool than the MMSE for assessment of MCI in stroke-free patients with advanced ICS whose decline was most pronounced in the visuospatial/executive, delayed recall and abstraction subtest of the MoCA

(continued)

Table 6.2 (continued)

Author (year)		Subject (*n*)	
MoCA language	Objective of study	Measurement	Results
Dong (2010) [143] English, Chinese, Malay	To assess cognitive impairment in acute post-stroke patients (mean 4.2 ± 2.4 days post-stroke)	Stable post-stroke patients (*n* = 100) MoCA and MMSE	32 % of the normal MMSE (>24) patients were defined as cognitively impaired patients by the MoCA (≤21) The visuospatial/executive function, attention and delayed recall subtest of the MoCA provided a good discriminative power
Pendlebury (2010) [144] English	To assess cognitive impairment in 6-month and 5-year post-stroke patients	Stable TIA/stroke patients (*n* = 413) MoCA& MMSE	57 % of patients with normal MMSE (≥27) had abnormal MoCA (<26) which were associated with deficits in the delayed recall, abstraction, visuospatial/executive function, and sustained attention subtest of the MoCA
Cumming (2011) [145] English	To assess the feasibility of the MoCA as a global cognitive screening tool in stroke trials	3-month post-stroke patients (*n* = 294) MoCA	Of those surviving to 3 months, the MoCA was completed by 80 % of the patients. A majority of patients with stroke (65 %) were considered as cognitive impairment according to the MoCA cutoff scores <26
Harkness (2011) [146] English	To assess MCI in patients with heart failure (HF) aged 65 years or more	HF (*n* = 44) MoCA	More than 70 % of patients scored <26 on the MoCA, suggesting MCI, had significant deficits in the delayed recall, visuospatial/executive function, and language compared with the patients who scored ≥26
Godefroy et al. (2011) [147] French	To assess the validity of the MoCA in detection of cognitive impairment in post-stroke patients	Infarct (*n* = 88), Hemorrhage (*n* = 7) MoCA, MMSE	Using the adjusted score with cutoff 20/21[b], the MoCA provided good sensitivity and specificity of 0.67 and 0.90, respectively, to detect of post-stroke cognitive impairment with the PPV of 0.93 and NPV of 0.57

McLennan et al. (2011) [148] English	To assess the validity of the MoCA in detection of MCI in patients with CVD and CV-RF	CVD and risk factors ($n=110$) MoCA	At cutoff 23/24[c], the MoCA sensitivity to detect aMCI and mMCI are 1.00 and 0.83, respectively. The specificity is poor at 0.50 and 0.52 in detection of aMCI and mMCI, respectively
Athilingam (2011) [149] English	To assess MCI in patients with heart failure (HF) aged 50 years of more	HF ($n=90$) MoCA and MMSE	54 % of participants scored ≤26 on the MoCA, whereas, only 2.2 % scored <24 on the MMSE. Delayed recall, visuospatial/executive function and language subtest of the MoCA were impaired in more than 60 % of patients
You et al. (2011) [124] Cantonese	To assess the validity of the MoCA in detection of mild to moderate VaD	NC 61, Mild VaD 30, moderate VaD 40 MoCA	At cutoff 21/22, the MoCA provided sensitivity of 0.87 and specificity of 0.93 in detection of mild VaD from normal controls At cutoff 13/14, the MoCA provided sensitivity of 0.81 and specificity of 0.86 in detection of moderate VaD from mild VaD

aMCI amnestic mild cognitive impairment, *mMCI* multi-domain mild cognitive impairment, *NC* normal control, *VaD* vascular dementia, *PPV* positive predictive value, *NPV* negative predictive value

[a]One additional point for subjects who have ≤6 years of education

[b]The score adjustment method according to age and education is available in the article [147].

[c]One additional point for subjects who have ≤12 years of education

performed at the same time as the MoCA (24 versus 7 days respectively) which could explain significant differences in sensitivity and specificity compared to other studies, and the MoCA cut-off used was MoCA ≤20 [151].

6.6.2.2 Heart Failure

Fifty-four to seventy percent of non-demented community-dwelling adults with heart failure (HF) (ejection fraction 37–40 %) had low cognitive scores on the MoCA (≤26) [149, 151]. Reduction in ejection fraction and various associated vascular risk factors such as hypertension, dyslipidemia or diabetes mellitus may contribute to chronic reduction of cerebral blood flow in HF patients [152–154].

6.6.2.3 Sub-optimal Self-Care and Functional Dependency

MoCA identified MCI in patients with heart failure that had suboptimal self-care behaviours [155]. Using the MoCA as a cognitive assessment instrument, the self-rated version of the instrumental activities of daily living (IADL) scale was administered to evaluate functional dependence among 219 non-demented patients with cardiovascular diseases and risk factors [156]. MCI was diagnosed when MoCA was less than 23/30. Less dependence was associated with higher MoCA scores, and a person who scored in the MCI range was 7.7 times more likely to report need for assistance with one or more activity of daily living. This study indicated that subtle cognitive impairment was an independent predictor of functional status in patient with cardiovascular disease [156].

6.6.2.4 Cerebral Small Vessel Disease

MoCA was shown to be sensitive to white matter disease and a history of stroke, detecting cognitive impairment with a sensitivity of 73 % and specificity of 75 % [78].

6.6.2.5 Subcortical Ischaemic Vascular Dementia (SIVD)

Subcortical ischemic vascular injury has been proposed to be associated with cognitive impairment as a result of neuronal circuit disconnection between subcortical regions, frontal cortex and other cerebral regions following repeated silent subcortical injuries [157–160]. Vascular dementia was also detected by the MoCA with a sensitivity of 86.8 % and specificity of 92.9 % [124].

6.6.2.6 Monitoring of Treatment

Cognitive outcomes after undergoing carotid endarterectomy (CEA) in severe unilateral internal carotid artery stenosis were studied using MoCA and MMSE as primary outcome measures. Symptomatic carotid stenosis (SCS) and asymptomatic severe carotid stenosis ≥60 % (ACS) patients with the age- and sex-matched control subjects who underwent laparoscopic cholecystectomy (LC) were compared. At baseline, the SCS group, but not the ACS, was significantly more impaired on the MoCA and MMSE total scores compared with the LC group. Postoperatively, only the SCS patients had significant improvement on both tests when comparing preoperative and 12-month post-operative performance [161].

6.7 Parkinson's Disease (PD)

The prevalence of dementia in PD is between 20 and 40 % [162]. The early cognitive changes are mediated by fronto-striatal disconnection, such as executive function and attention [163]. Single domain impairment is found more frequently than multiple domain deficits in early stage disease [163, 164]. Progression of PD affects other cognitive domains such as memory [162, 165]. The association between cognitive impairment and cholinergic denervation and frontostriatal dopaminergic deficits among patients with PD and PD with dementia (PDD) has been demonstrated by neuroimaging studies [166, 167]. Detection of cognitive impairment in PD is clinically useful as it predicts the conversion to PDD [165], contributes to caregiver's distress [168], and guides timing to initiate cognitive enhancing treatment [169].

The MoCA has an adequate sensitivity as a screening tool for detection of PD-MCI or PDD in a clinical setting (see Table 6.3), based on diagnostic criteria and neuropsychological test batteries [173, 174]. Half of PD patients with normal age and education-adjusted MMSE scores were cognitively impaired according to the recommended MoCA cutoff (25/26) [172, 177] as it lacks a ceiling [170, 171, 173]. Sensitivity and specificity for PDD was 81–82 and 75–95 % respectively. Sensitivity and specificity for PD-MCI was 83–90 and 53–75 % respectively [173, 174].

Baseline MoCA scores predicted the rate of cognitive deterioration among PD patients. The group of rapid decliners had lower scores on total MoCA score, clock drawing, attention, verbal fluency and abstraction subtest when compared with slow decliners [175].

MoCA was shown to have good reliability in this population. The test–retest correlation coefficient is 0.79, and the inter-rater correlation coefficient is 0.81 [170]. The superiority of the MoCA compared to the MMSE is probably explained by its

Table 6.3 MoCA in Parkinson's disease (PD)

Author (year) Language	Objective of study	Subject (n) Measurement	Results
Gill (2008) [170] English	To establish the cognitive screening characteristics of the MoCA in PD patients	PD ($n=38$) MoCA and MMSE	There was no ceiling effect of the MoCA The test–retest intraclass correlation coefficient was 0.79 The inter-rater intraclass correlation coefficient was 0.81 The correlation coefficient between the MoCA and a neuropsychological battery was 0.72
Zadikoff (2008) [171] English	To establish the MoCA and MMSE scores characteristics in PD	PD ($n=88$) MoCA and MMSE	The MoCA was less prone to ceiling effect and iidentified more MCI in PD patients than the MMSE
Nazem (2009) [172] English	To examine the MoCA performance in PD patients with normal global cognition according to the MMSE score	PD ($n=100$) MoCA and MMSE	52 % of subjects with normal MMSE scores had cognitive impairment according to their MoCA scores (<26). The impaired patients scored worse than unimpaired patients on visuospatial/executive, naming, attention, language and delayed recall subtest of the MoCA
Hoops et al. (2009) [173] English	To assess the validity of the MoCA in detection of MCI and dementia among PD patients	PD-N ($n=92$), PD-MCI ($n=23$), PDD ($n=17$)	At cutoff 26/27,[a] the MoCA provided sensitivity of 0.83 and specificity of 0.53 in detection of PD-MCI
		MoCA	At cutoff 24/25,[a] the MoCA provided sensitivity of 0.82 and specificity of 0.75 in detection PDD At cutoff 26/27,[a] the MoCA provided sensitivity of 0.90 and specificity of 0.53 in detection of PD with cognitive impairment (PD-MCI and PDD)

Dalrymple-Alford et al. (2010) [174] English	To assess the validity of the MoCA in detection of MCI and dementia among PD patients	PD-N ($n=72$), PD-MCI ($n=21$), PDD ($n=21$)	At cutoff 20/21,[a] the MoCA provided sensitivity of 0.81 and specificity of 0.95 in detection of PDD from PD-MCI/PD-N
		MoCA	At cutoff 25/26,[a] the MoCA provided sensitivity of 0.90 and specificity of 0.75 in detection PD-MCI
Luo (2010) [175] Chinese	To define and compare the cognitive profiles and clinical features of PD patients with slow or rapid cognitive deterioration rate (CDR),with normal controls (NC)	PD($n=73$) NC ($n=41$) MoCA	The total scores and subscores for visuospatial abilities, verbal fluency and delayed recall of the MoCA were significantly lower in the PD than NC. The rapid CDR group (MoCA decline >1 point/year) was older, later age at onset, faster movement deteriorated and more impaired in CDT, attention, verbal fluency and abstraction subtest than the slow CDR group
Robben (2010) [176] Dutch	To pilot a three-step cognitive diagnostic model for patients with PD dementia (PDD)	PDD ($n=15$) PD no dementia ($n=26$) Screening questionnaire; MoCA/FAB/ACE-R; Detailed NPE	It is efficient and feasible to use the three consecutive diagnostic steps for PDD as the following: Screening questionnaire → if + → the MoCA or FAB or ACE-R as screening tools → if + → a detailed NPE as diagnostic tools.

PD-N cognitively normal Parkinson's disease, *PD-MCI* mild cognitive impairment Parkinson's disease, *PDD* Parkinson's disease with dementia, *ACE-R* Addenbrooke's Cognitive Examination-revised, *FAB* Frontal Assessment Battery, *NPE* neuropsychological examination

[a]One additional point for subjects who have ≤12 years of education

more sensitive testing of executive, visuospatial, and attention domains which are frequently impaired in PD. Some of MoCA's limitations are that there are no studies yet regarding its sensitivity to detect of cognitive change over time or after treatment [178] and MoCA contains items that require fine motor movement such as the trail making test, cube copy and clock drawing (5/30 points), which can impact on the results when administering the test to patients with severe motor symptoms.

6.8 Huntington's Disease

Subtle cognitive impairment has been shown to precede motor manifestations of Huntington's disease (HD) [179–182]. While global cognitive function is relatively preserved in asymptomatic carriers of HD mutation (AC), attention, psychomotor speed, working memory, verbal memory and executive function are often impaired early [180–182]. These impaired functions are caused by abnormal fronto-striatal circuitry as shown in morphological and functional studies [183, 184]. It is interesting to note that AC participants who were intact in memory subtest performed similarly to non-carriers on all other domains, and AC subjects with cognitive deficits performed qualitatively similarly to the symptomatic HD patients [182].

Two studies compared the ability of the MoCA and the MMSE to detect cognitive impairment in HD patients with mild to moderate motor symptoms. Compared with the MMSE, the MoCA achieved higher sensitivity (MoCA 97.4 %; MMSE 84.6 %), however, comparable but not impressive specificity (MoCA 30.1 %; MMSE 31.5 %), in discriminating the HD from normal subjects [185, 186]. The superiority of the MoCA compared to the MMSE in this population is explained by more emphasis in the MoCA on cognitive domains frequently impaired in early HD. Clock drawing, trail making, cube copy, abstraction and letter F fluency in the MoCA increase its ability to detect executive and visuo-spatial dysfunction. Five word delayed recall, digit span, letter tapping/vigilance test in the MoCA provide a better assessment of memory and attention. The limitation for interpreting these results is that the available studies did not use standardized neuropsychological evaluation as a gold standard for classifying cognitive function in HD.

6.9 Brain Tumours

MoCA detected cognitive impairment among patients with brain metastases in 70 % of patients who performed the MMSE in the normal range (≥26/30). Patients had abnormal delayed recall (90 %) or language (90 %) followed by deficits in visuospatial/executive function (60 %) and the other sub-domains [187].

Detection of MCI among patients with primary and metastatic brain tumors using a standardized neuropsychological assessment as a gold standard has also shown the superiority of the MoCA compared to the MMSE in sensitivity but at the expense of lower specificity. MoCA sensitivities and specificities were 62 and 56 %

respectively, whereas MMSE sensitivities and specificities were 19 and 94 % respectively. Visuospatial/executive function items of the MoCA correlated with patients' perceived quality of life (ability to work, sleep, enjoy life, enjoy regular activities and accept their illness) [188].

The cognitive function is one of the survival prognostic factors and correlates with tumor volume in metastatic brain cancer [189, 190]. The survival prognostic value of the MoCA was studied among patients with brain metastases [191]. After dichotomizing MoCA scores into two groups based on average scores (≥22 and <22), below-average MoCA scores were predictive of worse median overall survival (OS) compared with above-average group (6.3 versus 50.0 weeks). Stratified MoCA scores were also predictive of median OS, as the median OS of patients who performed with MoCA scores in the range of >26, 22–26, and <22, were 61.7, 30.9 and 6.3 weeks, respectively. MoCA scores were superior to the MMSE scores as a prognostic marker. Although the MoCA scores correlated with the median OS, it is essential to clarify that cognitive impairment does not directly result in decreased survival. Lower MoCA scores may represent other unmeasured confounders such as the extent of disease, location of tumor or previous treatment [191].

6.10 Systemic Lupus Erythematosus (SLE)

Cognitive dysfunction is a common symptom of SLE-associated neuropsychiatric manifestation. It can occur independently of clinical overt neuropsychiatric SLE [192–198]. Magnetic resonance spectroscopy reveals the association between metabolic change in white matter of non-neuropsychiatric SLE (non-NSLE) patients and cognitive impairment [193, 199]. Early cognitive impairments in non-NSLE patients are verbal fluency, digit symbol substitution and attention [198–200]. Some investigators suggested that the pattern of cognitive decline in non-NSLE is mostly classified as subcortical brain disease since the psychomotor and mental tracking impairment are observed early [201]. The domains which are subsequently impaired in patients who develop neuropsychiatric SLE (NSLE) symptoms are memory, psychomotor speed, reasoning and complex attention [200, 202].

The MoCA was validated among SLE patients in hospital-based recruitment, using the Automated Neuropsychologic Assessment Metrics (ANAM) as a gold standard. At the standard cutoff scores <26/30, the MoCA provided good sensitivity (83 %), specificity (73 %) and overall accuracy (75 %) in detection of cognitive impairment [203].

6.11 Substance Use Disorders

The validity of the MoCA to detect cognitive impairment in subjects with non-nicotine substance dependence disorders according to the DSM-IV criteria was established by using the Neuropsychological Assessment Battery-Screening Module

(NAB-SM) as a gold standard to define cognitively impaired participants. The NAB-SM is composed of five domains: attention, language, memory, visuospatial, and executive function. The participants were composed of alcohol dependence (65 %; $n=39$), dependence on opioids (32 %; $n=19$), cocaine (17 %; $n=10$), cannabis (12 %; $n=7$), benzodiazepine (10 %; $n=6$), and amphetamine (8 %; $n=5$). At the optimal cutoff point of 25/26, the MoCA provided acceptable sensitivity and specificity of 83 and 73 %, respectively, with good patient acceptability [204].

6.12 Idiopathic Rapid Eye Movement Sleep Behavior Disorder (Idiopathic RBD)

RBD is characterized by the intermittent loss of REM sleep electromyographic atonia that elaborate motor activity associated with dream mentation. Approximately 60 % of cases are idiopathic [205]. MCI is found in 50 % of idiopathic RBD and most of them are single domain MCI with executive dysfunction and attention impairment [206]. Visuospatial construction and visuospatial learning may be impaired in neuropsychologically asymptomatic idiopathic RBD patients who have normal brain MRI [207]. Subtle cognitive changes in idiopathic RBD may reflect the early stage of neurodegenerative diseases [207] as some studies reported an association between idiopathic RBD and subsequent development of Parkinson's disease (PD), Lewy body dementia (LBD) and multiple system atrophy [208–210]. Moreover, cognitive changes in idiopathic RBD are similar (visuoconstructional and visuospatial dysfunction) to LBD [211] and (executive dysfunction) to early PD [163].

The MCI screening property of the MoCA was validated among 38 idiopathic RBD patients, based on neuropsychological assessment as a gold standard. At the original cutoff point of 25/26, the MoCA had sensitivity for cognitive impairment of 76 % and specificity of 85 % with an accuracy of 79 %. However, for screening purposes, the higher cutoff (26/27) may be applied as it increases sensitivity to 88 %, at the expense of reduced specificity (61 %). The demanding visuospatial/executive functions subtests of the MoCA makes it sensitive for detection of mild cognitive impairment in idiopathic RBD patients who are impaired early in these domains [212].

6.13 Obstructive Sleep Apnoea (OSA)

In a recent study by Chen et al. [213], the MoCA was administered to 394 obstructive sleep apnea (OSA) patients categorized into four groups according to severity based on the total number of apnea and hypopnea per hour of sleep (AHI), measured by polysomnography. The groups were composed of primary snoring (AHI<5 events/h), mild OSA (AHI 5–20 events/h), moderate OSA (AHI 21–40 events/h)

and severe OSA (AHI > 40 events/h). The total MoCA scores progressively decreased as the severity of OSA increased. The scores of moderate-to-severe OSA groups were significantly lower than the scores of the primary snoring and mild OSA groups. Furthermore, defining MCI with a cutoff of 25/26, the moderate-to-severe OSA groups were more classified as MCI than the other groups. Domains that were significantly impaired in severe OSA group, compared to the primary snoring group, were delayed recall, visuospatial/executive function, and attention/concentration. Even though the mild OSA group performed similarly to the primary snoring group on total MoCA scores, impairment in the visuospatial/executive function and delayed recall domains were more prominent. Moreover, MoCA scores correlated with oxygen saturation levels [213].

6.14 Risk of Falls

Liu-Ambrose and colleagues used the MoCA to classify 158 community-dwelling women as MCI or cognitively intact by the cutoff point of 25/26 [214]. The short form of Physiologic Profile Assessment (PPA) was used to assess the fall risk profile. In the PPA, the postural sway, quadriceps femoris muscle strength, hand reaction time, proprioception and edge contrast sensitivity are evaluated. Participants with MCI had higher global physiological risk of falling and greater postural sway compared with the counterparts. However, the other four PPA components were not significantly different between the two groups. This study suggested that screening for MCI using the MoCA is valuable in preventing falls in the elderly.

6.15 Rehabilitation Outcome

The MoCA has been shown to be more sensitive than the MMSE for detection of MCI in inpatient rehabilitation setting [215]. The association between cognitive status measured by the MoCA and rehabilitation outcomes was studied among 47 patients admitted to a geriatric rehabilitation inpatient service [216]. Patients had an orthopedic injury (62 %), neurological condition (19 %), medically complex condition (11 %) and cardiac diseases (4 %). MoCA had good sensitivity (80 %), but poor specificity (30 %), at the cutoff scores 25/26 to predict successful rehabilitation outcome. The patients who reached the successful rehabilitation criteria tended to have higher MoCA scores at admission than the patients who did not achieve the rehabilitation goal. Many studies have reported the negative effect of cognitive impairment on rehabilitation outcomes [216–219].

In a short term rehabilitation program in post-stroke patients (median time post-stroke 8.5 days) who had MCI, the MoCA had a significant association with discharge functional status. The discharge functional status was measured by the motor subscale of Functional Independence Measures (mFIM) and motor relative

functional efficacy taking the individual's potential for improvement into account [220]. The visuospatial/executive domain of the MoCA was the strongest predictor of functional status and improvement. This domain was previously shown as an independent predictor of post-stroke long term functional outcome [221].

6.16 MoCA in Epilepsy

A cross-sectional study examined the MoCA performance in cryptogenic epileptic patients aged more than 15 years with normal global cognition according to the MMSE score. The mean MoCA score was 22.44 (± 4.32). In spite of a normal MMSE score, which was an inclusion criterion, cognitive impairment was detected in 60 % patients based on the MoCA score. The variable that correlated with a higher risk of cognitive impairment was the number of antiepileptic drugs (polytherapy: OR 2.71; CI 1.03–7.15). No neuropsychological batteries were used for comparison [222].

6.17 Normative Data in Multiple Languages, Cultures, Age and Education Levels

The Montreal Cognitive Assessment has been translated into 36 languages and dialects and has been used in several populations (Table 6.4 summarizes published studies and not abstracts). Test and instructions for all languages and dialects are available on the MoCA's official website (www.mocatest.org).

Performance on the MoCA varied significantly among populations. Differences on MoCA performance in healthy subjects are probably accounted for by cultural, ethnic, age, educational, and linguistic factors. As with all neuropsychological tests, it is recommended that local normative values be obtained in communities around the world utilizing the MoCA. A large community based cognitive survey in Texas included a multi-ethnic sample of Caucasians, Blacks, and Hispanics, of varying educational levels. In this study, the majority of subjects (62 %) scored below 26 on the MoCA [126]. When one considers only the more educated Caucasian group of normal participants in this study, the mean score was 25.6/30 which is only slightly lower than the original cutoff score (25/26). However since standard neuropsychological assessment, neurological examination, and imaging studies, were not performed on the healthy volunteers, subtle cognitive deficits, neurological conditions, or imaging abnormalities may have been missed, which could account for lower performance on the MoCA [128]. This is most likely to happen in subjects with lower education and in ethnic communities that are prone to vascular risk factors with consequent subtle vascular cognitive impairment [128].

Table 6.4 Studies using non-English versions of the MoCA

Language	Number of articles	References
Arabic	1	[130]
Brazilian	1	[223]
Chinese	7	[78, 121, 123, 124, 143, 175, 213]
Croatian	4	[138, 139, 141, 142]
Dutch	2	[176, 224]
French	3	[1, 147, 212]
Italian	1	[161]
Japanese	1	[127]
Korean	1	[79]
Malay	1	[143]
Portuguese	2	[132, 137]
Sinhala	1	[135]
Thai	2	[131, 222]
Turkish	1	[133]

6.18 MoCA for the Blind

A version of the MoCA for assessment of cognition in the blind population has been published [225].

6.19 Future Research

To provide reliable and valid intercultural multi-lingual norms on the MoCA, a strict protocol (see MoCA-ACE: Age, Culture and Education Study, unpublished protocol) defining cognitively healthy subjects has been devised with strict criteria excluding subjects with any known risks for cognitive impairment. The MoCA-ACE protocol excludes for example subjects with vascular risk factors, sleep apnea, obesity, or who take sedative medications that may be important confounders in community based surveys [126].

To decrease possible learning effects when administering the MoCA multiple times in a short period of time, two new alternative and equivalent English versions of the MoCA have been validated [120], and are available on www.mocatest.org.

To better address the need for a specific and sensitive cognitive screening tool for illiterate and lower educated populations, a new version of the MoCA, the MoCA-Basic (MoCA-B) is being validated.

To better predict AD conversion among MCI subjects, a new MoCA Memory Index Score (MoCA-MIS) that takes into account delayed recall cueing performance has been devised (Abstract submitted for presentation at the Alzheimer Association International Conference, Vancouver, July 2012).

6.20 Conclusion

The MoCA promises to be a potentially useful, sensitive and specific cognitive screening instrument for detection of mild cognitive impairment in multiple neurological and systemic diseases that affect cognition across various cultures and languages.

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Chapter 7
DemTect

Elke Kalbe and Josef Kessler

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Abstract DemTect is a cognitive screening instrument, first published in 2000, which was designed to be sensitive to the early cognitive symptoms of dementia even in the stage of mild cognitive impairment. It covers a wide range of cognitive domains so that it is valid not only for patients with Alzheimer's disease but also for

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patients with other types of dementia. DemTect provides cutoff scores for dementia and for cognitive impairment typical of MCI. Much favored for cognitive screening purposes in Germany, English versions are also available.

Keywords DemTect • Cognitive screening • Dementia

7.1 Introduction

The cognitive screening tool DemTect was first published in 2000 in a German version [1] and in 2004 in an English version [2]; also, a Polish [3], a French [4], and some other versions are in use. The DemTect has attracted much attention since then and is not only recommended by German national guidelines [5] and authors reviewing cognitive screening tools (e.g., [6]) but also by international guidelines and recommendations to be used as a brief cognitive test for early detection of dementia [7] and mild cognitive impairment (MCI) [8, 9]. In a well-attended symposium on screening instruments at the conference of the German Society for Gerontopsychiatry and Psychotherapy (DGPPN, Deutsche Gesellschaft für Gerontopsychiatrie und psychotherapie) in 2005, the DemTect was elected as the favorite cognitive screening tool by the auditorium. In fact, the DemTect is the most used cognitive screening test in Germany next to the Mini-Mental State Examination (MMSE) [10].

7.2 Description of the Test

7.2.1 Subtests: Construction and Administration

The ambition of the DemTect construction was that it should (i) be sensitive to detect early cognitive symptoms of dementia even in the stage of MCI, (ii) have high specificity, (iii) cover a wide range of cognitive domains so that it is valid not only for patients with Alzheimer's disease (AD) for which assessment of learning and memory tests clearly is the most important issue but also for patients with other types of dementia, (iv) provide a total score that is independent of sociodemographic variables, and (v) provide cutoff scores for dementia but also a cutoff score that points to cognitive impairment rather belonging to the stage of MCI.

After some pilot work, five subtests were chosen for the DemTect (Table 7.1) that follow established test paradigms and which were able to fulfill the demands outlined above (for the rationale to select these subtests, see [2]):

1 and 5: Word list/delayed recall. A word list with ten words with immediate recall in two trials at the beginning of the test and a delayed recall at the end of the test (i.e., approximately 8 min later).
2: Number transcoding. A number transcoding task in which two Arabic numbers have to be transformed into verbal numerals and two verbal written numerals have

Table 7.1 Description of the DemTect subtests, its maximum raw scores, and its maximum transformed scores

DemTect subtest	Description	Max. raw score	Max. transformed score
Word list	Ten items have to be recalled in two trials; subjects are not informed of a delayed recall	20	3
Number transcoding	Two Arabic numbers have to be transformed into verbal numerals, and two verbal written numerals have to be transcoded into Arabic numbers	4	3
Verbal fluency	Within 1 min, the subjects have to name articles that can be bought in a supermarket (DemTect) or animals (DemTect B)	30	4
Digit span reverse	The subjects have to repeat digits in reverse order to a maximum length of six	6	3
Word list delayed recall	The ten items presented at the beginning of the test have to be recalled once more	10	5
Total transformed score			18

to be transcoded into Arabic numbers (for typical errors in dementia patients as described in [11], see Fig. 7.1).
3: Verbal fluency. In the semantic verbal fluency task, the subjects have to name articles that can be bought in a supermarket within 1 min.
4: Digit span. In the digit span task, the subject has to repeat digits in reverse order to a maximum length of six.

With these subtests, the DemTect assesses short- and long-term verbal memory (word list), working memory (in the digit span task but also needed in the verbal fluency task), executive functions (set shifting in the number transcoding task as well as cognitive flexibility in the verbal fluency task), and language (needed in all tasks but especially demanded in the verbal fluency task).

7.2.2 Scoring

The DemTect has a maximum transformed score of 18. The selection of this maximum score was random. For each subtest, transformation tables for two age groups (<60 years and ≥60 years) were provided for the first version of the DemTect. The maximum scores for each subtest range from 3 (word list, number

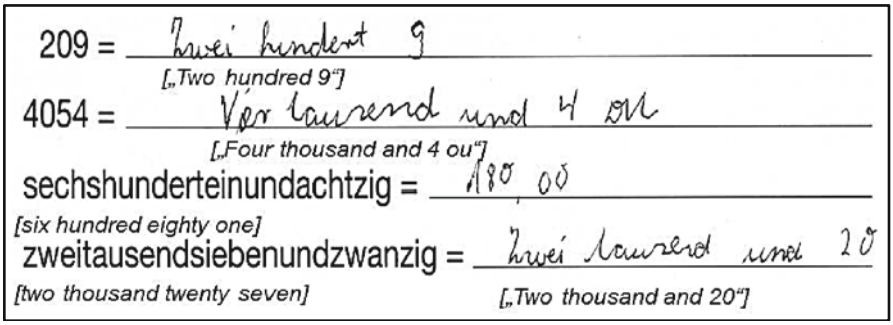

Fig. 7.1 Typical "shift errors," i.e., problems with shifting from one number code to the other (Arabic to number words or vice versa), and other errors in the number transcoding task in a patient with Alzheimer's disease

transcoding, digit span) to 4 (verbal fluency) up to 5 (delayed recall). The decision on each maximum score was based on the subtests' different sensitivities and specificities in a population of healthy control subjects, AD patients, and MCI patients [1, 2]. The age correction was necessary due to significant age effects in the control groups in both normative studies. Furthermore, an education correction is provided in the English version [2]. Here, it was defined that one point is added to the transformed total score in subjects with only basic education (≤11 years).

After much feedback from clinicians that the DemTect is frequently used in elderly patients aged 80 years or above, but also in young patients of 40 years or younger (with a wide range of clinical states), further normative work was done by our own group [12] that has lead to norms for the age groups "40–" and "80+." With these scores, the total score of the DemTect is now independent of the factor age for adult patients from young adulthood until old age. The relevance of the age correction is demonstrated in Fig. 7.2.

7.2.3 Interpretation of the Total Transformed Score

From the transformed total DemTect scores, it can be decided whether performance of the subject can be interpreted as age adequate (13–18 points), or whether MCI (9–12 points) or dementia must be suspected (≤8 points) (Table 7.2). Again, these scores were derived from the normative studies and show high sensitivity and specificity [1, 2].

It is important to emphasize that any interpretation from a screening tool must be preliminary; especially if a cognitive disorder is indicated, an elaborate neuropsychological examination is strongly recommended.

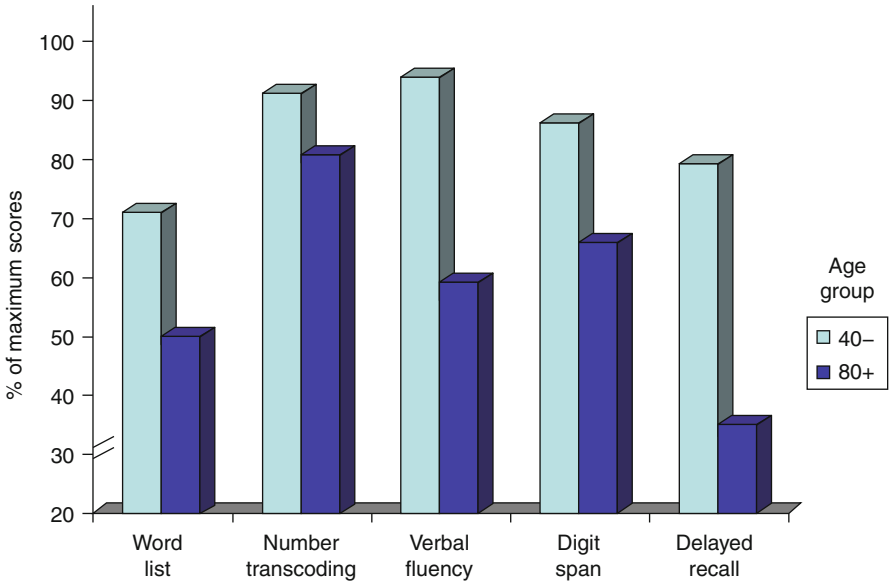

Fig. 7.2 Performance of the age groups "40–" (40 years and younger) and "80+" (80 years and older). Thirty words were taken as the maximum score for the verbal fluency task. The figure shows the age dependence of the different subtests

Table 7.2 Interpretation of DemTect scores

Transformed total score	Interpretation valid for DemTect and DemTect B scores
13–18 points	Cognitive abilities appropriate for the subjects age
9–12 points	Mild cognitive impairment suspected
≤8 points	Dementia suspected

7.2.4 Administration Time

The administration time for the DemTect, including transformation of the raw scores and interpretation, is 8–10 minutes.

7.2.5 Avoiding Retest Effects with the Parallel Version of the DemTect: DemTect B

When patients are retested in follow-up examinations, explicit or implicit learning effects can occur when the same test versions are used. Thus, a parallel version of the DemTect, "DemTect B," was developed [13].

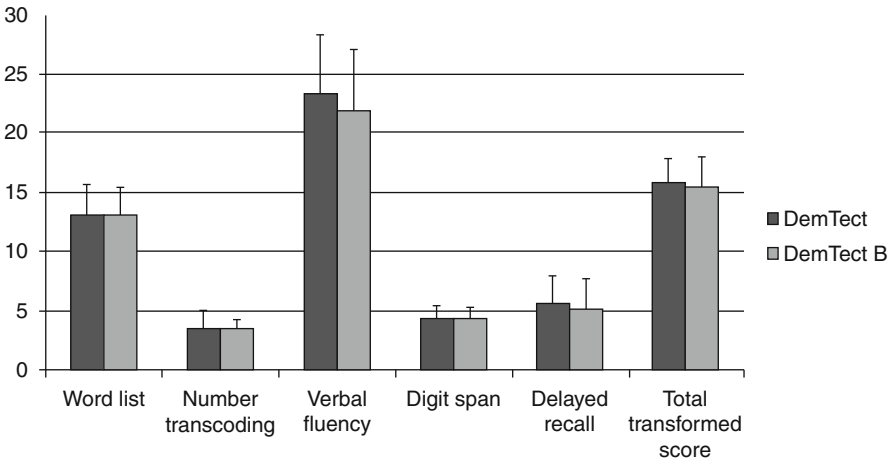

Fig. 7.3 Equivalence of performance in the parallel test versions DemTect and DemTect B in healthy control subjects

Parallel versions of the five original DemTect subtests were designed (modifications are indicated in Table 7.1). The equivalence of the new and original subtests was analyzed in 80 healthy control subjects. There were no significant differences between the corresponding subtests of the two test versions except for the semantic verbal fluency task (category "supermarket" in DemTect and category "animals" in DemTect B) (Fig. 7.3). Thus, different algorithms for transforming raw scores into transformed scores were calculated for this subtest. For all other subtests, the transformation tables of the original DemTect can be used. Using this procedure, there were no significant differences between the transformed scores of the DemTect and DemTect B, including the total scores (max. 18 points, mean score 15.9, SD 1.9 in DemTect versus 15.5, SD 2.4 in DemTect B). Thus, the interpretation of specific score ranges of the DemTect could be adopted for DemTect B, and the total DemTect B can be regarded as equivalent to the DemTect.

7.2.6 Psychometric Criteria

Besides the two normative studies for the German and English version of the DemTect [1, 2], some other studies have demonstrated a high sensitivity and specificity of the tool (overview in Table 7.3) [14]. The sensitivity across all studies ranges between 83 and 100 % for AD patients, 67 and 86 % for patients with MCI or mild cognitive disorder, and was 90 % for vascular dementia (VD) patients; the specificity ranged between 90 and 100 % [1, 2, 15–17]. In a validation of the DemTect with 18-fluoro-2-deoxyglucose positron emission tomography (18-FDG-PET), the ROC analysis showed an area under the curve (AUC) of 0.78 with a cutoff score of ≤13 (95 % CI 0.62–0.94; $p = 0.006$) [17].

Table 7.3 Sensitivity and specificity of the DemTect in studies with patients with dementia or mild cognitive impairment and healthy controls

Reference	Study samples	Sensitivity (sens.) and specificity (spec.)
Kessler et al. [1]	169 AD patients, 175 CG ($n=82<60$ yrs., $n=93\geq60$ yrs.)	AD versus CG ≥ 60 yrs.: sens.: 94 %, spec.: 90 %
Perneczky [15]	CG ($n=13$), AD patients ($n=13$), patients with mild cognitive disorder ($n=9$)	AD versus CG: sens.: 92 %, spec.: 100 %; mild cognitive disorder versus CG: sens.: 67 %, spec.: 92 %
Kalbe et al. [16]	AD patients ($n=36$), VD patients ($n=28$), CG ($n=31$)	AD versus CG and VD versus CG: sens. > 90 %, spec.: > 95 %
Kalbe et al. [2]	AD patients ($n=121$), MCI patients ($n=97$), CG ($n=145$)	AD versus CG: sens.: 100 %, spec.: 92 %; MCI versus CG: sens.: 86 %, spec.: 92 %
Scheurich et al. [17]	AD patients ($n=18$), MCI patients ($n=13$)	Sens. Compared to clinical diagnosis: AD: 83 %, MCI: 84.6 %; sens. compared to FDG-PET in all patients: 93 %

Modified from [14]
AD Alzheimer's disease, *CG* healthy control group, *yrs.* years, *VD* vascular dementia, *MCI* mild cognitive impairment, *FDG-PET* 18-fluoro-2-deoxyglucose positron emission tomography

The DemTect total transformed score is highly correlated with the MMSE (e.g., [2]; control group: $p<0.001$, $r=0.43$; AD group: $p<0.001$, $r=0.55$; MCI group: $p<0.01$, $r=0.31$). However, a regression analysis showed that although DemTect scores could be transformed into MMSE scores with the formula MMSE = 0.567 × DemTect score plus 19.997, DemTect scores only corresponded to MMSE scores higher than 20. This result reflects the fact that while the MMSE is a tool with which staging up to more severe stages of dementia is possible, the DemTect is a tool that is valuable for detecting and differentiating cognitive dysfunction when symptoms begin. Accordingly, the superiority of the DemTect compared to the MMSE regarding the sensitivity to assess early symptoms has been demonstrated [2, 15].

A good retest reliability with no significant differences in total transformed scores in 30 healthy controls which were tested two times with a time interval of 6 weeks (mean scores were 16.63 at t1 and 17.13 at t2) has been demonstrated [1].

7.3 Neural Correlates of the DemTect Subtests

Neural networks associated with the performance in the DemTect's five subtests regarding both atrophy of brain tissue and cerebral glucose metabolism were examined in 29 AD patients with magnetic resonance imaging (MRI) and FDG-PET by Woost et al. [18]. Higher scores in the word list were related to higher glucose

metabolism in the left superior, middle, and inferior temporal gyri and in the left angular gyrus; for the number transcoding task, significant metabolic effects were found in a widespread left frontotemporal network. Furthermore, a correlation with gray matter density in the left insular cortex and the triangular and opercular part of the inferior frontal gyrus, the left putamen, the caput of the left caudate, the left and right precuneus, and an area including the right angular gyrus was found. Performance in the digit span task showed positive correlations with pronounced glucose utilization in the left frontal cortex and the left putamen. Finally, the word list recall was associated with higher metabolism in the middle and superior temporal gyrus. No correlations were found for the supermarket verbal fluency task. The authors came to the conclusion that the structural and functional neural correlates of the subtests of the DemTect point to the fact that changes in networks of the brain can be detected by this screening tool. Thus, this study may be understood as a further validation of the DemTect.

In another study by the same group [19] with AD patients, patients with frontotemporal dementia, and patients with subjective memory complaints, a correlation of a reduced 18-FDG glucose utilization in a temporoparietal network and memory impairment in the DemTect was demonstrated. Reduced metabolism in left frontolateral and subcortical network was associated with reduced working memory, and a large left hemispheric network was related to number transcoding performance. Finally, delayed recall correlated with metabolism in temporolateral areas.

7.4 The DemTect in Clinical Practice and Scientific Contexts

The DemTect is a frequently used cognitive screening tool both in clinical practice and in scientific studies. Most of these studies and reports include patients with dementia (e.g., [20–24]) or cognitive impairment [25]. However, the DemTect has also been used in patients in other neurological conditions [26], patients with hypertension [27], implantable cardioverter-defibrillators [28], diabetes [29], primary hyperparathyroidism [30], possible osteoporosis [31], and even in school children from 6 to 11 years to assess their cognitive functions [32]. Finally, the DemTect has been taken as an instrument to show effects of different kinds of interventions on cognitive functions, e.g., neuropsychological [33] and neuropsychological and physical training in AD patients [34], herb extracts in elderly subjects with below-average cognitive performance [35], and provision of optical aid in patients with macular degeneration [36].

7.5 The "SIMARD: A Modification of the DemTect": A Tool for the Identification of Cognitively Impaired Medically At-Risk Drivers

In 2011, a modification of the DemTect that aimed at identifying at-risk drivers was developed by a Canadian work group. Dobbs and Schopflocher pointed out that physicians are well placed to identify medically at-risk drivers, but that there is a

lack of a valid screening tools that are easy to administer. Thus, the group carried out some research and validation work to develop such a brief screening tool for use in the primary care setting. The cohort comprised 146 consecutive referrals from community-based family physicians diagnosed with cognitive impairment or dementia and 35 community dwelling healthy controls who underwent an on-road evaluation with a subsequent "pass" or "fail" judgment. Among a set of neuropsychological tests, the best predictors for the on-road outcome was a combination of three DemTect subtests: the number conversion task, the supermarket task, and the repeat of the word list. With these three measures and with a modified scoring scheme, a further validation study with 123 individuals showed a sensitivity of the "SIMARD: A Modification of the DemTect" of 80 % and a specificity of 87 % for failing or passing in the on-road examination. Thus, the instrument can be regarded as a brief paper-and-pencil screening tool with a high degree of accuracy that can be used for immediate decisions on at-risk drivers in the clinical setting.

7.6 Conclusion

The DemTect, introduced in 2000 [1], is an easy-to-use cognitive screening tool that is valuable for the early detection of dementia and MCI. It has attracted much attention both in clinical and scientific contexts. Other language versions exist (English, Polish, French, and others), a parallel test version, DemTect B, has been developed, and new normative data for subjects aged 40 years or younger and 80 years or older have been published. SIMARD, a modification of the DemTect, sensitive for the detection for elderly at-risk drivers, has been developed. Furthermore, the DemTect has been modified to permit assessment of cognitive functions in school children.

The sensitivity of the DemTect has been demonstrated in patients with AD, VD, and MCI, but also various other diseases, and is superior to that of the MMSE. Its validity has also been shown with FDG-PET. Also, the DemTect has been included in studies that examine the effect of pharmacological and non-pharmacological interventions.

As for all cognitive screening instruments, it must be emphasized that these instruments can only serve as tools to detect patients suffering cognitive dysfunction. It represents the first step in a cascade of diagnostic procedures that, if a suspicion of decline has been verified by screening, include elaborate neuropsychological testing as well as extensive neurological and psychiatric examination. For this purpose though, screening tests are of crucial help. With its high sensitivity, easy administration and independency of sociodemographic factors, the DemTect fulfills all essential criteria for a cognitive screening instrument. It can be used by a wide range of professionals such as neuropsychologists, neurologists, or primary care physicians.

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Chapter 8
The IQCODE: Using Informant Reports to Assess Cognitive Change in the Clinic and in Older Individuals Living in the Community

Nicolas Cherbuin and Anthony F. Jorm

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Abstract The Informant Questionnaire on Cognitive Decline in the Elderly (IQCODE) uses the report of an informant to assess an individual's change in cognition in the last 10 years. Unlike cognitive screening tests administered at one point in time, it is unaffected by pre-morbid cognitive ability or by level of education. When used as a screening test for dementia, the IQCODE performs as well as the Mini-Mental State Examination (MMSE), which is the most widely used cognitive

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screening instrument. Other evidence of validity comes from correlations with change in cognitive test scores and associations with neuropathological and neuroimaging changes. The main limitation of the IQCODE is that it can be affected by the informant's emotional state. The IQCODE is suitable for use as a screening test in clinical settings, for retrospective cognitive assessment where direct data are not available, and for assessment in large-scale epidemiological studies. Versions are available in many languages.

Keywords Dementia • Alzheimer's disease • Mild cognitive impairment • Cognitive decline • Screening • Informant • Validity • Diagnosis

8.1 Introduction

The Informant Questionnaire on Cognitive Decline in the Elderly (IQCODE) is a brief screening instrument designed to assess cognitive change in older populations based on informant reports [1]. To date, its main applications have been in screening individuals for cognitive decline and dementia in large clinical or epidemiological studies, assessing pre-morbid cognitive status in clinical settings or estimating cognitive change after stroke, trauma, or surgery. However, available evidence suggests that the IQCODE can be useful in many other situations where retrospective assessment of cognitive change is needed and an informant is available.

8.2 IQCODE History and Development

The IQCODE is based on a parent interview which required informants to respond to 39 questions assessing the magnitude of change over the previous 10 years in two cognitive domains: memory function (acquisition and retrieval) and intelligence (verbal and performance). Following an initial psychometric evaluation, the size of the questionnaire was reduced to 26 questions which were easy to rate and whose responses correlated well together. The new instrument was named IQCODE and was formatted for easy self-completion by informants. Questions take the form "Compared to 10 years ago, how is this person at … " (e.g., remembering things about family and friends such as occupations, birthdays, addresses, etc.). Informants are asked to respond to each question using a Likert scale ranging from 1, "much improved," to 5, "much worse" [2].

The size of the IQCODE has subsequently been further reduced to 16 items [2]. This short version is typically preferred and recommended since it has been found to be highly correlated with the full version (0.98) and to have equivalent validity against clinical diagnosis. The full questionnaire of the short IQCODE is presented in Table 8.1.

Table 8.1 Short form of the IQCODE

Compared with 10 years ago, how is this person at:

	1	2	3	4	5
1. Remembering things about family and friends, e.g., occupations, birthdays, addresses	Much improved	A bit improved	Not much change	A bit worse	Much worse
2. Remembering things that have happened recently	Much improved	A bit improved	Not much change	A bit worse	Much worse
3. Recalling conversations a few days later	Much improved	A bit improved	Not much change	A bit worse	Much worse
4. Remembering his/her address and telephone number	Much improved	A bit improved	Not much change	A bit worse	Much worse
5. Remembering what day and month it is	Much improved	A bit improved	Not much change	A bit worse	Much worse
6. Remembering where things are usually kept	Much improved	A bit improved	Not much change	A bit worse	Much worse
7. Remembering where to find things which have been put in a different place from usual	Much improved	A bit improved	Not much change	A bit worse	Much worse
8. Knowing how to work familiar machines around the house	Much improved	A bit improved	Not much change	A bit worse	Much worse
9. Learning to use a new gadget or machine around the house	Much improved	A bit improved	Not much change	A bit worse	Much worse
10. Learning new things in general	Much improved	A bit improved	Not much change	A bit worse	Much worse
11. Following a story in a book or on TV	Much improved	A bit improved	Not much change	A bit worse	Much worse

(continued)

Table 8.1 (continued)

Compared with 10 years ago, how is this person at:

	1	2	3	4	5
12. Making decisions on everyday matters	Much improved	A bit improved	Not much change	A bit worse	Much worse
13. Handling money for shopping	Much improved	A bit improved	Not much change	A bit worse	Much worse
14. Handling financial matters, e.g., the pension, dealing with the bank	Much improved	A bit improved	Not much change	A bit worse	Much worse
15. Handling other everyday arithmetic problems, e.g., knowing how much food to buy, knowing how long between visits from family or friends	Much improved	A bit improved	Not much change	A bit worse	Much worse
16. Using his/her intelligence to understand what is going on and to reason things through	Much improved	A bit improved	Not much change	A bit worse	Much worse

Adapted versions of the IQCODE have also been produced to allow assessment in other languages (Chinese, Dutch, Finnish, French, Canadian French, German, Italian, Japanese, Korean, Norwegian, Persian, Polish, Portuguese, Spanish, Thai, and Turkish) or based on shorter [3–5] or more flexible [6] time frames than 10 years. Short forms of the IQCODE are also available in Spanish [7], Chinese [8], Portuguese [9], and in other languages (which to our knowledge have not been validated). In addition, in a recent review of the literature on dementia screening instruments suitable for self- or informant-assessment, particularly in a format that could be applicable for digital administration (e.g., computer based or on the internet), the IQCODE was found to be one of three most promising instruments which warranted further validation for delivery on digital platforms [10].

8.3 Administration and Scoring

The IQCODE takes between 10 and 25 minute to complete depending on the form chosen (long/short) and whether it is administered in pen-and-paper form or electronically. It is generally perceived as easy to answer and can be mailed to informants or administered by telephone or by computer (although we are not aware of any validation data with non-pen-and-paper administration media).

Scoring the IQCODE requires adding up all ratings and dividing by the number of items, thus yielding a measure ranging from 1 to 5. An alternative scoring strategy used by some investigators involves using the sum of all responses as a summary measure. Norms have been developed by Jorm and Jacomb [11] for 5-year age groups from 70 to 85+ years. However, the use of an absolute cutoff ranging from 3.3–3.6 in community samples to 3.4–4.0 in patient samples is typically preferred and easier to communicate. A practical way of selecting a valid and effective cutoff is to identify studies (see Table 8.2) with characteristics most similar to the target population in the planned study and apply their cutoffs. Alternatively, a weighted average computed from Table 8.2 of 3.3 for community samples and of 3.5 in patient samples is also defensible.

8.4 Psychometric Characteristics

The reliability and validity of the IQCODE have been thoroughly researched. Its internal consistency assessed using Cronbach's alpha can be viewed as excellent and has been found to range between 0.93 and 0.97 across ten studies [1, 8, 9, 11, 12, 32, 36–39]. Receiver Operating Curve (ROC) analysis of the predictive value of single short-IQCODE questions indicates that all items have areas under the curve of more than 0.80 except for item 7 (0.75), which further confirms the internal consistency of the questionnaire [9]. In addition, test-retest reliability has been shown to be very good over short and long periods with correlations of 0.96 over 3 days and 0.75 over 1 year [11, 24].

Table 8.2 Performance of the MMSE, and the long and short versions of the IQCODE as screening tests for dementia [1–5]

Study	Sample	Diagnostic criteria[a]	Cutoff	*N*	Mean age/age range	Sens.	Spec.	ROC curve
MMSE								
Morales et al. [12]	Urban epidemiological study (Spain)	1	21/22	97	75	0.73	0.78	–
Morales et al. [12]	Rural epidemiological study (Spain)	1	21/22	160	74	0.83	0.74	–
Callahan et al. [13]	Epidemiological study (USA)	1	23/24	344	74	0.95	0.87	0.96
Swearer et al. [14]	Primary care clinic outpatients and independent retirement community residents (USA)	2	23/24	46	80	0.13	1.00	–
Ferrucci et al. [15]	Geriatric clinic patients (Italy)	2	23/24	104	75	0.97	0.55	–
Flicker et al. [16]	Memory clinic patients (young, Australia)	1, 5	21/22	299	73	0.91	0.82	–
Flicker et al. [16]	Memory clinic patients (old, Australia)	1, 5	21/22	78	80	0.75	0.71	–
Heun et al. [17]	Epidemiological study (Germany)	1, 4	23/24	287	77	0.84	0.99	–
Jorm et al. [18, 19]	Ex-servicemen (half former prisoners of war) (Australia)		23/24	144	73	0.45	0.99	0.81
Knafelc et al. [20]	Memory clinic patients (Australia)	1	23/24	323	75	0.84	0.73	0.86
Nasreddine et al. [21]	Memory clinic patients (Canada)	2	25/26	183	75	0.78	1.00	–
Isella et al. [22]	Cognitively normal volunteers and 45 MCI patients (Spain)	6	28	100	71	0.82	0.73	–
Bustamante et al. [23]	Hospital outpatients and controls (Brazil)	1, 4	25/26	76	71	0.80	0.91	–
Perroco et al. [9]	Old-age clinic patients with low education (Brazil)	1, 4	25/26	91	71	0.94	0.78	0.94
IQCODE (*long version*)								
Jorm et al. [24]	Patients seen by a geriatrician (Australia)	3, 4	3.60+	69	80	0.80	0.82	0.87
Jorm [2]	Epidemiological study (Australia)	1	3.60+	684	70	0.69	0.80	0.77
Law and Wolfson [25]	Epidemiological study (Canada)	1	3.30+	237	81	0.76	0.96	–
Fuh et al. [8]	Non-demented community resident and dementia patients (Taiwan)	1	3.40+	399	69	0.89	0.88	0.91
Hancock and Larner [26]	Memory clinic patients	2, 5	3.60+	144	67	0.86	0.39	0.71

Morales et al. [12]	Urban epidemiological study (Spain)	1	3.27+	97	75	0.82	0.90	0.89
Morales et al. [12]	Rural epidemiological study (Spain)	1	3.31+	160	74	0.83	0.83	0.83
Jorm et al. [18, 19]	Ex-servicemen (half former prisoners of war) (Australia)	3	3.30+	144	73	0.79	0.65	0.77
Mulligan et al. [27]	Geriatric patients (Switzerland)	1	3.60+	76	82	0.76	0.70	0.86
Del-Ser et al. [28]	Neurology clinic outpatients (Spain)	1	3.62+	53	69	0.84	0.73	0.81
Flicker et al. [16]	Memory clinic patients (young, Australia)	1, 5	3.90	299	73	0.74	0.71	–
Flicker et al. [16]	Memory clinic patients (old, Australia)	1, 5	3.90	78	80	0.79	0.78	–
De Jonghe et al. [29]	Psychiatric patients (49 with dementia) (Netherlands)	1	3.90+	82	78	0.88	0.79	–
Bustamante et al. [23]	Hospital outpatients and controls (Brazil)	1, 4	3.41+	76	71	0.83	0.97	–
Perroco et al. [9]	Old-age clinic patients with low education (Brazil)	1, 4	3.53+	91	71	0.85	1.00	0.94
Lim et al. [30]	Cognitively normal volunteers and 53 dementia patients (Singapore)	2	3.40+	153	–	0.94	0.94	–
Stratford et al. [31]	Memory clinic patients (Australia)	4	4.00+	577	73	–	–	0.82
Tang et al. [32]	Stroke patients (China)	2	3.40+	189	68	0.88	0.75	0.88
Isella et al. [22]	Cognitively normal volunteers and 45 MCI patients (Spain)	6	3.45	100	71	0.84	0.75	–
IQCODE (*short version*)								
Ayalon [5]	Epidemiological study (USA)	1, 2	3.30+	462	80	0.77	0.93	0.89
Ayalon [5]	Epidemiological study (USA)	7	3.30+	441	79	0.55	0.93	0.89
Jorm [2]	Epidemiological study (Australia)	1	3.38	684	70+	0.79	0.82	0.85
Jorm et al. [18, 19]	Ex-servicemen (half former prisoners of war) (Australia)	3	3.38+	144	73	0.75	0.68	0.77
Del-Ser et al. [28]	Neurology clinic outpatients (Spain)	1	3.88	53	69	0.79	0.73	0.77
Harwood et al. [33]	Medical inpatients (England)	1	3.44	177	65+	1.00	0.86	–

(continued)

Table 8.2 (continued)

Study	Sample	Diagnostic criteria[a]	Cutoff	*N*	Mean age/age range	Sens.	Spec.	ROC curve
Knafelc et al. [20]	Memory clinic patients (Australia)	1	3.60+	323	44–93	0.94	0.47	0.82
Narasimhalu et al. [34]	Dementia clinic patients and stroke patients (Singapore)	2	3.38+	576	66	0.78	0.86	0.89
Perroco et al. [9]	Old-age clinic patients with low education (Brazil)	1, 4	3.53+	91	71	0.85	1.00	0.96
IQCODE-MMSE (3MS) (combined)								
Bustamante et al. [23]	Hospital outpatients and controls (Brazil)	1, 4	25/26 or 3.41+	76	71	0.83	0.98	–
Flicker et al. [16]	Memory clinic patients (young, Australia)	1, 5	21/22 or 4+	299	73	0.86	0.57	–
Flicker et al. [16]	Memory clinic patients (old, Australia)	1, 5	21/22 or 4+	78	80	0.92	0.61	–
Hancock and Larner [26]	Memory clinic patients	2, 5	23/24 or 3.60+	144	67	0.95	0.36	–
Khachaturian et al. [b][35]	Stratified population survey (USA)	5, 8	86/87 or 3.27	839	~81 65–90	0.98	0.68	0.96
Knafelc et al. [20]	Memory clinic patients (Australia)	1	Weighted sum	323	44–93	0.91	0.63	0.88

[a]1, DSM-IIIR Dementia; 2, DSM-IV Dementia; 3, ICD-9; 4, ICD-10 Dementia; 5, Clinical diagnosis; 6, Mild Cognitive Impairment (Petersen 1996 criteria); 7, Cognitive Impairment No Dementia (CIND); 8, NINCDS-ADRDA

[b]Using the 3MS

The structure of the IQCODE has been examined through factor analysis in several studies. All found a large main factor thought to represent "cognitive decline" and accounting for 42–73 % of the variance, while other factors were small, explaining at most 10 % of the variance [8, 11, 12, 29, 37, 39].

8.5 Validation Against Clinical Diagnosis

The validity of the IQCODE against clinical diagnosis has been demonstrated in multiple studies. Table 8.2 presents sensitivity and specificity statistics of the long and short forms of the IQCODE and the MMSE against clinical diagnoses [10, 40]. The IQCODE characteristics compare well with those of the MMSE which suggests that it is a valid screen for dementia and that in some circumstances, it may be a more sensitive instrument. However, moderate correlations between the IQCODE and the MMSE in 15 studies (4,538 participants) ranging from −0.245 to −0.78 [5, 26, 40, 41] with a sample-size weighted average of −0.49 suggest that each of these two tests, although largely overlapping, has some unique variance. As a consequence, a number of studies have investigated whether the concurrent administration and scoring of the IQCODE and the MMSE improve dementia detection. They generally reported somewhat increased sensitivity and/or specificity of the combined tests but cost benefits of this combination varied depending on the methodology or the type of sample used [16, 20, 23, 26, 27, 40].

In any case, where the MMSE is selected as the main screening instrument, the IQCODE can be used as an alternative screening test when individuals are not able to complete it and in order to minimize missing values. For example, in a survey of 839 community-based older individuals, Khachaturian et al. found 74 subjects who were unable to complete the Modified Mini-Mental State (3MS; see Sect. 3.2.2) but for whom the IQCODE could be completed by an informant. Seventy-one of these were subsequently diagnosed with dementia [35].

In addition to being a screening tool for dementia, the IQCODE has also been investigated as a predictor of Mild Cognitive Impairment (MCI). Isella et al. found the IQCODE was as sensitive as the MMSE for discriminating between MCI and healthy controls (sensitivity 0.82, specificity 0.71 for a cutoff of 3.19) [22]. In addition, while the IQCODE was a good predictor of conversion from MCI to dementia over a 2-year follow-up period (sensitivity 0.84, specificity 0.75 for a cutoff of 3.45), the MMSE was not a significant predictor. In another study which included 441 participants with an average age of 79 years and using the clinical criterion of Cognitive Impairment No Dementia (CIND), Ayalon reported that the IQCODE (based on ratings of change over the previous 2 years) had moderate sensitivity (0.55) but excellent specificity (0.93) in discriminating between CIND and normal controls (with a cutoff of 3.30) [5].

The validity of the IQCODE has also been assessed using postmortem dementia diagnosis based on histological analyses. One study using a cutoff of 3.7 and a neuropathological diagnosis of Alzheimer's disease (AD) found the IQCODE to have a

sensitivity of 73 % and a specificity of 75 % [42]. Another study used a cutoff of 3.42 and a diagnosis of AD, vascular, or mixed dementia, and reported a sensitivity of 97 % and a specificity of 33 % [43].

The IQCODE is not generally useful in differential diagnosis of specific neurodegenerative diseases, although one study found that patients with behavioral variant frontotemporal dementia scored higher than those with probable Alzheimer's disease [44].

8.6 Neuropsychological Correlates

In addition to studies specifically aimed at validating the IQCODE against some other standard, a number of studies have investigated associations between IQCODE ratings and neuropsychological functioning. IQCODE scores were found to be significantly associated with the following cognitive domains in neuropsychological testing: executive function (Visual Verbal Test, Trail Making Test B [41]), language (Boston Naming Test [41], Verbal Conceptual Thinking [45]), memory (CERAD Word List, WMS-R Logical Memory [41], Verbal Memory [45]), and attention (Trail Making Test A [41], Forward Digit Span [45]).

The IQCODE has also been validated against change in cognitive tests over time. In a community sample, scores on the IQCODE were found to correlate with change over 7–8 years in the MMSE, episodic memory, and mental speed [46]. In another study, surveying women living in the community aged 60 years and above, IQCODE scores were found to be associated with change in language, memory, and attention [41].

In another study, Slavin et al. used a modified version of the short IQCODE with a 5-year timeframe to assess associations between subjective memory difficulties reported by participants, informant reports, and objective memory impairment on neuropsychological tests in a cohort including individuals with ($n=493$) and without impairment ($n=334$). While participants' reports of subjective memory difficulties did not differ between those with and without impairment, informants' reports did with a mean score of 2.42 in those with no objective memory impairment, 3.51 in those with difficulty in one memory domain, and 3.91 in those with difficulties in multiple memory domains [47].

8.7 Neuroimaging Correlates

If the cognitive changes estimated with the IQCODE are due to progressive conditions such as dementia and other neurodegenerative diseases, these changes would be expected to be associated with concurrent or precursor changes in brain health. Indeed, a number of studies have reported such associations. For instance, in a community sample of older ex-servicemen, Jorm et al. found significant associations

between the IQCODE and the width of the third ventricle ($r=0.29$), and infarcts in the left ($r=0.35$) and right ($r=0.26$) hemispheres [18]. Cordoliani-Mackowiak et al. reported significant correlations between leukoaraiosis ($r=0.38$) and IQCODE in elderly stroke patients [48], while another study found that leukoaraiosis accounted for 18 % of variance in IQCODE scores [45]. Henon et al. found significantly higher mean IQCODE measures in individuals with smaller medial temporal lobe measures [49]. In a diffusion tensor imaging study of stroke patients, Viswanathan et al. detected lower diffusion measures in the non-affected hemisphere, which were interpreted as showing decreased cerebral tissue integrity in those whose pre-morbid cognition was below a cutoff of 3.4 on the IQCODE [50]. High scores on the IQCODE have also been associated with greater cerebral atrophy [51, 52]. Moreover, Henon et al. studied 170 consecutive stroke patients who underwent a CT scan at admission and for whom an informant completed the IQCODE. They found that 55.3 % of patients who were rated 104 or above on the long version of the IQCODE had medial temporal lobe atrophy compared to only 5.3 % of those who scored below this cutoff [49].

8.8 Alternate Applications

Although the IQCODE was developed to assess cognitive decline from a pre-morbid state in older populations, it has also been successfully applied in other contexts.

8.8.1 Retrospective Estimate of Cognitive Change

It would generally be preferable to assess baseline cognition before events that may adversely affect cognition occur. However, there are many occasions when such events cannot be foreseen or, when they can, where conducting a baseline assessment is either impractical or unlikely to produce reliable results. In such cases, the IQCODE can be a useful instrument to estimate cognitive change once acute effects of injury or treatment have waned.

8.8.1.1 Post-surgery

de Rooij et al. investigated the cognitive and functional outcomes of planned and unplanned surgical interventions in a population of older (>80 years) individuals after a follow-up of 3.7 years [53]. The IQCODE was used to assess cognitive decline. Of 169 individuals assessed, 17 % were found to have a severe cognitive impairment (IQCODE > 3.9) and 56 % were found to have mild to moderate impairment (3.9 > IQCODE > 3.1). Importantly, those patients who underwent unplanned

surgery were found to have a more than twofold increased risk of cognitive impairment at follow-up. It should be noted that this study has significant limitations, as cognitive status prior to surgery was not available and could explain the events leading to unplanned surgery and/or the subsequent assessment of cognitive impairment. Nevertheless, in such clinical contexts, the IQCODE can provide useful information on cognitive change potentially relating to clinical factors which otherwise could not have been studied in this cohort.

8.8.1.2 Post-pharmacological Treatment

The IQCODE may be used as a supplementary outcome measure following pharmacological treatments or intervention where neuropsychological measures are also available. For example, in a randomized controlled trial of B-vitamin aimed at lowering homocysteine levels in 266 MCI individuals to optimize cognition, the IQCODE was used as a clinical outcome [54]. As well as being associated with decreased homocysteine levels and improved cognition on executive function (but not the MMSE, episodic or semantic memory, or delayed recall), B-vitamin treatment was found to be associated with better IQCODE and Clinical Dementia Rating (CDR) scores in those with homocysteine levels in the top quartile. By contrast, the IQCODE was not found to be useful in a study by Aaldriks et al. in which it was used to estimate cognitive change following different doses of chemotherapy for cancer treatment. Although cognitive decline was detected with other instruments posttreatment, the IQCODE was not found to be sensitive to these changes [55].

8.8.1.3 Poststroke or Trauma

The IQCODE has been shown to be a predictor of incident dementia in stroke patients [3, 56] and in non-demented hospital inpatients [57] over 2-3 years of follow-up. Moreover, Tang et al. reported that in a population of 3-month poststroke patients where the IQCODE was validated against a clinical diagnosis of dementia (DSM-IV), the IQCODE had good psychometric characteristics (sensitivity 88 %, specificity 75 %), albeit not sufficient for use of the IQCODE as a sole dementia screening instrument [32]. Overall, application of the IQCODE to complex clinical populations should be considered carefully, as another study found that the IQCODE and the MMSE were poor at detecting dementia in a sample of first-ever stroke patients [58].

However, the IQCODE can be used to detect cognitive decline preexisting to strokes or trauma to avoid misattributing cognitive change to a clinical event when impairment was preexisting. For example, Jackson et al. used the IQCODE with a cutoff of 4 to determine whether cognitive impairment detected following traumatic brain injury was due to this injury or whether it was preexisting and found that one patient, representing 3 % of the sample, had preexisting cognitive impairment [59]. In another study, Klimkowicz et al. were interested in assessing factors associated

with prestroke dementia. Using the long version of the IQCODE with a cutoff of 104, they estimated that 12 % of 250 stroke patients had likely suffered from prestroke dementia and found that old infarcts on CT, cerebrovascular disease, and gamma-globulin levels at admission were the strongest factors associated with prestroke dementia. Moreover, based on their IQCODE classification, they found that patients with poststroke dementia were more likely to carry a variant of the alpha-1-antichimotrypsin gene than controls or those classified as suffering from prestroke dementia [51].

8.8.2 Prospective Risk Assessment

Priner and colleagues [60] assessed the short form of the IQCODE as a predictor of postoperative delirium following hip or knee surgery. Using a cutoff of 3.1, they found that those with preexisting impairment at admission had a more than 12-fold increased risk of delirium. In another study, the pre-morbid cognitive status of stroke patients was assessed retrospectively with the IQCODE and those with a score greater than 4 were found to be at higher risk of developing epileptic seizures [61] and of dying [62]. Pasquini et al. also investigated the risk of institutionalization in stroke patients and found that those with an IQCODE score greater than 4 at admission had a higher risk of being institutionalized 3 years later [63].

8.8.3 Self-Assessment with the IQCODE

It is unclear whether cognitive decline can be assessed by self-report, as neurodegenerative diseases are also associated with a progressive loss of insight. To investigate this question, a version of the IQCODE adapted for self-report (the IQCODE-SR) has been produced. Jansen et al. investigated whether using the IQCODE as a self-report instrument was feasible [38]. They administered the questionnaire by mail to 2,841 individuals (58.9 % of target population) recruited while visiting their general practitioner. More than 60 % of participants reported completing the questionnaire without help. While IQCODE scores were not validated against clinical diagnoses, patients suspected of having dementia by their GP scored higher than those who were not (3.7 vs. 3.3). Moreover, the authors found that the questionnaire had good internal consistency and concluded “the IQCODE-SR meets the basic requirements of a good measurement instrument” [38].

Using data from a 3-year longitudinal study, Gavett et al. compared informant- and self-IQCODE ratings at the final assessment with performance and change in performance on a range of neuropsychological tests [41]. They found that while the informants’ ratings correlated negatively with the participants’ cognitive performance on all tests, associations between self-report and cognitive measures were weak and mixed. More important, however, is that the change in informant ratings

over 3 years was significantly associated with change in cognitive performance but also with the subject's report of increased depressive symptomatology and decrease in Instrumental Activities of Daily Living (IADL). This suggested that as greater impairment was reported by informants, independently assessed measures of functioning were also declining.

Recently, we also investigated the validity of the IQCODE-SR against cognitive decline in a large longitudinal study of aging, the PATH Through Life project [64]. In a cohort of 1,641 individuals followed up over 8 years, IQCODE-SR ratings were found to be associated with decline in processing speed but not with performance in a number of cognitive domains including verbal fluency, working memory, and immediate and delayed recall. Higher IQCODE-SR scores were also modestly associated with report of IADL problems and with the APOE E4 genotype.

Ries et al. investigated the cerebral correlates of self-awareness in MCI [65]. They computed a discrepancy score between self-rated and informant-rated IQCODE scores as a measure of awareness and also asked individuals to reflect on whether adjectives presented to them described them accurately while undergoing functional Magnetic Resonance Imaging (fMRI). Analyses showed that in MCI individuals, decreased activation in the medial frontal cortex and posterior cingulate was associated with increased discrepancy scores, suggesting that decreased awareness has an organic origin in cognitive impairment. An implication of this research is that, as disease processes progress, self-assessment on the IQCODE or other instruments is unlikely to be reliable. There is, however, the possibility that in addition to informant reports, discrepancy scores between informant- and self-reports might provide useful additional information.

In aggregate, the findings reviewed suggest that the IQCODE-SR may be somewhat indicative of objective cognitive and functional decline but are also strongly influenced by depressive symptomatology. This is not surprising in itself since depression and loss of insight are known risk factors/correlates for AD and other dementias. However, the implication of the available evidence is that the IQCODE-SR is not a robust indicator of cognitive decline by itself but could be useful as a complement to the IQCODE ratings and should be investigated further.

8.9 Bias and Limitations

A concern for all instruments assessing cognition is that they may be influenced by factors unrelated to the measure they have been designed to assess such as sociodemographic, ethnic, language, gender, clinical, or cultural characteristics of the person being assessed. For example, performance on the most widely used dementia screening test, the MMSE, has been found to be influenced by gender, age, education, socioeconomic status, occupation, cultural background, language spoken at home, and presence of a mood disorder [66, 67]. The IQCODE has been found to be minimally influenced by education [2, 8, 11, 25, 27, 28, 36, 68, 69] and by proficiency in the language of the country of residence [70]. On the other hand, the

IQCODE can be biased by informant characteristics. Informants who are depressed, anxious, or stressed tend to report greater cognitive decline than indicated by direct cognitive testing [41, 71], so the emotional state of the informant needs to be considered when interpreting IQCODE scores. Furthermore, two recent studies have found that IQCODE scores from African-American informants are less sensitive to CIND than those of white informants [72, 73]. One of these studies attributed this difference to the lower average level of education in African-Americans.

8.10 Conclusion

The IQCODE is a simple, quick, and valid instrument to assess cognitive change. It can be administered in paper form, on the telephone, or in electronic format. It has been mainly validated in older populations, but recent evidence suggests it is a useful tool to investigate change in cognitive status in clinical contexts.

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Chapter 9
TYM (Test Your Memory) Testing

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Abstract The Test Your Memory (TYM) test is a new short cognitive test for the detection of Alzheimer's disease and other cognitive problems. The TYM test is a form with ten tasks which is filled in by the patient and takes little medical time to administer. TYM test studies have shown that it is easy to use and can be reliably scored. The TYM test is more sensitive to mild Alzheimer's disease (AD) than the Mini-Mental State Examination (MMSE). TYM scores in AD correlate strongly with scores from the Addenbrooke's Cognitive Examination (ACE-R) and MMSE. The TYM test is being adapted for use in many different countries and cultures. Validation studies are under way around the world and successful studies from Japan, China, and the UK have been published. The TYM test is also useful in the detection of non-Alzheimer dementias. The TYM test is also being adapted and validated for use in a variety of clinical areas in primary and secondary care. The website (www.tymtest.com) is a source of further information and allows the test to be downloaded by health professionals.

Keywords TYM • Alzheimer's disease • Dementia • Short cognitive tests

9.1 Introduction

The Test Your Memory (TYM) test is a new short cognitive test designed to help health professionals in the diagnosis of Alzheimer's disease and other forms of dementia. It was invented by the author in 2007 and first published in 2009.

9.2 Origins

There are a multitude of different cognitive tests available. Therefore, a good excuse is needed before introducing yet another.

The need for a new test seemed obvious to me. I have a "hub and spoke" consultant neurology post working at Addenbrooke's Hospital, Cambridge, as the center with a commitment to the memory clinic and at the Queen Elizabeth Hospital, King's Lynn, as the peripheral hospital. Working in the memory clinic at Addenbrooke's all seems fine. A research nurse administers the latest version of the Addenbrooke's Cognitive Examination (ACE-R; see Chap. 4) [1] to the patients before they are seen. The ACE-R contains the Mini-Mental State Examination (MMSE; see Chap. 2) [2]. The ACE-R takes about 20 min to administer and gives a good overall impression of a patient's cognitive function.

At King's Lynn, the story is very different. The ACE-R is a distant dream. The MMSE is the gold standard filled in by the more diligent physicians. The vast majority of patients admitted with memory problems have no assessment at all. There has been some improvement in recent years and the Mental Test Score (MTS) [3] is now included in the medical clerking. However, a recent local audit of elderly inpatients

revealed that two thirds have no cognitive assessment at all, a quarter have the MTS, and 5 % have the MMSE. Conversations with colleagues and audit results elsewhere revealed a similar picture at other hospitals.

In primary care, there are similar problems. Many patients with dementia never have a cognitive assessment. Referral letters for the memory clinic from primary care often include no memory assessment and those which do have an assessment generally have the MTS or MMSE.

Therefore, there is a need, not for a replacement for the MMSE, but for a test to do when currently no test is done. The challenge was to produce a memory test which was comparable in usefulness to the ACE-R, but which would take less medical time to administer than the MMSE.

A solution came with a patient who was waiting to see me in my overbooked outpatient clinic. The doctor's referral letter said they had a memory problem. The patient was filling the waiting time by doing Sudoku puzzles. With the MMSE taking 10 min or an ACE-R taking 20 min, I hardly had time to test their memory during the consultation. If the patient could do Sudoku, then surely they could complete other cognitive tests while waiting to be seen. The test could be supervised by the clinic nurse. Testing recall for new material could be done by registering a sentence on the first page and then writing it out on the reverse side of the paper. The first TYM prototype followed.

The TYM test [4] was designed to be attractive and friendly. I wanted the patient to feel they were filling in a puzzle, not undergoing a threatening examination. Hence the name "Test Your Memory" rather than "mental examination." Early versions were tried out on the family and volunteers. Numerous small changes were needed, all were in the same direction – to make the TYM clearer and easier (Fig. 9.1).

9.3 Administering the TYM Test

The TYM test is very easy to administer. I can explain how to supervise the TYM test to a new nurse in clinic in about 30 s. The time a patient takes to do the test varies from 2 minutes up to 10 minutes. Patients with significant dementia generally take the longest time to complete the test. The test and instructions can be downloaded from the website (www.tymtest.com).

9.4 Requirements of a New Test

The key requirements for a test to be successful in primary care or general medicine are that it uses a minimum of medical time, tests a wide range of cognitive functions, and is sensitive to mild Alzheimer's disease. The gold standard test is the MMSE; it has proven remarkably robust but arguably fails all three of these

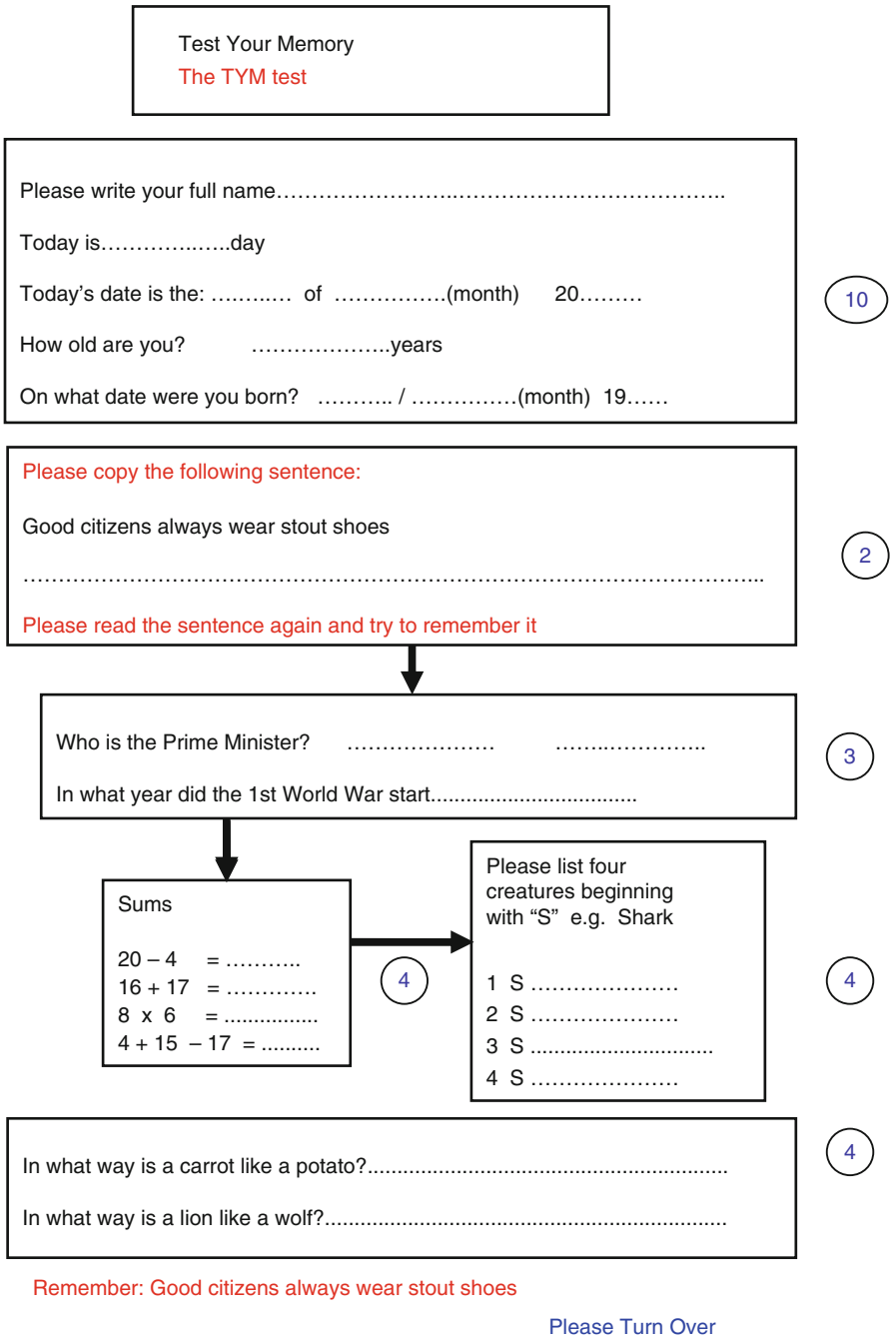


Fig. 9.1 The Test Your Memory (TYM) test

Please name these items

1 ……

2 ……

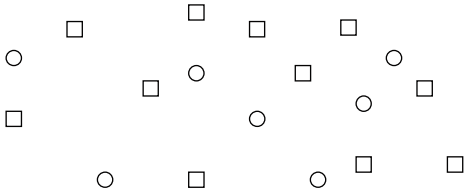
3 ……

4 ……

5 ……

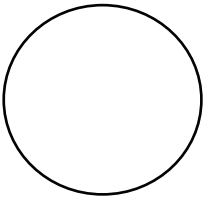
5

Please join the circles together to form a letter
- ignore the squares



3

Please draw in a clock face, put in the numbers 1 – 12 and place the hands at 9.20



4

Without turning back the page, please write down the sentence you copied earlier :

……

6

FOR THE TYM TESTER:
HELP GIVEN: NONE/TRIVIAL/MINOR/MODERATE/MAJOR

5

TICK BOX IFANSWERS WRITTEN FOR PATIENT ☐

/50

Fig. 9.1 (continued)

requirements [4–7]. Tests which pass the time requirement such as the Mental Test Score are less useful than the MMSE [8].

Test such as the ACE-R [1] test an excellent range of functions and are now used in memory clinics throughout the world, but take far too long to administer for most clinicians. Of the current short tests, only the ACE-R is sensitive to the milder forms of Alzheimer's disease.

There was a paradox to resolve of how to test a patient's cognition more thoroughly but to use less medical time. The TYM test was designed to overcome this paradox by using a test which the patient fills in under supervision before or after the consultation. The TYM (Fig. 9.1) is marked out of 50; the distribution of the marks and some comments are shown in Table 9.1.

There are several features of the TYM worth emphasizing:

1. The TYM test avoids orientation in place. 5/30 marks in the MMSE are awarded for orientation in place, and a patient with dementia is much more likely to score well on this part of the test in their own home than in hospital. If a patient is transported over the county line to an outpatient clinic, they may instantly lose four points (not five as the country remains the same). This is a serious drawback of the MMSE.
2. The sentence recall is the most sensitive of the subtests to mild Alzheimer's disease. Each of the six words conveys information; there are no pronouns. The sentence is not logical, so cannot be recalled from the first couple of words and is not a well-known phrase. The sentence has ended up as a slightly odd, rather "British," phrase, and we have needed to alter it for other countries.

Table 9.1 Subsection scores for the TYM test

Box	Task	Score	Comments
1	Orientation	10	Avoids orientation in place
2	Copying	2	This is an easy task for most patients and is included to ensure the sentence is registered
3	Semantic knowledge	3	Has to be varied for different countries, e.g., president for prime minister
4	Calculation	4	Often done well in mild Alzheimer's disease.
5	Fluency	4	As it is category and letter specific, a surprisingly difficult task
6	Similarities	4	Often done well in Alzheimer's but can be impaired in frontal dementias
7	Naming	5	This is an easy naming task which most patients have little trouble with. A poor score suggests possible semantic dementia
8	Visuospatial 1	3	A task of visual skill but also of executive function (not unlike the trails tests) This task is hard for the normal, very elderly
9	Visuospatial 2	4	A typical clock drawing task
10	Sentence recall	6	The most difficult task for a patient with Alzheimer's disease
11	Help given	5	An executive task – filling in the test

3. It is important to have some tasks which most patients can do. If the patient fails all the tests they may become dispirited and stop trying. Equally it is important for the clinician to see what patients can do as well as what they cannot.
4. The fluency test demands a specific category and letter and so is more exacting than the equivalent tests on the ACE-R. Some patients tend to keep to furry mammals – this makes the task more difficult – there are lots of invertebrates and fish whose name starts with S but not too many mammals. The example "shark" is supposed to help lead people away from furry mammals.
5. Similarities is conventionally a test of frontal lobe function and is included in the TYM for this purpose.
6. It is now part of our routine to check that the patient has read the sentence again before turning over the page.
7. The naming test is quite straightforward for most patients; if they lack the visual skills to follow the arrows, then they only lose one point.
8. The first visuospatial skill task (VS1) is probably a test of executive function as much as of visual skills.
9. The TYM test contains three subsections which are designed to test executive function – the test VS1, the similarities, and help needed. This is unusual in short cognitive tests.
10. Most patients with mild AD do much better on the first page of the TYM than on the second.

9.5 Help Provided

The idea of using how well the patient fills in the test as a test of executive function is novel but works well in the TYM test. This is the part of the TYM test which new testers find most difficult. The aim of the tester is to give the patient a chance to show their abilities and to help them realize their best score – but not to do the test for them. Ordinary enquiries for clarification "will any kind of animal do?" or "how about vegetable?" do not count as help, and the patient may still score full marks. If the tester needs to intervene for the patient to improve their score, then this counts. Therefore, if the tester has to read out and explain the circles or squares or gently remind the patient that they have missed a section, this counts as help.

The TYM test can be administered very strictly by a trained tester; however, clinical experience suggests that it also gives useful results when used more casually.

9.6 Scoring the TYM Test

The TYM test was designed to be scored easily. TYM tests can be scored intuitively and such scoring is largely correct. For research and some clinical purposes, a more rigorous scoring system is needed. Box 9.1 shows the basic version which covers many possibilities. There is also a research guide which is three pages long and covers nearly every answer and is available from the author.

Box 9.1: TYM Scoring
Spelling/abbreviations/punctuation are unimportant if the words make sense (with the exception of box 2). Minimum score on a question is 0

Box 1 2 points for full name, 1 for initials/other minor error

1 point for each space correctly filled in the remainder of the box. If the date is wrong by a day, it still scores a point

Box 2 2 points all correct, 1 point – mistake in 1 word, 0 – mistakes in 2

Box 3 1 point for first name 1 for surname. 1,914 scores 1 point, total 3

Box 4 1 point for each correct sum

Box 5 Any creature is fine: bug, fish, bird, or mammal. Breeds of dog/cat, e.g., spaniel, are fine. Mythical creatures (e.g., sea monster) and shark not allowed

Box 6 2 marks for precise word such as "vegetable" or "animal/mammal/hunter/meat eater/pack animal." Reasonable but less precise answer such as food, four legs, or fierce scores 1 point. Two such statements score 2, e.g., "grows in ground," "fierce and four legs" = 2

Jacket naming Answers are collar/lapel/tie/pocket/button, 1 each. Shirt is acceptable for answer 1 and jacket/blazer acceptable once for 2 or 4. Correct names but muddled order – lose 1 point

Letter W If traced with no mistakes 3 points, another letter formed 2 points, if all circles are joined, 1 point

Clockface All numbers 1, correct number position 1, correct hands 1 each

Sentence Score 1 point for each word remembered up to maximum 6

Please add the score for the amount of help the patient needed:

The definitions of trivial, etc., are in the TYM testing sheet

None	Score + 5
Trivial	Score + 4
Minor	Score + 3
Moderate	Score + 2
Major	Score + 1

A more detailed scoring sheet is available at www.tymtest.com.

In the original validation study, three different individuals with different degrees of training scored the TYM tests independently with the help of the brief guide. There was excellent correlation between the three scorers (Pearson r (r^2) correlation = 0.99). This contrasts with other short tests, for example, the MTS, for which scoring can be surprisingly variable [9].

9.7 Validation of the TYM Test

9.7.1 Index Study

There are different ways of validating a new cognitive test. The easiest trial of a new test is to compare the performance of patients with established Alzheimer's disease with pre-screened healthy controls. In this environment, a reasonable test will perform extremely well. The specificities and sensitivities produced by such a protocol can be impressive and are sometimes used in review papers to compare tests. The problem is that this is too easy; the more advanced the dementia and the more pre-screened the controls, the more impressive will be the sensitivity and specificity.

A second method is to use patients with mild disease and matched, unscreened controls. This is the model we used.

A third method of validation is to use the test in the clinic on all patients presenting with memory problems and then compare the results of patients diagnosed with Alzheimer's disease with those not given a diagnosis of dementia. This has the advantage of having direct clinical application but leads to other problems. The major problem is that in memory clinics, not all patients on their first visit are divided into two groups: Alzheimer's disease (or dementia) and normal. Many patients are in between. Some of these are regarded as having mild cognitive impairment (MCI). One form of MCI, amnestic MCI, is on a spectrum with AD [10]. Should these patients be regarded as having mild AD or as "not demented?" If they are treated as not demented, then a sensitive test which picks up their deficits will appear inferior to an easier test which fails to detect milder problems.

The original TYM test validation [4] was performed with patients, with predominantly mild AD, usually on their first visit to a memory clinic. The setting was the Cambridge Memory Clinic at Addenbrooke's Hospital. The controls were relatives of the patients attending the clinic. When we needed to extend the age range and number of controls, relatives of other patients attending Addenbrooke's Hospital and the Queen Elizabeth and north Cambridgeshire hospitals were recruited. The memory clinic controls are likely to be of the same educational background as the patients and are the most useful group to compare to the patients.

In the study, 108 patients with a clinical diagnosis of Alzheimer's disease or amnestic MCI were compared to age-matched controls. There is a problem deciding where amnestic MCI ends and where AD begins. The official discriminator, whether the cognitive problems affect lifestyle, is too subjective. The patients with a clinical diagnosis of amnestic MCI were divided into AD and amnestic MCI on the basis of their ACE-R score using the official cut-off of <83/100 [1]. Therefore, patients with a clinical diagnosis of amnestic MCI who scored 82 or less were included in the AD cohort. Patients with a clinical diagnosis of amnestic MCI who scored 83 or more on the ACE-R were treated separately as amnestic MCI.

The 94 patients in the AD cohort had an average age of 69 years. These patients had mild to moderate AD, scoring an average of 67/100 on the ACE-R and 23/30 on

the MMSE. On the TYM test, they scored an average of 33/50. The age-matched controls scored 47/50 – so there was a very clear difference between the patients and controls. This was highly significant and indeed all the subtest scores (except copying) showed significant differences between AD patients and controls. The data from this study and a second TYM validation study are shown in Table 9.2. The second validation study excluded all patients with "moderate" AD, that is, patients scoring less than 20 on the MMSE, and this is reflected in higher TYM, ACE-R, and MMSE scores. The results from the two studies show an almost identical pattern.

Examining the contribution of the subtests, the largest differences were observed in delayed recall where patients scored only 17 % of the score of the controls. There were also major changes in semantic knowledge, where average AD patients scored 53 % of the score of the average control, and fluency where AD patients scored 62 % of the controls.

Analysis of the controls of all ages showed that the TYM score was relatively constant until the age of 70 years, averaging 47/50, but there was then a decline more marked after the age of 80 years. The stability of the score up until age 70 is in part the result of slightly poorer scores on most sections but better scores on semantic knowledge with increasing age.

Educational effects are present but are relatively mild; this is probably because the TYM is quite an easy test so there is a ceiling effect. The effect of education has been studied thoroughly in some of the foreign validations (not published yet).

Table 9.2 TYM testing in Alzheimer's disease

	Maximum score	Controls	AD first study	AD second study
Number		482	94	100
Average age (years)		69	69	70
Orientation	10	9.8	8.3	8.8
Copying	2	1.9	1.7	1.9
Knowledge	3	2.5	1.4	1.7
Calculation	4	3.7	3.1	3.4
Fluencies	4	3.4	2.2	2.4
Similarities	4	3.5	3.0	3.3
Naming	5	4.9	4.4	4.6
Visuospatial 1	3	2.7	1.8	2.2
Visuospatial 2	4	3.7	2.9	3.5
Recall	6	5.0	0.9	0.9
Help	5	4.9	3.7	4.5
Overall score	50	46	33	38
MMSE			23	25
ACE-R			67	76

Adapted from [4]

Comparison of performance on TYM between patients with Alzheimer's disease and controls in the first and second studies

The Cronbach's α was 0.8 for all participants and subsets showing good internal consistency. The area under the ROC curve for differentiating Alzheimer's disease from controls was 0.95. With the help of a scoring guide, the TYM scoring showed excellent inter-rater agreement between experienced and less experienced scorers. Analysis of the ROC showed that the optimal cut-off for the TYM test was ≤42/50. Negative predictive values were very high, close to 100 % at a prevalence of AD of 5 %, showing that, in this population, the combination of a low initial suspicion of AD plus a TYM score>42/50 makes AD very unlikely. The positive predictive value for the TYM test at 42/50 was much lower, only 26 % – there are other reasons beside AD why patients may do poorly on the TYM test. This emphasizes that the TYM test is not a diagnostic test but is a useful screening test.

There are a number of other advantages of the TYM test including the relatively small influence of the tester. The test can also be scored and analyzed later by someone not present at the time.

9.7.2 Other UK Validation

Hancock and Larner [11] examined the use of the TYM test in two memory clinics. They minimized medical input by using relatives of patients to administer the tests to the patients. The authors used the third method of validation described above, testing all patients attending memory clinics. They placed patients with amnestic MCI in the "not demented" group. This is partly responsible for the lower cut-off for the TYM test in this study compared to the original study. They concluded that the TYM test was a useful screening test.

9.7.3 Validations in Other Languages

The TYM test has rapidly spread across five continents. It is interesting that the earliest validations came from countries with a very different culture to the UK with not only a different language but also a different alphabet – Japanese, Arabic, and Chinese. The successful validation of the TYM test in these languages suggests that it should be usable throughout much of the world.

Hanyu and colleagues [12] published the first foreign language TYM validation. This was a very thorough Japanese study which included neuropsychology and functional imaging for their Alzheimer's patients. Their findings were very similar to the original UK validation. Recently, a second Japanese group have also shown that the Japanese TYM is a useful test in the detection of early AD [13].

At the time of writing, validation studies have been published in Japan and China [12–14]. TYM studies have started in over 30 other countries including France, Greece, Norway, Egypt, South Africa, and Chile.

Important features of the TYM test are that it is environmentally friendly ("green"), low technology, and adaptable for use in the developing world. Dementia is common in the developing world and there are many treatable dementias, for example, those linked to HIV infection. It is going to be many years before magnetic resonance imaging or neuropsychological testing is available to the population of every country, but written tests such as the TYM are a more realistic prospect.

9.8 Why Use the TYM Test?

The case for the TYM test (or any other short test) is simple: a patient presenting with leg problems ought to have an examination of the legs. A patient presenting with cognitive problems ought to have a cognitive examination.

In medicine, the combination of a history that does not suggest a serious problem plus a normal examination helps exclude serious disease, a principle which underpins clinical medicine. The examination findings alone often do not lead to a clear diagnosis and may be misinterpreted if analyzed in isolation. It is the combination of the history and an adequate examination which is crucial.

To diagnose or manage patients purely on the TYM score is unwise, just as deciding whether a patient needs MRI scan of the spine purely on the presence or absence of ankle jerks is unwise. However, to neglect the examination and rely on the history alone may be equally foolish. Patients with cognitive complaints need a history and an examination by an experienced clinician – just as in other branches of medicine. The TYM test is a valuable part of the cognitive examination.

9.9 TYM Test in Specific Situations

9.9.1 Amnestic MCI

Thirty-one patients with amnestic MCI were tested on the TYM. These patients all scored ≥83/100 on the ACE-R (and greater than 25/30 on the MMSE). Their average scores were 87/100 on the ACE-R and 28/30 on the MMSE. On the TYM test, they scored on average 43/50. Their scores are compared to those of the controls and 94 patients in the original validation (Table 9.3).

The only significant difference between the two groups is in sentence recall. There is a non-significant decrease in semantic knowledge and fluencies (which are the next two tasks which patients with AD find most difficult). Therefore, the TYM test can detect many patients with amnestic MCI but on the pattern of scores, not the overall score.

Table 9.3 TYM testing in amnestic MCI

	Maximum score	Controls	AD first study	Amnestic MCI
Number		482	94	31
Average age (years)		69	69	69
Orientation	10	9.8 (96)	8.3 (83)	9.7 (97)
Copying	2	1.9 (95)	1.7 (85)	1.9 (95)
Knowledge	3	2.5 (83)	1.4 (47)	2.3 (76)
Calculation	4	3.7 (93)	3.1 (78)	3.7 (93)
Fluencies	4	3.4 (85)	2.2 (55)	3.2 (80)
Similarities	4	3.5 (88)	3.0 (75)	3.8 (95)
Naming	5	4.9 (98)	4.4 (88)	4.8 (96)
Visuospatial 1	3	2.7 (90)	1.8 (60)	2.7 (90)
Visuospatial 2	4	3.7 (93)	2.9 (73)	3.8 (95)
Recall	6	5.0 (83)	0.9 (15)	2.2 (36)
Help	5	4.9 (98)	3.7 (74)	4.8 (96)
Overall score	50	46 (92)	33 (66)	43 (86)
MMSE			23	28
ACE-R			67	87

Adapted from [4]
Comparison of performance on TYM between patients with Alzheimer's disease, amnestic MCI, and controls

9.9.2 TYM Test in Non-Alzheimer Dementias

Many patients with non-Alzheimer dementias have now completed the TYM test. Patients with dementia with Lewy bodies (DLB), frontotemporal dementia (FTD), and vascular dementia all score significantly worse than controls on the TYM test. In our original validation, non-AD patients scored 39/50 on the TYM. The MMSE was less good at detecting these diseases. These patients with non-Alzheimer dementias scored 25/30 on the MMSE (above the cut-off). The average ACE-R score was 77/100.

The pattern of scoring varies with the different forms of dementia. We are still analyzing results but certain trends are emerging:

1. Dementia with Lewy bodies. Patients tend to do worse on the copying, verbal fluencies, and the visuospatial tasks than patients with AD, but do better on the sentence recall.
2. Semantic dementia. The patients do very badly on the semantic fluencies and on the naming tests (the only group with this pattern). Tasks with more complex written instructions such as the similarities and first visuospatial task are also done more poorly than in AD. Because of the language disturbance, the sentence recall does not distinguish AD from Semantic Dementia.

3. Behavioral variant FTD (bvFTD). Patients can do very well but tend to do worse on fluencies, similarities, and help needed than patients with AD and better on knowledge and recall. Any patient who adds their own material to the TYM sheet has a high probability of bvFTD.
4. Progressive non-fluent aphasia. Patients do better on orientation and sentence recall but less well on similarities and fluencies.

It is a common fallacy that a short cognitive test might replace clinical experience in distinguishing the various types of dementia. Proper clinical assessment is always superior to short tests (for obvious reasons, e.g., many patients with DLB will have clinical features of parkinsonism). There are clear group differences between the different dementias, but it is not sensible to try and make the diagnosis on a TYM test alone.

9.9.3 TYM Testing Prior to Discharge or Surgery

The TYM test has been validated in the diagnosis of Alzheimer's disease, but its ease of use allows it to be used in purely "medical" ways. For example, it can be used by nurses planning the discharge of patients, or in patients prior to elective surgery. In these scenarios, the TYM test is used to try to predict the medical or surgical outcome of the patient rather than to make a specific diagnosis. Such studies are underway at the Queen Elizabeth Hospital, King's Lynn.

9.10 Comparison of TYM with the ACE-R and MMSE

In all our studies, there is a highly significant correlation between TYM scores and ACE-R scores, the percentage scores on the two tests are very similar in most dementias. As the ACE-R is scored out of 100 and the TYM 50, then the TYM score is approximately 50 % of the ACE-R score.

There is some overlap between the two tests but there are significant differences: the TYM has a more precise fluency test and is not dependent on orientation to place, but the ACE-R is superior for naming and tests a wider range of visuospatial skills. The TYM test contains more subtests designed to test executive function. Patients with bvFTD and those with more severe dementia do relatively worse on the TYM than the ACE-R which may reflect these tests of executive function.

In the Cambridge Memory Clinic, the ACE-R is used. The main disadvantage is that two people are needed in clinic to test all the patients – a resource not available in most clinical settings.

In the original study [4], the TYM test was clearly superior to the MMSE in detecting mild AD. There are other advantages of the TYM test: the influence of the tester is relatively small, and as with the ACE-R, the test can be analyzed later by someone not present at the time of testing.

9.11 Limitations of the TYM and Possible Solutions

9.11.1 Sensitivity to Mild Alzheimer's Disease

One problem, which is shared with all other short tests, is that the TYM test is not very sensitive to the earliest forms of AD. Early detection of AD will become particularly important once effective treatments are found. It is much more likely that such treatments will halt progression of AD rather than reverse the pathology, so there is a need for tests to detect AD at the earliest opportunity. All short tests only have a single task of verbal recall and no task for visual recall. A harder version of the TYM, the "Hippocampal" TYM, has been designed with five tasks of recall including visual recall to try to detect the earliest cases of AD.

9.11.2 Patients with Visual or Physical Problems

The TYM is less useful for patients with severe physical handicaps or blindness, although it is useful for patients who are deaf. These problems are being overcome. It is quite possible to fill in the ordinary TYM sheet for a person unable to write, like other short tests. This has been formalized in a version called the Talking TYM which has not yet been validated. A version easier to read and fill in has also been developed for patients with visual handicaps.

9.11.3 Self-Testing

The controversy over self-testing is based on a misunderstanding. The TYM was never intended as a self-test. It now seems obvious that the name gives this impression. After initial publication, numerous websites offered the public the chance to self-diagnose. Strenuous efforts have persuaded most to stop. In the paper itself [4] and in subsequent correspondence [15], I have tried to correct this impression.

9.11.4 Cultural Bias

A valid criticism of the TYM test is that it is culturally biased. Any cognitive test will show a bias; all our knowledge is culturally based and any test of our cognitive function will need to use this. The choice of the suit and tie is a male bias – although intended to be of widespread relevance. The sentence "Good citizens always wear stout shoes" is also rather more "English" than originally intended.

It was also envisaged that the TYM could be adapted to other cultures. Some adaptations are easier than others: the substitution of the word “tough” for “stout” makes the sentence more American. For European users, an alternative sentence “Great cooks always bake chocolate biscuits” is probably more appropriate.

Similarly, the semantic knowledge and the semantic fluencies need adaptations for different cultures. There are less predictable problems. In languages in which W is rarely used, inverting the W to form an M makes the letter tracing test too difficult (because M is not an inverted W). For some other languages, new drawings and more major changes are needed.

9.11.5 Safety

Another area for debate is whether the TYM is a safe test: could it lead to false reassurance in patients who have very early AD? This question is to misunderstand the use of the TYM test. It is simply a way to examine cognitive function in a formal way. The addition of a TYM test to a clinical assessment should add to the value of the assessment; TYM is not a substitute for a clinical assessment. As explained above, the TYM test alone should not be used for diagnosis and management of patients.

9.12 Tymtest.com

The website (www.tymtest.com) supports the TYM test, with more detailed instructions, downloading of the test, scoring systems, etc. The website was launched shortly after the original validation. It is designed for medical professionals, and the general public are discouraged from self-testing.

The website has a steady stream of visitors and several health professionals download the test daily; over 3,500 individuals from 65 different countries have downloaded the TYM test since the launch.

9.13 Conclusion

The TYM test is a valid short cognitive test with clear advantages over more established tests in some clinical areas. It is more sensitive than the MMSE in the detection of Alzheimer’s disease and takes much less medical time than the MMSE or ACE-R.

The future vision for the TYM test is of a website from which an interested professional anywhere in the world can download a series of short cognitive tests suitable for many different patients from various backgrounds. For example, an English

general practitioner would be able to print a short test suitable for a Chinese patient with very mild problems or a Lithuanian patient with visual problems. A start has been made, but there is a very long way to go.

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Chapter 10
The General Practitioner Assessment of Cognition (GPCOG)

Katrin M. Seeher and Henry Brodaty

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Abstract The General Practitioner Assessment of Cognition (GPCOG) is a very brief cognitive screening tool specifically designed for use in general practice. It is available free of charge as paper-and-pencil test or web-based interactive instrument via the GPCOG website (www.gpcog.com.au). Unlike other brief screening instruments, the GPCOG consists of a 5-component patient assessment and a brief informant interview (Six questions). Total administration time is less than 5 min. The diagnostic performance of the GPCOG was validated against DSM-IV-defined dementia diagnosis. In comparison to other widely-used cognitive screens such as the

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Mini-Mental State Examination (MMSE) or the Abbreviated Mental Test (AMT) the GPCOG performed at least as well as, if not better, than the MMSE and the AMT. The sensitivity and specificity ranges of the English GPCOG were 0.81–0.98 and 0.72–0.95, respectively. Validated translations of the instrument are published and available online (www.gpcog.com.au). The GPCOG and its informant component in particular were found to be free of demographic biases. In conclusion, recent reviews of dementia screening tools recommended the GPCOG as one of three tools to be used in the primary care setting based on its psychometric properties and time efficiency.

Keywords General practitioner • Primary care • Brief screening • Cognitive impairment • Clock drawing • Informant

10.1 Introduction

General practitioners (GPs) often blame lack of time, absence of suitable screening instruments or difficult access to screening tools as well as the uncertainty about management of dementia patients for not diagnosing dementia [1]. The General Practitioner Assessment of Cognition (GPCOG) was specifically designed to fill this gap [2]. Its administration time is much quicker than the commonly used Mini-Mental State Examination (MMSE). It has been specifically developed for the use in primary care and is easily available free of charge as paper-and-pencil test or web-based interactive instrument (www.gpcog.com.au) which automatically calculates total scores and recommends further diagnostic steps as appropriate to facilitate GPs' work [3].

Unlike other brief cognitive screening tools, the GPCOG consists of a cognitive assessment of the patient and a brief informant interview [2] which can be administered separately, together or sequentially [2]. It is recommended to use the parts sequentially. This will not only increase the predictive power of the test result as compared to the administration of the patient component alone [2, 4] but it will also improve time efficiency of the test [2] as only certain patient scores require additional information being collected from an informant (for more details see below). The administration of both parts takes less than 5 min, with about 3 min for the patient assessment and less than 2 min for the informant interview [2, 5].

10.2 Test Instructions

The administration of the GPCOG is very simple and intuitive and requires little training [5]. This is particularly favourable in the context of primary care since GPs lack time to undergo lengthy training. Prior to first administration, users are required to familiarise themselves with the items of the GPCOG [3].

Unless specified, every question of the cognitive component (i.e. patient assessment) is to be asked only once and items should be read to the patient as they are

presented on the paper form/computer screen [3]. Furthermore, it is advisable to ensure patients are wearing their glasses/hearing aids as appropriate. This will allow for the most accurate and fairest test result being obtained. Noises and disruptions should be minimised.

The informant interview should involve someone who preferably lives with the patient or at least knows him/her well enough to answer questions about his/her functional abilities compared to 5–10 years ago [2]. The interview can be conducted face-to-face or if more convenient over the phone [2]. Patient assessment and informant interview should be completed within a few days of each other.

10.3 Development of the GPCOG

The items of the GPCOG originated from three different instruments: The Cambridge Cognitive Examination (CAMCOG) as part of the Cambridge Examination of Mental Disorders of the Elderly (CAMDEX) [6]; the Psychogeriatric Assessment Scales (PAS) [7]; and the Instrumental Activities of Daily Living Scale [8]. Items were selected on grounds of sensitivity, concision and patient/GP acceptability [2]. From a large initial item pool, items with unsatisfactory difficulty or items that did not discriminate significantly between subjects with or without dementia in logistic regression analysis were eliminated [2].

10.4 Patient Cognitive Assessment

The GPCOG patient assessment consists of 9 items covering the following aspects of cognition: 'orientation' (1 item), 'visual spatial abilities and executive function' (2 items), 'retrieval of recent information' (1 item) and 'delayed verbal recall' (5 items; 5-component name and address for immediate and delayed recall).

The patient assessment starts with the acquisition of a 5-component name and address for the subsequent delayed recall task ('John' 'Brown' '42' 'West Street' 'Kensington'). The immediate recall is not scored as part of the GPCOG. It is followed by three evaluable and scored distractors: (a) one item testing orientation to time ('What is today's date?'; exact date required to score 1), (b) a 2-component clock-drawing test with simplified scoring rules (1 point for correctly placing numbers, 1 point for drawing in hands correctly), and (c) an item assessing retrieval of recent information ('Can you tell me something that happened in the news recently?'; detailed answer required). The patient assessment is completed by the delayed recall task ('What was the name and address I asked you to remember?'; one point for each component). Each correct answer scores one point leading to a possible range for the total score of 0–9 (with higher scores reflecting better function) [2].

10.5 Informant Interview

The GPCOG informant interview comprises 6 questions covering cognitive and functional abilities concerning problems recalling recent events (1 question), misplacing objects (1 question), word finding difficulties (1 question), managing finances (1 question), managing medications (1 question) and requiring help for transportation (1 question) [2]. For each question, the informant is asked to indicate whether compared to 5–10 years ago the patient's performance is worse or not. Each question not endorsed (i.e. reflecting no impairment) scores one point leading to a possible score of 6/6 with higher scores reflecting better function.

As mentioned, the two parts of the GPCOG were developed to allow for sequential administration of the patient and the informant component in order to maximise time efficiency for GPs. In other words, conducting the informant interview only adds incremental predictive value to performing the patient assessment alone if the patient scores between 5 and 8 on the patient assessment. Thus, the informant interview can be omitted without significantly worsening classificatory power of the test if a patient scores 9 (i.e. perfect score) or less than 5 (i.e. indicative of cognitive impairment) on the GPCOG patient assessment. In both cases, the GPCOG patient assessment alone has a diagnostic accuracy of about 90 % [5]. Scoring rules and cut-off scores are shown in Box 10.1.

Box 10.1: Scoring Rules and Suggested cut-off Scores of the GPCOG

- *GPCOG patient assessment*:

  Total score = sum of all correctly answered items
  Range of total score: 0–9 (higher scores indicating less impairment)
  9 = no significant cognitive impairment; further testing is not required (GP may consider follow-up assessment in 12 months)
  5–8 = more information is needed; conduct the GPCOG informant interview
  0–4 = cognitive impairment is indicated; standard investigations should be conducted

- *GPCOG informant interview*:

  Total score = sum of all rejected items, i.e. no worse than 5–10 years ago
  Range of total score: 0–6 (higher scores reflect less impairment)
  4–6 = no significant cognitive impairment; further testing is not required (GP may consider follow-up assessment in 12 months)
  0–3 = cognitive impairment is indicated; standard investigations should be conducted

Table 10.1 Psychometric properties of the GPCOG in different samples

Reference	N	% dementia	Sensitivity	Specificity	PPV	NPV	MC	AUC
Two-stage [2]	246	29 %	0.85	0.86	0.71	0.93	14.2 %	0.89
Aged < 75 [14]	32		0.82	0.94	0.90	0.88	11.1 %	
Aged 75 ≤ 80 [14]	128		0.81	0.95	0.77	0.96	7.9 %	
Aged > 80 [14]	123		0.88	0.72	0.67	0.90	21.9 %	
Edu ≤ 8 year [14]			0.82	0.89	0.78	0.91	13.5 %	
Edu > 8 year [14]			0.86	0.85	0.68	0.94	14.8 %	
Basic et al. [13]	151	38 %	0.98	0.77				0.97
Italian [5]	200	66 %	0.82	0.92	0.95	0.70	17.4 %	0.96
French [15]	280	65 %	0.96	0.62	0.83	0.90		

N = sample size, *%* = dementia prevalence, *PPV* = positive predictive value, *NPV* = negative predictive value, *MC* = misclassification rate, *AUC* = Area under the curve, *Edu* = education

10.6 Diagnostic Utility

The psychometric properties of the GPCOG (original English version) were determined using a sample of 283 community-dwelling GP patients aged 55–94 with a mean age of 79.6 ± 6.1 years of whom 29 % had dementia [2]. The diagnostic performance of the GPCOG was validated against the DSM-IV-defined dementia diagnosis as criterion standard and compared to the MMSE (see Chap. 2) and the Abbreviated Mental Test (AMT) [9]. The two-step sequential approach (i.e. GPCOG patient assessment followed by GPCOG informant interview if applicable) performed at least as well as, if not better than, the AMT and the MMSE in detecting dementia. The sensitivity and specificity (for the two-step sequential approach) was 0.85 and 0.86, respectively. The positive and negative predictive values (PPV and NPV, respectively) based on the 29 % dementia prevalence in this sample were 71 % and 93 %, respectively [2], making it a powerful tool to rule out dementia. The misclassification rate was 14.2 % for the GPCOG, compared to 23.0 % and 21.8 % for MMSE and AMT, respectively [2]. Psychometric properties of translated GPCOG versions (i.e. Italian and French) and for sub-samples (e.g. age, education) or other patient cohorts are shown in Table 10.1.

The GPCOG's ability to differentiate between various dementia subtypes or dementia and mild cognitive impairment has not been established yet. However, the GPCOG total score as well as its patient and informant sub-scores were found to differentiate between varying stages of dementia severity as defined by the Clinical Dementia Rating Scale (CDR; [10]) scores of 0, 0.5 and ≥ 1 [5]. This was still true when authors controlled for confounding variables such as age and education [5].

10.7 Demographic and Other Biases

Cognitive screening tools are often affected by patients' age, gender, education or cultural background [11, 12]. While being associated with patient's age in some [2, 5] but not all studies [13], the GPCOG was independent of patient's

gender [5, 13], education [13, 14] and cultural and linguistic background [13]. Additionally, the GPCOG informant interview was found to be free of any demographic (patient and informant) bias at all [14]. Patients' performance on the GPCOG also seems to be unrelated to their physical and mental health [2, 5], even though results are mixed [13].

10.8 Patient and GP Acceptability of the GPCOG

The vast majority of surveyed GPs rate the GPCOG as practical (87.8 %), economically viable (87.8 %), and most importantly acceptable to their patients (98 %) [2]. Most GPs were also either satisfied or very satisfied with the GPCOG (83.7 %) and indicated they would use it again (89.8 %) [2].

In an evaluation of the GPCOG website (unpublished data, evaluation still ongoing), the majority of participating GPs to date (N = 52 as at 31 December 2011) rated the web-based GPCOG as well as its accompanying website as useful tools (90 % and 100 %, respectively) and 86 % found the national guidelines that are provided helpful. The time spent on administering the GPCOG was regarded 'about right' by just over two thirds of surveyed GPs while one third rated it "as 'short'".

10.9 Conclusion

The GPCOG was developed as a screening instrument. It is not designed to measure cognitive or functional change over time nor should it be used as a stand-alone test to diagnose dementia. An abnormal GPCOG result is rather indicative for generally impaired cognitive function and warrants further investigation.

Research on the influence of patients' cultural and linguistic background implies that patients' performance on the GPCOG is not compromised by their cultural or linguistic status [13]. However, unless replicated by other studies, future research may still consider cultural and linguistic background as a potential confound. As mentioned previously, GPCOG's ability to differentiate between various dementia subtypes or mild cognitive impairment has not been established.

Nonetheless, there are practical advantages of the GPCOG over other screening tools. The GPCOG was specially designed for use in primary care. Its brevity together with its easy and intuitive administration (i.e. no lengthy training required) reduce the time constraints often reported by GPs [1]. Since the development of the GPCOG website (www.gpcog.com.au), the tool is easily accessible free of charge as a paper-and-pencil test but also as a web-based instrument which further facilitates GPs' daily routines [3]. Validated translations of the GPCOG are published and available online [3, 5, 15]. The GPCOG has been thoroughly studied in patient populations that it is intended to be used for (i.e. primary care setting and geriatric outpatients) demonstrating sound psychometric properties [2, 5, 14, 15]. Most

importantly, unlike other brief screening tools for cognitive impairment, the GPCOG contains an informant as well as a patient component. Incorporating informant data is particularly important as it not only adds to the predictive power of the screening tool [2, 4], but it also offers the chance of including information which is free of demographic biases; an artefact of many cognitive screening tools . As outlined above, the GPCOG informant interview has been shown to be free of any demographic bias [14]. Last but not least, in separate reviews of screening tools, the GPCOG was recommended as one of three screening tools (alongside the Mini-cog [16] and the Memory Impairment Screen (MIS) [17]) to be used in the primary care setting [18–20] based on its administration time being less than 5 minutes, a NPV greater or equal to MMSE's (0.92), misclassification rates less than or equal to the MMSE, and high sensitivity/specificity (greater or equal to 80 %) [18].

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Chapter 11
6-CIT: Six-Item Cognitive Impairment Test

Kiri Jefferies and Tim M. Gale

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Abstract The Six-item Cognitive Impairment Test (6-CIT) was designed to assess global cognitive status in dementia. Developed in the 1980s as an abbreviated version of the 26-item Blessed Information-Memory-Concentration Scale, the 6-CIT is an internationally used and well-validated screening tool for use in primary care. In recent years, it has been compared favorably to the Mini-Mental State Examination (MMSE) due to its brevity and ease of use, although it is still less widely used than the MMSE. Some evidence suggests that it outperforms the MMSE as a screening tool for dementia, especially in its mildest stage. The 6-CIT has been translated into many different languages. It comprises 6 questions: one memory (remembering an address), two calculations (recalling numbers and months backward), and three orientations (e.g. time of day, month, and year). The time taken to administer the scale is approximately 2 min, which compares favorably to other scales. However, this brevity has also been seen as disadvantageous, with the suggestion that more features

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of dementia can be detected in more comprehensive screening tools. Criticisms that the scoring system is too complex have been raised, but plans for the 6-CIT to be distributed with computer software could go some way to resolving this. In summary, the 6-CIT is a brief, validated screening tool that may be preferable to the currently, and more widely, used MMSE. Since a typical UK primary care consultation stands at only 7.5 minutes, the brevity and simplicity of the scale are its greatest advantages.

Keywords Dementia • Alzheimer's disease • Cognitive impairment • Test Screening

11.1 Introduction

The Six-Item Cognitive Impairment Test (6-CIT) is a short questionnaire for assessing global cognitive status in dementia [1]. It is an abbreviated version of the 26-item Blessed Information-Memory-Concentration Scale [2] and is sometimes known as the Short Blessed Test (SBT). 6-CIT was popularized by Brooke and Bullock in the UK [3], where it is sometimes known as the Kingshill test or version.

The scale is popular in both the UK and the US and has been widely used across different nationalities [4], especially in primary care. Validated in a number of studies (e.g. [1, 3]), the 6-CIT has been suggested as a favorable alternative to the Mini-Mental State Examination (MMSE) [5] owing to its brevity and simplicity of use. With the average duration of a typical UK primary care consultation being only 7.5 minutes, it is important that screening assessments are brief to administer. The 6-CIT excels over the MMSE in its short administration time, ease of use for practitioners, and simplicity for patients – for example, it does not include a figure copying section, thereby allowing individuals with visual impairment and tremors to complete the questionnaire.

Although the 6-CIT is brief, there is some evidence that it can outperform the MMSE in detecting dementia, particularly at its mildest stage [6]. Limitations of the MMSE have been discussed in comparison studies investigating multiple screening tools for cognitive impairment. Findings have frequently highlighted insensitivity to mild cognitive impairment (MCI) and mild Alzheimer's disease (AD) [7] with MCI often testing in the "normal" range on the MMSE [8]. Moreover, 35–50 % of early AD cases are missed when the classic MMSE cutoff is used [9, 10]. One further study asked 709 participants over the age of 80 to complete the MMSE as part of their annual checkup in a primary care setting [11]. Individuals who scored at or below the standard MMSE cutoff point of 26/30 were then asked to complete the GMS–AGECAT (GMS) diagnostic system [12] to identify case level dementia further. Two hundred and two individuals were assessed on the GMS, and of those, 29 (14 %) were found to have dementia. The MMSE cutoff used resulted in a false-positive rate of 86 %. Improvements in predictive value were made by adopting more

stringent cutoff points of 24/30 and 21/30; however, this still resulted in false-positive rates of 78 % and 59 %, respectively. These results further suggest that the MMSE may not be the ideal screening instrument for dementia in primary care [11].

A UK postal survey study carried out in 2008, which investigated the use of screening tools in primary care, found that 79 % of practices used at least one dementia screening tool, including the following: the MMSE and its variants (51 %), the Abbreviated Mental Test (AMT) (11 %), MMSE and AMT (10 %), MMSE and Clock Drawing Test (CDT) (8 %), MMSE and the Six-Item Cognitive Impairment Test (6-CIT) (6 %), and the CDT (5 %). The study touched upon the need for screening tools, other than the MMSE, to be more available to general practice surgeries [13]. It is important to note, however, that these findings may be limited to suggesting the intention by practices to use these scales rather than actual usage figures. Nonetheless, despite its limitations, the MMSE remains the most widely used screening tool [14].

The 6-CIT is easily translated into other languages, as demonstrated by Barua and Kar in an investigation of depression in elderly Indian patients [15]. The 6-CIT was used to assess cognitive impairment in individuals over 60 years of age and was translated into both Hindi and Kannada for the purposes of the study. To ensure its correct translation, Barua and Kar asked a study-blind psychiatrist to translate the test back into English, where it was found to remain textually correct to the original. Further evidence for multilingual translation of the scale is suggested by Broderick in which a modified 6-CIT was used in the Xhosa language of South Africa [16]. The 6-CIT is also used in two parallel versions for use in British and American populations [17].

11.2 6-CIT: Item Contents

The 6-CIT comprises one memory question, two calculation questions, and three orientation questions. In Table 11.1, these are discussed in more detail in relation to scoring criteria and acceptable responses.

The 6-CIT uses an inverse scoring method (better score = less points), and questions are weighted to produce a total score out of 28. The original validation of the scale by Katzman et al. [1] suggested a score of six points or less to be a normal score, with scores of seven or higher warranting further investigation to rule out a dementia-related disorder. However, based on the clinical research findings of Morris et al. [4], more specific criteria can be given as follows:

0–4: Normal cognition
5–9: Questionable impairment
10 or more: Impairment consistent with dementia (evaluate further)

The 6-CIT takes approximately 2 min to complete.

Table 11.1 Questions within the 6-CIT, scoring criteria, and acceptable responses

Question 1 - What year is it? (orientation)
The exact year must be given; however, an incomplete numerical value for the year (e.g. 11 instead of 2011) is accepted as correct
Scoring: The patient will score 0 for a correct answer and 4 for an incorrect answer
Question 2 - What month is it? (orientation)
The exact month must be given; however, a numerical value for the month (e.g. 10 for October) is accepted as correct
Scoring: The patient will score 0 for a correct answer and 3 for an incorrect answer
Question 3 - (memory – part 1)
In this part of the questionnaire, the practitioner gives the patient an address phrase with five components to remember, for example, John, Smith, 42, High Street, Bedford (this phrase is to be recalled after question 6). The practitioner should say *I will give you a name and address to remember for a few minutes. Listen to me say the entire name and address and then repeat it after me.* The trial phrase should be re-administered until the subject is able to repeat the entire phrase without assistance or until a maximum of three attempts. If the subject is unable to learn the phrase after three attempts, a "C" should be recorded. This indicates the subject could not learn the phrase in three tries. Whether or not the trial phrase is learned, the clinician should instruct "Good, now remember that name and address for a few minutes"
Question 4 - About what time is it? (orientation)
A correct response should be given without the participant referring to a watch or clock and should be accurate to ±1 h. If the answer given is rather vague (e.g. almost 2 pm) the patient should be prompted for a more specific answer
Scoring: The patient will score 0 for a correct answer and 3 for an incorrect answer
Question 5 - Count backward from 20 to 1 (calculation)
If the patient skips a number after 20, an error should be recorded. If the patient starts counting forward or forgets the task at any point, the instructions should be repeated and an error recorded
Scoring: The patient will score 0 for a correct answer (no errors), 2 points for 1 error, and 4 points for more than 1 error
Question 6 - Say the months of the year in reverse (calculation)
To get the subject started, the examiner may state, *Start with the last month of the year. The last month of the year is: (patient to fill in the gap)*
If the patient cannot recall the last month of the year, the examiner may prompt with "December". However, one error should be recorded. If the patient skips a month, an error should be recorded. If the patient begins saying the months forward upon initiation of the task, the instructions should be repeated and no error recorded. If the patient starts saying the months forward during the task or forgets the task, the instructions should be repeated and one error recorded
Scoring: The patient will score 0 for a correct answer (no errors), 2 points for 1 error, and 4 points for more than 1 error
Memory - part 2 Repeat the name and address I asked you to remember.
The patient should state each item verbatim. The address number must be exact (e.g. 420 instead of 42 is incorrect). Omitting the thoroughfare term (street, road, drive, crescent) from the street name or substituting it for a different one *will not* constitute an incorrect answer – score as correct
Scoring: The patient will score 0 for a correct answer (no errors), 2 points for 1 error, 4 points for 2 errors, 6 points for 3 errors, 8 points for 4 errors, and 10 points if they got all of the components wrong

11.3 Diagnostic Utility

Sensitivity for the 6-CIT was measured by Brooke and Bullock [3], who conducted a study to compare the 6-CIT, the MMSE, and the Global Deterioration Scale (GDS) in a sample of 287 community and outpatient participants: 135 controls, 70 with mild dementia (GDS 3–5), and 82 with more severe dementia (GDS 6–7). A sensitivity score of around 80 % was reported for the 6-CIT, this being considerably higher than that of the MMSE (50–65 % depending on cutoff). Although the 6-CIT scores correlated highly with the MMSE scores, its superior sensitivity led the researchers to conclude that the 6-CIT was a better tool for detecting mild dementia.

A recent study confirmed the results of Brooke and Bullock [3]. The study conducted by Upadhyaya et al. [17] compared the performance of the 6-CIT with the MMSE in a sample of 209 participants with a mean age of around 79 years. Individuals with and without dementia were retrospectively studied from data provided by an old age psychiatry service. The study reported a sensitivity score of 82.5 % and a specificity score of 90.9 % at a cutoff of 10/11 in the 6-CIT. When the cutoff was lowered to 9/10, the sensitivity of the scale increased to 90.2 %, but the corresponding specificity decreased to 83.3 %. When compared with the MMSE, the two scales had a very strong negative correlation ($r = -0.822$), and the MMSE had a lower sensitivity and specificity of 79.7 % and 86.4 %, respectively. When analyzing the receiver operating characteristic (ROC) curves for the MMSE and 6-CIT, Upadhyaya et al. also showed superior screening properties of the 6-CIT over the MMSE for dementia [17].

In a very similar study into the use of the 6-CIT and MMSE, 253 general hospital patients over the age of 70 were asked to complete both tests [18]. Similarly to the previous two studies mentioned, a very high negative correlation was found between the 6-CIT and MMSE ($r = -0.82$). This study adjusted the cut-off points in the MMSE for lower educated (<19) and higher educated (<23), comparable with the >11 cutoff on the 6-CIT which was not sensitive to educational level. The study found sensitivity and specificity scores in the 6-CIT of 0.90 and 0.96, respectively, and a positive predictive value of 0.83 and negative predictive value of 0.98. The area under the ROC curve was reported as 0.95. This study, as in previous research, concluded that 6-CIT is a suitable screening instrument for cognitive impairment in a general hospital setting owing to its brevity and ease of use for both patients and professionals [18].

There are several other brief cognitive tests that can be used as screening instruments for dementia, which, in general, take less time to complete and perform better than the MMSE. The General Practitioner Assessment of Cognition (GPCOG; see Chap. 10), Mini-Cog, and Memory Impairment Screen (MIS) are examples of other screening measures used for dementia, all of which were found to be the recommended screening tools for general practitioners and were even suggested to be a better tool than the 6-CIT in general practice [19].

Table 11.2 Timescales for screening instruments (compared in Brodaty et al. [19])

Task	Time (min)
Time and Change Test	0.4
Mental Alternation Test	0.5
Short Informant Questionnaire on Cognitive Decline in the Elderly	0.5
Ashford Memory Test	1
Six-Item Cognitive Impairment Test	2
Clock Drawing Test	2
Mini-Cog	2–4
Abbreviated Mental Test	3
Memory Impairment Screen	4
General Practitioner Assessment of Cognition	4.5
Short Test of Mental Status	5
Mini-Mental Status Examination	5–10
7-min Screen	7.5
Rowland Universal Dementia Assessment Scale	10
Short and Sweet Screening Instrument	10
Cambridge Cognitive Examination	20

11.4 Advantages and Disadvantages

11.4.1 Time

The 6-CIT takes as little as 2 minutes to complete [17]. This is much shorter than the commonly used MMSE (5–10 minutes) and many other screening instruments mentioned in Brodaty et al. [19] (see Table 11.2). However, Brodaty et al. suggested 5 minutes for completion of the 6-CIT. Even at 2 minutes, the 6-CIT still presents a longer completion time than the Time and Change Test (T&C), the Mental Alternation Test (MAT), the Short Informant Questionnaire on Cognitive Decline in the Elderly (SIQ), and the Ashford Memory Test (AMT), all of which may be administered in 1 minute or less.

However, the brevity of the scale may also be seen as a disadvantage. Other scales that take longer to complete, such as the GPCOG, may detect more features of dementia. The GPCOG comprises the testing of time orientation, clock drawing (numbering and spacing as well as placing hands correctly), awareness of a current news event, and recall of a name and an address (first name, last name, number, street, and suburb). Longer screening instruments (over 10 minutes) may probe a greater number of cognitive domains (i.e. have more questions to allow deeper enquiry), but due to their length, they would not generally be used in general practice (e.g. Cambridge Cognitive Examination, CAMCOG).

11.4.2 Content

Although the 6-CIT takes slightly longer to administer than four of the other screening tools (see Table 11.2), it probes a higher number of cognitive functions than the shorter tests. For example, the Time and Change Test includes the patient being asked to read the time from a watch or clock and then asked to make a desired amount of money from a selection of coins given; the Mental Alternation Test requires patients to count from 1 to 20, recount the alphabet, and then alternate the two (1A, 2B, 3C, 4D, etc.); the Short Informant Questionnaire on Cognitive Decline in the Elderly is completed by a relative or friend, asking how much the patient has declined in certain every day situations.

The test uses a simple language that can be understood by individuals of differing educational levels. This important consideration was further illustrated in Tuijl et al. [18] where it was found that the 6-CIT is not sensitive to educational level, thus making it a preferable screening tool over many others, including the MMSE, which need to adjust cutoff scores to account for patient educational level.

11.4.3 Scoring

The scoring system for the 6-CIT is rather complex compared with other screening tools for dementia. This may account for its use being less widespread than the MMSE in general practice. This complex scoring system may even be suggested to counteract the advantage of its brevity. However, as discussed by Brooke and Bullock [3], the plan for the 6-CIT to be distributed through general practice surgeries would involve the scores from the test being analyzed by computer software, which would calculate the scores for each patient and advise whether further evaluations or referrals were necessary.

11.4.4 Diagnosis of Dementia Subtypes

The 6-CIT is not currently well researched in its use in detecting differing types of dementia, such as AD, dementia with Lewy Bodies, vascular dementia, and frontotemporal dementia. However, due to its sensitivity in detecting cognitive impairment at the early stages of dementia, this would suggest its use in identifying all types of dementia early on. Research into the specific features of the test would need to be carried out to identify its capacity in the recognition of different dementias. However, it seems likely that a much more detailed battery of tests would be required to distinguish subtypes of dementia.

There is very little research into the use of the 6-CIT. Some studies have included the test in comparisons with other screening instruments, only for it to fall short in comparison to others, not due to its length or content but to the lack of research into its use. One such study shortlisted the 6-CIT in its top 8 tests for dementia (based on 16 separate criteria); however, 6-CIT did not rate as highly as others, such as the GPCOG, the Mini-Cog, and the Memory Impairment Screen (MIS), as it was not easily available and was specifically penalized by "the paucity of evidence about its use" [13].

11.5 Other Reported Uses

The use of the 6-CIT has not been limited to studies of dementias but extends to cognitive impairment in other physical disorders. One such study investigated the association between metabolic syndrome (characterized by abdominal obesity, hypertriglyceridemia, low high-density lipoprotein cholesterol (HDL-C) level, high blood pressure, and hyperglyceridemia) and cognitive impairment and utilized the SBT as the scale of choice for detecting dementia in a large-scale study which included around 5,000 women from 180 centers across 25 countries [20]. Further research using the SBT includes studies investigating associations between atherosclerosis and cognitive decline [21] and between physical activity and cognitive impairment [22]. The scale has even been utilized in the investigation of an acceptable screening tool in accident and emergency departments, with the SBT providing the best diagnostic test characteristics over the Ottawa 3DY, the Brief Alzheimer's Screen, and the caregiver-completed AD8 [23].

11.6 Conclusion

The 6-CIT is a reliable, well-validated [3], and sensitive scale that can be easily used by professionals in general practice. Its brevity is its greatest advantage, along with uncomplicated instructions and the potential to be translated into different languages. Although not a diagnostic tool for dementia(s), it is indicative of cognitive deficits, especially at the mild stages of dementia, thus surpassing the MMSE as a test of global cognitive status. The notion that the 6-CIT detects dementia at its early stages raises the issue around the importance of early detection of dementia and commencing appropriate treatment. Nevertheless, it remains less frequently used than other scales, such as the popular MMSE, a fact that may have been influenced by its complicated scoring system and the relatively small amount of research conducted into its use. Although relatively unknown, its recognition by the UK Royal College of General Practitioners, and the scope for computerized versions, should increase its use in general practice. Further evidence by way of large-scale studies should be conducted before the 6-CIT can begin to approach the widespread usage levels of scales such as the MMSE.

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Chapter 12
Conclusion: Place of Cognitive Screening Instruments: Test Characteristics and Suspected Diagnosis

Andrew J. Larner

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Abstract Many cognitive screening instruments have been described in the literature over the past 40 years and find use around the world, but this superabundance may be bewildering for the clinician approaching a patient with cognitive complaints. Appropriate test selection may depend on a variety of factors related to the particular clinical situation, including, but not limited to, the time available to undertake cognitive assessment (e.g., primary or secondary care settings), requirement to test general or specific cognitive functions, and the availability of informants. Although many neurological and general medical disorders of varying etiology (neurodegenerative, vascular, inflammatory, endocrine, structural, infective, psychiatric) may cause cognitive impairment, most cognitive disorders in

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specialist settings result from a relatively small number of conditions, such as Alzheimer's disease, vascular dementia/vascular cognitive impairment, Parkinson's disease dementia and dementia with Lewy bodies (DLB), and frontotemporal lobar degeneration syndromes. Clinical suspicion of these entities based on clinical history and physical examination may determine which cognitive screening instruments are best used, as in the investigation of other neurological disorders.

Keywords Cognitive screening instruments • Test characteristics • Alzheimer's disease • Vascular cognitive impairment • Parkinson's disease dementia • Frontotemporal lobar degenerations

12.1 Introduction

This volume has examined in detail a selection of cognitive screening instruments suitable for use by clinicians in day-to-day practice in both primary and secondary care settings. Perforce, this has been only a small selection of the many such instruments which have been described in the literature (see Table 12.1 for examples [1–54] of other tests not described in detail in this volume: this listing does not purport to be exhaustive, for example, telephone and computerized test batteries have not been included, nor tests designed to detect cognitive decline in individuals with learning (disability, nor many tests initially developed in a language other than English). Summaries of the use and utility of some of these tests have appeared [55, 56]. New cognitive screening instruments continue to be described. How should the clinician approach such a potentially bewildering array of tests?

The clinical approach to the use of cognitive screening instruments will most likely be influenced by two factors: the characteristics of the instrument and the suspected clinical diagnosis.

12.2 Test Characteristics

Cognitive screening instruments may be categorized in a number of ways, which might influence clinical preferences as to usage.

12.2.1 Primary Versus Secondary Care Settings: Test Duration

Some cognitive screening instruments are more suitable for and/or are specifically designed for use in primary care settings rather than secondary care settings, with time for administration being one of the key factors determining such suitability

Table 12.1 Examples of cognitive screening instruments (in alphabetical order)

Test	Reference(s)
Abbreviated Mental Test Score (AMTS)	Hodkinson [1]
AB Cognitive Screen 135 (ABCS135)	Molloy et al. [2]; Standish et al. [3]
AD8	Galvin et al. [4, 5]
Brief Alzheimer's Screen (BAS)	Mendiondo et al. [6]
Brief Cognitive Assessment Tool (BCAT)	Mansbach et al. [7]
Brief Cognitive Rating Scale (BCRS)	Reisberg and Ferris [80]
Cambridge Cognitive Examination (CAMCOG)	Huppert et al. [9]
Clifton Assessment Procedures for the Elderly (CAPE)	Pattie and Gilleard [10]
Cognistat (Neurobehavioral Cognitive Status Examination)	Kiernan et al. [11]
Cognitive Abilities Screening Instrument (CASI)	Teng et al. [12]
Cognitive Capacity Screening Examination (CCSE)	Jacobs et al. [13]
Cognitive Disorders Examination (Codex)	Belmin et al. [14]
Cognitive Failures Questionnaire (CFQ)	Broadbent et al. [15]
Cognitive Screening Battery for Dementia in the Elderly	Jacqmin-Gadda et al. [16]
Continuous Recognition Test	Ashford et al. [17]
Dementia Questionnaire (DQ)	Kawas et al. [18]
Fototest	Carnero-Pardo et al. [19]
Free and Cued Selective Reminding Test/Five Words Test	Dubois et al. [20]
Hasegawa Dementia Scale-Revised (HDS-R)	Imai and Hasegawa [21]; Kim et al. [22]
Hopkins Verbal Learning Test (HVLT)	Brandt [23]; Frank and Byrne [24]
Kingston Standardized Cognitive Assessment	Hopkins et al. [25]
Memory Alteration Test (M@T)	Rami et al. [26]
Memory Impairment Screen (MIS)	Buschke et al. [27]
Memory Orientation Screening Test (MOST™)	Clionsky and Clionsky [28]
Mental Alternation Test (MAT)	Jones et al. [29]; Salib and McCarthy [30]
Mental Status Questionnaire (MSQ)	Kahn et al. [31]
Middlesex Elderly Assessment of Mental State (MEAMS)	Golding [32]
Mini-Cog	Borson et al. [33, 34]
Mini-Severe Impairment Battery (Mini-SIB)	Qazi et al. [35]
Philadelphia Brief Assessment of Cognition	Libon et al. [36]
Poppelreuter (overlapping) figure	Sells and Larner [37]
Queen Square Screening Test for Cognitive Deficits	Warrington [38]
Rowland Universal Dementia Assessment Scale (RUDAS)	Storey et al. [39]
Saint Louis University Mental Status (SLUMS) examination	Tariq et al. [40]
7-minute screen	Solomon et al. [41]
Severe Impairment Battery (SIB)	Saxton and Swihart [42]
Short and Sweet Screening Instrument (SAS-SI)	Belle et al. [43]
Short Cognitive Battery (B2C), Short Cognitive Evaluation Battery (SCEB)	Robert et al. [44]

(continued)

Table 12.1 (continued)

Test	Reference(s)
Short Memory Questionnaire (SMQ)	Koss et al. [45]
Short Portable Mental Status Questionnaire (SPMSQ)	Pfeiffer [46]
Short Test of Mental Status	Kokmen et al. [47]
Structured interview for the diagnosis of dementia of the Alzheimer type, multi-infarct dementia and dementias of other etiology (SIDAM)	Zaudig et al. [48]
Sweet 16	Fong et al. [49]
Takeda Three Colors Combination Test	Takeda et al. [50]
TE4D-Cog	Mahoney et al. [51]
Time and Change Test (T&C)	Froehlich et al. [52]; Inouye et al. [53]
Visual Association Test	Lindeboom et al. [54]

[57, 58]. Examples include the Clock Drawing Test (see Chap. 5), short IQCODE (see Chap. 8), GPCog (see Chap. 10), 6-CIT (see Chap. 11), Mini-Cog [33, 34], Time and Change Test (T&C) [52, 53], the Mental Alternation Test (MAT) [29, 30], and the cognitive disorders examination decision tree (Codex) [14]. Generally, these tests require little specialized test equipment beyond a pencil and paper and do not require significant training to administer.

Surveys of cognitive screening instrument use in primary care have found rather divergent results, perhaps dependent on study methodology, with postal surveys suggesting widespread use (ca. 80 %; [59]) while analysis of referral letters directed to cognitive clinics in secondary care suggests more limited application (ca. 10–25 %; [60–62]). In all of these surveys, the Mini-Mental State Examination (MMSE) [63] has been the test most commonly reported to be used in primary care. Enforcement of copyright restrictions on the use of the MMSE [64] may change this situation in the future.

If test duration is an issue affecting applicability, then ultrashort screening tests or "microscreening" tests, comprising just a single or two questions, may be desirable. Subjective memory complaint (SMC) is recognized to be predictive of dementia (e.g., [65, 66]). Hence, asking for the presence of symptoms of progressive forgetfulness may have diagnostic value: a Chinese study reported sensitivity of 0.96 and specificity 0.45 for the diagnosis of dementia by asking a single question concerning progressive forgetfulness [67]. Another study found SMC to correlate with MMSE score, but it had poor sensitivity (0.58) and specificity (0.76) for dementia [68]. SMC is predictive of dementia especially if associated with impaired functional activity [69].

Single clinical observations may also be useful as screening tests. Verbal repetition, that is, repeating the same question or information after only a few minutes, was observed in 100/130 mild-to-moderate AD patients [70]. Observation of the head-turning sign (patient looks at the caregiver when asked a question) may also have screening value, although the exact operationalization of the sign has differed

between reported studies [71, 72]. Attending a cognitive clinic alone, despite written instructions to bring a relative or friend to give collateral history, is a robust indicator of (i.e., is very sensitive for) the absence of dementia [73].

Some cognitive instruments may, by contrast, be too long for routine application in day-to-day clinical practice even in secondary care settings and indeed, for that reason, may not be regarded as cognitive screening instruments. For example, the Alzheimer's Disease Assessment Scale-Cognitive Section (ADAS-Cog) [74] has become widely used as a reference measure, for example, as an outcome measure of drug efficacy in AD clinical trial practice, and takes significantly longer to perform than the MMSE (around 30–45 minutes). A "calculator" to convert MMSE scores to equivalent ADAS-Cog scores is available, reflecting the strong correlation between ADAS-Cog and MMSE scores [75]. The cognitive battery proposed by the Consortium to Establish a Registry for Alzheimer's Disease (CERAD) investigators is also time consuming, incorporating the MMSE and other subtests of memory, naming, and verbal fluency [76]. Likewise, the Dementia Rating Scale (DRS) and its successor (DRS-2) [77] which comprise a number of subtests (attention, initiation, construction, conceptualization, memory) to give a global measure of dementia (score 0–144) take about 30 minutes to perform.

In this context, it is also necessary to mention the Clinical Dementia Rating (CDR) [78, 79] and the Global Deterioration Scale (GDS) [8]. These are global staging measures based on both cognitive and functional capacities, which have gained prominence through their use in the definition of mild cognitive impairment (CDR 0.5 and GDS 3 correlate, but are not necessarily synonymous, with MCI). CDR has been reported to be useful in screening for dementia [81].

12.2.2 General Versus Specific Cognitive Functions

Cognitive screening instruments may be classified according to whether they test general or specific cognitive functions [56, 82, 83]. One of the desiderata for cognitive screening instruments as formulated by the American Neuropsychiatric Association was sampling of all the major cognitive domains, including memory, attention/concentration, executive function, visual-spatial skills, language, and orientation ([84]; see Sect. 1.3). Many cognitive screening instruments attempt this broad, multidomain sampling to a greater or lesser extent (e.g., MMSE, ACE and ACE-R, MoCA; see Chaps. 2, 4, and 6, respectively). Generally, the more comprehensive the neuropsychological coverage, the longer the test takes to administer, although the Clock Drawing Test (see Chap. 5) may be an exception.

On the other hand, instruments which test a specific cognitive function may have a place in screening [83]. For example, since episodic memory impairment is typically the earliest deficit manifest in AD patients, tests for anterograde ("hippocampal") amnesia may be particularly pertinent, such as the Memory Impairment Screen (MIS) [27], the Free and Cued Selective Reminding Test, or Five Words Test [20], and the Visual Association Test [54]. Similarly, tests of visuoperceptual function

such as the Poppelreuter (overlapping) figure may identify deficits in this cognitive domain which may occur early, for example, in posterior cortical atrophy or the visual variant of AD [37]. Scales specifically measuring attention, executive functions, and language are also available [56], some of which may be of particular value in specific clinical situations, for example, assessing executive and/or language function in suspected frontotemporal lobar degeneration syndromes (see Sect. 12.3.4).

12.2.3 Patient Versus Informant Scales

Cognitive screening instruments are most often administered to patients, most usually by the clinician, but are sometimes undertaken by the patient themselves, usually with medical supervision (e.g., TYM; see Chap. 9). Clinician administration of a cognitive screening instrument permits a qualitative patient-clinician interaction during testing which may inform clinical judgments over and above the raw test scores which emerge. The clinician's gentle, persuasive technique of test administration may also ensure that liability to drop out is less likely than with patient self-administered tests.

Because of the importance of collateral history in the assessment of possible cognitive disorders, such that diagnostic guidelines for dementia emphasize the importance of informant interview [85, 86], scales to be completed by a knowledgeable informant may also have a place in assessment. Examples include the Informant Questionnaire on Cognitive Decline in the Elderly (IQCODE; see Chap. 8), the Neuropsychiatric Inventory (NPI) [87], the Short Memory Questionnaire (SMQ) [45], and the Dementia Questionnaire (DQ) [18]. Some scales may be suitable for both patient- and informant-administration purposes (e.g., AD8; [4, 5]). Informant scales which help in the differential diagnosis of dementia subtype have also been reported: the Cambridge Behavioural Inventory (CBI) may assist in differentiating AD and frontotemporal lobar degenerations [88, 89] (see Sect. 12.3.4), and the Fluctuations Composite Scale may assist in diagnosis of DLB [90, 91] (see Sect. 12.3.3).

12.2.4 Quantitative Versus Qualitative Scales

Most cognitive screening instruments produce a global score to be compared against cutoffs said to define normal/abnormal test performance. Test subscores may identify particular areas of weak cognitive performance. However, too much reliance should not be placed on such overall numerical values since there are many factors other than cognitive decline which may influence test performance, including patient age, educational status, culture, language, presence of primary psychiatric disorder (anxiety, depression), and presence of primary sensory deficits (see Sect. 1.3).

Table 12.2 Cognitive screening instruments designed for use in multiple sclerosis (in alphabetical order)

Test	Reference(s)
Brief Repeatable Battery of Neuropsychological Tests (BRB-N)	Rao [101]
Minimal Assessment of Cognitive Function in Multiple Sclerosis (MACFIMS)	Benedict et al. [102]
Multiple Sclerosis Inventory of Cognition (MUSIC)	Calabrese [103]
Multiple Sclerosis Neuropsychology Questionnaire (MSNQ)	Benedict et al. [104]

As previously mentioned (Sect. 12.2.3), qualitative cognitive screening instrument performance may also inform clinical diagnosis. Moreover, test cutoffs defined in index studies, which may utilize highly selected patient cohorts and normal control groups, may not be applicable in day-to-day clinical practice wherein all patients have at least subjective memory complaint, itself not necessarily a benign condition [92]. Revision of test cutoffs to scores more appropriate for the casemix seen in a particular clinic has been reported for several cognitive screening instruments including ACE-R (see Sect. 4.4.1), MoCA (see Chap. 6; [93]), and TYM (see Chap. 9; [94]).

Some tests are qualitative, such as the Queen Square Screening Test for Cognitive Deficits [38]. Although the Cambridge Behavioural Inventory can be scored [95], the authors of the test suggested that the overall benefit of the instrument was in providing a structured behavioral symptom profile rather than a summated behavioral score [96].

12.3 Suspected Diagnosis

What strategies should the clinician adopt when faced with a patient with a complaint of cognitive impairment, such as poor memory? As in all clinical situations, taking a history, including a collateral history, is the key initial element of assessment [85, 86], since a focused history may permit the development of diagnostic hypotheses which may then direct appropriate testing, just as in all neurological situations [97]. For example, memory complaints are common and not necessarily pathological [98], memory lapses, or slips being observed in many healthy individuals [99]. A clinical suspicion of depression and/or anxiety underlying cognitive complaints may direct specific assessment of affective state. Presence of the "attended alone" sign [73] may reduce clinical suspicion of a cognitive disorder, whereas presence of the head-turning test [71, 72] may increase it.

Cognitive impairment may occur in many neurological diseases [100]. Some cognitive screening instruments have been developed for use in specific conditions in which cognitive impairment is common, for example, multiple sclerosis [101–104] (Table 12.2). Some tests designed for use in specific neurological conditions

have had their role subsequently extended to more general settings, for example, the Mental Alternation Test originally designed for HIV-related neurocognitive syndromes [29, 30] and the Mini-Mental Parkinson originally designed for Parkinson's disease [105, 106].

However, the focus here will be on the disorders most commonly encountered in cognitive disorders clinics, that is, AD, vascular dementia/vascular cognitive impairment, Parkinson's disease dementia (PDD) and dementia with Lewy bodies (DLB), and frontotemporal lobar degeneration syndromes [89]. The intention is neither to be prescriptive nor proscriptive but to outline instruments which might be suitable when these specific diagnoses are being considered.

Some instruments are reported to assist with differential diagnosis of these disorders. For example, the Dementia Rating Scale of Mattis (DRS) was designed to assist in the differential diagnosis of dementia syndromes (e.g., [107–109]) and is reported to be able to distinguish subcortical dementing disorders from AD [110].

12.3.1 Tests for Suspected AD and MCI

AD is the most common dementing disorder with over 20 million cases estimated worldwide [111, 112]. As episodic memory impairment is most commonly the earliest symptom of AD, tests specific for this construct may be most appropriate when clinical suspicion of this diagnosis is entertained. Options include the Memory Impairment Screen (MIS) [27] and the Free and Cued Selective Reminding Test, or Five Words Test [20, 113].

Of the general cognitive function tests, TYM (see Chap. 9) is reported to be better at identifying AD cases than the MMSE [114]. Some MMSE derivatives have been reported to identify AD (see Chap. 3). Combination of the MMSE and the Clock Drawing Test ("mini-clock") was reported to be highly sensitive and specific in detection of mild AD [115]. If time permits use of the ACE or ACE-R, the VLOM subscore of these tests has good sensitivity and specificity for the diagnosis of AD (see Sects. 4.2.1, 4.2.2, and 4.4.2). IQCODE has also been reported to show excellent screening properties for AD (see Sect. 8.5; [116]).

Other tests reported to be effective in screening for AD include the Scenery Picture Memory Test [117], the screening test for Alzheimer's disease with proverbs [118], the Philadelphia Brief Assessment of Cognition [36], the Memory Alteration Test [26], the three-objects-three-places test [119], the traveling salesman problem (a visual problem-solving task; [120]), the Short Cognitive Evaluation Battery [44], the Visual Association Test [54], and the 7-minute neurocognitive screening battery [41].

The evolution of AD is characterized by predementia and dementia phases, the former with or without symptoms [121]. Clinical criteria for predementia AD remain to be developed [122], although in the later, symptomatic stage of the predementia phase, a syndrome of prodromal AD or mild cognitive impairment (MCI)

may be defined [123, 124]. Identification of MCI is, at least theoretically, a high clinical priority since early interventions might possibly arrest or slow disease progress sufficient to prevent the development of dementia. Although probably a heterogeneous disorder at the clinical level, nevertheless tests highly sensitive for detection of MCI are desirable. In a systematic review, a number of cognitive screening instruments capable of identifying MCI were found [125]. For example, MoCA (see Chap. 6) was reported to be very sensitive for diagnosis of MCI, more so than the MMSE [126]. A recent study suggested that both MoCA and ACE-R are highly sensitive for the diagnosis of MCI [127]. IQCODE has also been reported to show excellent screening properties for MCI [116]. A Quick Mild Cognitive Impairment (Qmci) screen derived from the ABCS135 [3] may be added to the list of potential screening instruments for MCI, but a systematic review concluded that the Clock Drawing Test was not suitable for MCI screening [128] (see Sect. 5.6.2 for fuller discussion). Combination of the MMSE and the Clock Drawing Test ("mini-clock") is reasonably accurate in separating MCI cases from healthy controls [115]. However, it remains to be shown that any of these cognitive screening instruments can permit reliable inferences about course and outcome of MCI [125].

12.3.2 Tests for Suspected Vascular Dementia

"Vascular dementia" (VaD) is not a unitary construct, encompassing such entities as vascular cognitive impairment (VCI) short of dementia, poststroke dementia, multi-infarct dementia, subcortical ischemic vascular dementia (SIVD), and selective infarct dementia [129]. Such heterogeneity at clinical, etiological, and neuropathological levels poses significant problems in devising cognitive screening instruments specific for "vascular dementia," the more so when the frequent overlap with neurodegenerative processes such as AD is taken into account [130]. Furthermore, it is recognized that some cognitive screening instruments may be "Alzheimerized," that is, suitable for picking up the characteristic deficits in AD but not necessarily those in VaD/VCI. Although there is overlap in the profile of neuropsychological deficits, vascular cognitive syndromes may show greater impairments in attention, working memory, and executive function than encountered in AD patients [131].

To detect cognitive impairment related to cerebrovascular disease, derivations from existing tests such as the MMSE [132] (see Sect. 3.3.1) may be used, or adaptations of existing tests, such as the CAMCOG (R-CAMCOG) [133] or ADAS-Cog (VADAS-Cog) [134]. Screening for vascular cognitive impairment using the Diagnostic Checklist for Vascular Dementia but with the MMSE rather than the detailed neuropsychological part of the checklist has been reported [135].

The Hachinski Ischaemic Score (Table 12.3) is a brief clinically based scale used to differentiate AD and multi-infarct dementia [136], in which context, it performs well, although there are problems with the diagnosis of mixed dementia [137]. The scale score is still used in some AD drug trials as an exclusion criterion for possible cases of vascular dementia.

Table 12.3 Hachinski Ischaemic Score (after Hachinski et al. [136])

Clinical feature	Score
Abrupt onset	2
Stepwise deterioration	1
Fluctuating course	2
Nocturnal confusion	1
Relative preservation of personality	1
Depression	1
Somatic complaints	1
Emotional incontinence	1
History of hypertension	1
History of strokes	2
Evidence of associated atherosclerosis	1
Focal neurological symptoms	2
Focal neurological signs	2

Score ≤4 indicates AD; ≥7 indicates multi-infarct dementia

Of the general cognitive function tests, MoCA has been reported to identify cognitive impairment associated with cerebrovascular disease (see Sect. 6.6.2) more reliably than the MMSE [138, 139].

The Brief Memory and Executive Test (BMET) has been specifically designed as a quick bedside screening test for VCI due to cerebral small vessel disease and is reported to have high sensitivity and specificity for differentiating such patients from those with AD, in which it outperformed the MMSE [140].

12.3.3 Tests for Suspected Parkinson's Disease Dementia (PDD) and Dementia with Lewy Bodies (DLB)

Compared to AD, visual and executive cognitive functions are recognized to be more frequently impaired in Parkinson's disease (PD) and in dementia with Lewy bodies (DLB) with relative preservation of orientation in time and place (e.g., [141, 142]). Tests which seek to exploit these differences and thereby facilitate diagnosis of cognitive impairment in PD and DLB have been developed. The Mini-Mental Parkinson (MMP) [105], a derivative of the MMSE, has already been discussed (see Sect. 3.2.8), as has the subscore defined by Ala et al. [143] reported to facilitate detection of DLB (see Sects. 3.3.2 and 4.4.4). ACE-R (see Sect. 4.4.4) has been reported a valid tool for dementia evaluation in PD [144] and useful as one component of a three-step procedure to identify dementia in PD, as have MoCA and the Frontal Assessment Battery [145].

Other tests may be used to detect cognitive impairment in PD, both Parkinson's disease dementia (PDD) [146], and PD-MCI [147, 148]. For example, MoCA (see Sect. 6.7) has proved useful in detecting cognitive impairment in PD [149–151]. Scales for Outcomes in Parkinson's disease-Cognition (SCOPA-Cog) was specifically

designed for measuring cognition in PD [152]. Other scales reported for screening for cognitive deficits in PD include the Parkinson neuropsychiatric dementia assessment (PANDA) instrument [153] and the PDD-Short Screen (PDD-SS) [154].

The Fluctuations Composite Scale (FCS), derived from the Mayo Fluctuations Questionnaire of Ferman et al. [90], has been reported in a pragmatic study to identify synucleinopathies (PDD, PD-MCI, DLB) when these conditions have entered the initial differential diagnosis of cognitively impaired patients [91].

ACE may be used to detect cognitive impairment in the "atypical" parkinsonian syndromes (progressive supranuclear palsy, corticobasal degeneration, multiple system atrophy) [110, 155].

12.3.4 Tests for Suspected Frontotemporal Lobar Degeneration

The heterogeneous group of frontotemporal lobar degenerations (FTLD) may present with either behavioral or linguistic impairments. A number of instruments sensitive to frontal lobe dysfunction have been described, including the Frontal Assessment Battery (FAB) [156], the Frontal Behavioral Inventory (FBI) [157], the Middelheim Frontality Score [158], and the Institute of Cognitive Neurology Frontal Screening (IFS) [159], as well as tests sensitive to executive dysfunction (e.g., EXIT25; [160]).

FAB has been reported to assist in the differential diagnosis of the behavioral variant of FTLD (bvFTLD) from AD in selected patient cohorts, including the early stages of disease [161], although other groups have not corroborated these findings [162–165]. In a pragmatic study, FAB has been found useful to identify bvFTLD when this condition entered the initial differential diagnosis of cognitively impaired patients [166]. IFS is reported to be more sensitive and specific than FAB in differentiating bvFTLD from AD [159].

Informant tests may be particularly useful in detecting the behavioral features of FTLD, not volunteered by patients. The Cambridge Behavioural Inventory (CBI) may assist in differentiating AD and FTLD [88, 89].

Of the general cognitive function tests, ACE or ACE-R VLOM subscore has good specificity for the diagnosis of FTLD but rather poor sensitivity, probably because of inability to pick up cases of bvFTLD (see Sects. 4.2.1, 4.2.2, and 4.4.3). The Semantic Index, another ACE subscore (see Sect. 4.4.3), may be useful in differentiating semantic dementia from AD [167]. Other bedside screening instruments have been suggested for the differential diagnosis of AD and FTLD including the Digit Span Index [168], the Philadelphia Brief Assessment of Cognition [36], as well as other bespoke batteries [169–171].

Diagnosis of FTLDs, especially the behavioral variant, may be extremely challenging in the early stages, despite informant report of behavioral change. Risky decision-making may be seen in bvFTLD in early disease, sometimes without evidence of behavioral disinhibition or impulsiveness [172]. Risk taking and decision-making, which may be characterized as executive function tasks, may be amenable to testing with instruments such as the Iowa Gambling Task [173] and the Cambridge Gamble Task [174].

12.4 Conclusion

Cognitive screening instruments remain an integral part of the assessment of any patient with cognitive complaints. As with the investigation of any other neurological disorder [97], the deployment of cognitive screening instruments should be tailored to the clinical situation as elucidated by history taking and clinical examination. This should permit the development of hypotheses about diagnosis which may direct appropriate use (or nonuse) of such instruments to assist with differential diagnosis. Although not considered in this volume, appropriate patient evaluation may also require assessment of other, noncognitive, domains, using functional, behavioral and psychiatric, and neurovegetative scales, sometimes in combination with cognitive instruments (see Sect. 4.5) [89].

In primary care, identification of whether cognitive complaints are accompanied by cognitive impairment may be paramount, and cognitive screening instruments suitable for this purpose and amenable to the time frame available may be used in order to determine which patients may be reassured, which recommended for interval assessment, and which referred on to secondary care for further investigation. In the secondary care setting, a more fine-grained diagnosis may be attempted by means of more detailed instruments which may assist in differential diagnosis, supplemented if necessary with other investigation modalities including neuroimaging, neurophysiology, CSF studies, neurogenetic testing, and even tissue biopsy as appropriate [85, 86, 89, 175–177]. While there are narrative accounts of some of the available cognitive screening instruments [57, 58, 178, 179], meta-analytic studies of quantitative accuracy are still in their infancy [82, 83].

Future research may define reliable biomarkers for dementing disorders, which might possibly be applied in a systematic and unbiased way to differentiate disease from normal brain aging [180], and even to predict clinical scores [181]. However, these remain research prospects rather than day-to-day clinical realities. In the meantime, cognitive screening instruments, despite their various shortcomings, will remain part of clinical routine, and it will therefore behove practitioners who may encounter individuals with cognitive complaints in either primary or secondary care settings to be familiar with some of them.

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