Dementia in Clinical Practice: A Neurological Perspective

Pragmatic Studies in the Cognitive Function Clinic

Third Edition

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To L F

There are more data in heaven and earth, Horatio
Than are analysed in your philosophy
Anonymous

What is good, if brief, is twice as good; what is bad, if scarce, is not that bad
Baltasar Gracian

Preface to the Third Edition

As retirement (intellectual extinction?) approaches, ensuring that this third edition, based as it is on the pursuit of clinic-based pragmatic studies, will be the final iteration of this book, I recognise it to be a rhetoric of failure, and myself as a specialist in failure. But failure may nonetheless merit documentation since this can be as informative as success, highlighting dead ends which no longer require pursuit. And this should come as no surprise—use of screening instruments was perhaps never more than a crude stopgap pending more sophisticated understanding and assessment of the heterogeneous clinical phenotype of cognitive impairment, as pioneered by the movement to define disease biomarkers.

Hence this attempt to curate studies performed in one clinic over a period of nearly 20 years (2000–2018), to examine/explore the proposition that a non-academic clinician working in a provincial NHS clinic can make some contribution to the understanding of the diagnosis and management of cognitive disorders, should be subject to the minimum hypothesis. As the author is a passenger (if not prisoner) of circumstance, this summa may be no more than a work of medical historical curiosity, or perhaps may in due course help to inform any medical/social history of its time.

Liverpool, UK A. J. Larner

Acknowledgements

Thanks are due to esteemed colleagues from whom I have learned much over the years and who have contributed to some of the works described in this volume, in particular Mark Doran, Eric Ghadiali, Rhys Davies and Atik Baborie at the Cognitive Function Clinic, Walton Centre for Neurology and Neurosurgery, Liverpool; and Pavla Hancock at the Brooker Centre, Runcorn. I have been fortunate to work with some excellent junior colleagues over the years, one of whom, Alex Wojtowicz, moving with the times (unlike the author), has prepared two Youtube videos based on the second edition of this book:

Part 1: https://www.youtube.com/watch?v=xXAnOmZEpRg

Part 2: https://www.youtube.com/watch?v=2AXuZPdb22A&t

All errors or misconceptions which remain in this book are entirely my own work.

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Contents

Introduction

Previous editions of this book (Larner 2012, 2014a) have begun by asking what contribution(s) to the diagnosis and care of people with cognitive disorders can be made in a neurology-led dementia clinic. This question remains not only pertinent but central, particularly in an era of financial retrenchment.

Naïve readers of policy documents such as the guidelines from the United Kingdom (UK) National Institute for Health and Clinical Excellence/Social Care Institute for Excellence (NICE/SCIE; 2006 [NICE was later rebranded as the National Institute for Health and Care Excellence]) and the UK Government's National Dementia Strategy (NDS; Department of Health 2008, 2009) might have concluded the answer to be very little, if anything. Neurology merited only a single mention in the former document (Doran and Larner 2008), and was apparently ascribed only a marginal role in the latter (Larner 2009a).

The purpose of this book remains, at least in part, to rebut this apparent conclusion, by demonstrating the type of studies which may be undertaken in a neurology-led dementia/cognitive disorders clinic which is rooted in a clinical, as opposed to a research, ethos. This is not to underestimate or denigrate in any way the very significant contributions that have been made by research-oriented neurological dementia clinics, in particular over the past four decades. However, such clinics are in a minority, may be generously funded and staffed with research fellows and often have the benefit of considerable case selection as may befit the tertiary health care setting.

This book aims to summarise work undertaken in the setting of the Cognitive Function Clinic (CFC) at the Walton Centre for Neurology and Neurosurgery (WCNN), a regional neuroscience centre in Liverpool, United Kingdom (UK), and covers the eighteen-year period (2000–2017) during which the author has worked there, updating the previous editions (Larner 2012, 2014a). CFC was founded in 1993, with an initial remit to focus on early-onset dementias (Ferran et al. 1996), although strict age criteria for referrals have never been applied. Throughout, there have been close working relationships with local colleagues with an interest in dementia based in old age psychiatry and geriatric services.

The rich mulch of experience gained, and summarised here, encompasses a spectrum ranging from significant (illustrative) case material (summarised in Case Study

text boxes), through pragmatic diagnostic test accuracy studies (Larner 2015a) of neurological signs, cognitive and non-cognitive screening instruments (Chaps. 3–5), through to experience in clinical drug trials. This summary of what might be termed "field work" (i.e. grounded in the clinic, and ranging from the purely descriptive to the mathematical) in a resource-limited setting may help to inform others who are similarly placed when deciding what diagnostic and management strategies may be useful. Although a single-centre review might be deemed parochial, and of course inevitably shows selection bias, it might also be the case that CFC may be seen as a model for other similar clinics. Rather than simply a record of provincial empiricism, these pragmatic, "real-world", prospective observational studies of diagnostic signs and tests, and of policy interventions (= audit), in populations with marked clinical heterogeneity, without the option of significant case selection ("cherry picking"), may have high external validity (the book is aimed at practising clinicians). This approach may be seen as broadly supportive of the concept of "every doctor as a scientist and scholar" promulgated in recent times by the British Medical Association (2015).

The studies undertaken have mostly been hypothesis neutral (acknowledging that data gathering is not necessarily separated from grounded hypothesis testing), although there are some exceptions (e.g. effects of NICE/SCIE guidelines, NDS, NICE guidance, since in some sense these are experimental interventions in public health: McKee et al. 2012; see Chap. 10). It is true that the empirical, heuristic, practice-based strategy evolved from these studies may not be formally "evidence-based", and therefore attempts have been made to contextualise the work described by citing from some of the literature deemed relevant to these topics (no claim of exhaustive coverage is made, and the risk of confirmation bias acknowledged). What results is a hybrid: part monograph, part practical manual. It may be seen as the practical companion volume to a "theoretical" volume which attempted to summarise the various neurocognitive impairments described in a wide range of neurological and general medical disorders (Larner 2008a, 2013a). The apparent coherence of what results belies the fact that the work described evolved in a piecemeal fashion from the interstices of clinical practice. This third edition is entirely revised, reorganised, with much new information included and additional calculations (hitherto unpublished) undertaken, in particular a new chapter (6) on ways to compare, combine and convert screening instruments in the hope of improving diagnostic accuracy.

Speaking at a conference on "Current opportunities in clinical research" at the Royal College of Physicians of London in 1993, Professor Peter Lachmann suggested a distinction between different types of research, specifically ortho, meta and para (Warburton et al. 1993: 310. I am grateful to Professor Robert Edwards, formerly of the University of Liverpool, for drawing my attention to this taxonomy). "Ortho research" pushes back the frontiers of medical science; "meta research" helps to maintain a general research culture; whilst "para research" is done almost as a sideline, it may be interesting and valuable but it is not the stuff of headlines. Using this nomenclature, the current work falls (hopefully) somewhere between meta and para research. (Critics might take the view that it in fact represents

displacement activity, a vanity project, wish fulfilment, hobbyism, punding, philosophical consolation, ergotherapy or any combination of these; ultimately, however, the work must be autotelic.) Research funding has neither been sought nor received in pursuit of these studies, and no dedicated time allotted within a full-time UK National Health Service (NHS) consultant neurologist job plan (non-academic post), a phenomenon that I choose to characterise as "micro-research" due to the limited time and facilities available, in distinction to publicly and/or privately funded and time-allocated "macro-research". Whatever appellation is used, I hope that these researches will not be deemed an enemy of scholarship (Gratzer 1979).

The work undertaken in CFC has afforded a number of publications which not only cover clinical work but also reflect long-standing interests in the pathophysiology of disorders causing cognitive impairment and dementia (Larner 2008a, 2013a, 2017a), of Alzheimer's disease in particular (Larner 1995a, b, 1996, 1997a, b, c, 1998, 1999a, 2001, 2008b, 2014b; Larner and Keynes 2006; Towns et al. 1996), and the patent literature on possible therapies (Larner 1999b, 2000; Larner and Doran 2003; Larner and Rossor 1997; Prout and Larner 1998), as well as public policy documents (Larner 2015b). This has been leavened by an interest in the history of dementia, particularly Alzheimer's disease (Larner 2006a, 2013b), cognitive and psychiatric disorders (Fisher and Larner 2008; Larner 2003, 2006b; 2015c, d; 2016a, b; Larner and Fisher 2009; Larner and Gardner-Thorpe 2012; Larner and Leach 2002) and neuropsychology (Kelly and Larner 2014), as well as cultural responses to cognitive disorders as manifested in literary accounts (Ford and Larner 2010; Larner 2004, 2005, 2008c, 2013c, 2015e, 2017b, c), celluloid representations (Ford and Larner 2009; Case Study Introduction 1) and other pastimes (Larner 2009b).

Case Study Introduction 1: Lay Perception of Cognitive Impairment

A lady in her 40s was seen in the clinic with a complaint of memory problems in the context of a chronic headache disorder and occasional epileptic seizures requiring treatment with anti-epileptic drugs. Because of her forgetfulness, the patient's daughter reported that she and other family members called her mother "Dory", because her behaviour was reminiscent of the character of that name who appeared in the popular (and relentlessly anthropomorphic) computer animated movie *Finding Nemo* (2003). Dory is a friendly but forgetful regal blue tang fish. In the movie, Dory's memory for a piece of information key to the plot is finally retrieved, triggered by a visual lexical cue. In 2016, Dory was the central character in the film *Finding Dory*, following which another forgetful patient seen in the clinic was described by her family as "Dory".

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Patients: Referral Patterns

1

Contents

Abstract

This chapter examines referral patterns to a dedicated neurology-led cognitive disorders clinic located in a secondary care setting in terms of the numbers of patients seen over the period 2002–2016, referral sources (primary and secondary care), patient characteristics (age, gender, ethnicity, social class, handedness) and casemix in terms of diagnosis. Although referral numbers have increased over the 15-year period, the proportion receiving a diagnosis of dementia has fallen, which may indicate the persistence of a dementia diagnosis gap.

Keywords

Dementia · Demographics · Diagnosis · Referral patterns

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It is a truth universally acknowledged that dementia is a major global public health issue, set to increase as the world population ages (Ferri et al. 2005; World Health Organization 2012).

In 2010, a global cost of illness study suggested a "base case option" figure of US$604 billion, equivalent to the 18th largest national economy in the world at that time (between Turkey and Indonesia), and larger than the revenue of the world's largest companies (Wal-Mart, Exxon Mobil). In high income countries, which accounted for 89% of the costs but only 46% of dementia prevalence, this was mostly due to direct costs of social care, whilst in low and middle income countries, which accounted for only 11% of the costs but 54% of dementia prevalence, this was mostly due to informal care costs (Wimo and Prince 2010). By 2015 these costs had increased to an estimated US$818 billion, with 46 million people in the world living with dementia (Prince et al. 2015). Even if, as some data suggest, the age-specific incidence of dementia is declining in England and Wales, nevertheless because of the ageing of the population the numbers of people with dementia will continue to increase (Ahmadi-Abhari et al. 2017).

The need to address these issues is therefore obvious, from the human as well as the economic standpoint. This will require governments, individually and globally, to make dementia a priority, with the development of policies, investment in chronic care, and funding of research. It is heartening that some attempts have been made to develop such policies, both nationally (Department of Health 2009, 2012, 2015; Larner 2018) and internationally. A summit meeting of the G8 nations in London in December 2013 made a bold commitment to develop a cure or treatment for dementia by 2025 (Department of Health 2013).

Faced with such enormities, what can the individual clinician hope to contribute? The National Dementia Strategy (NDS) for England (Department of Health 2009) proposed three key themes to address the problem of dementia: improved awareness; early diagnosis and intervention; and a higher quality of care. Many of the 17 "key objectives" fell outwith the clinical domain, such as an information campaign to raise awareness and reduce stigma, and improvement in community personal support services, housing support and care homes. However, the early identification and appropriate initial management of dementia cases may be deemed to fall squarely within the remit of the individual clinician. The first issue to address, therefore, is the referral routes by which such patients arrive at the clinical encounter.

1.1 Referral Numbers

Referrals to the Cognitive Function Clinic (CFC) at the Walton Centre for Neurology and Neurosurgery (WCNN) in Liverpool represent a small but relatively complex caseload. Generally it may be said that the assessment and diagnosis of patients with memory complaints and/or cognitive disorders is ill-suited to the workings of general neurological outpatient clinics, partly for lack of adequate time to assess fully the history and cognitive performance of these patients. Longer cognitive screening instruments may have greater diagnostic accuracy (Sect. 6.1.3; Larner 2015a).

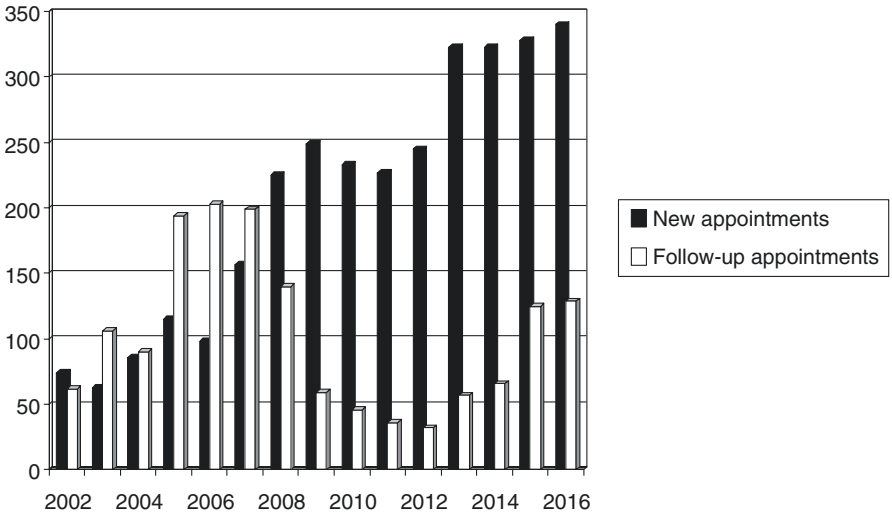

Fig. 1.1 Referral numbers to CFC, 2002–2016

Referral numbers to the author's clinic have gradually escalated over time (Fig. 1.1), which may possibly be a reflection of increasing public awareness of dementia. The 359% increase over the 15-year period 2002–2016 equates to an average increase of 23.9% per year, well ahead of the steady ~3% increase in general neurology outpatient numbers seen in the past decade. Patient numbers seen in 2008–2013 were more than twice those seen in 2002–2007, as reflected in recruitment for studies. For example, more patients were recruited in 6 months in 2013 than in 2 years in 2004–2006 in the analysis of primary care use of cognitive screening instruments (see below, Sect. 1.2.1, and Table 1.5 first two rows; for another example of doubled referral rate, see sequential studies on the "Attended alone" sign, Sect. 3.2.1).

To identify trends in the serial data, cumulative sum (cusum) points may be used (Wohl 1977). For annual CFC referrals over the decade 2007–2016, cusum points were calculated and plotted using the method of Kinsey et al. (1989), namely: selection of a reference point (the 2007 datum); subtraction of this reference point from successive recordings and the remainder added to the previous sum, with this cumulative sum plotted against time (Table 1.1; Fig. 1.2). Using this approach, if successive datapoints are the same as the reference point, the cusum plot remains at zero, if the successive datapoints rise (upward gradient) or fall (downward gradient) the cusum plot does likewise (Larner 2011:24–7;41–4). The upward gradient of the cusum plot of referrals to CFC is clearly seen (Fig. 1.2) reflecting an inexorable upward trend.

However, this increase may perhaps be contrary to the expectations of national policy documents such as the guidelines of the National Institute for Health and Clinical Excellence/Social Care Institute for Excellence (NICE/SCIE 2006), which, requiring a "single point of referral" for all cases (de facto, old age psychiatry),

Table 1.1 Cusum points for CFC referrals, 2007–2016: reference point = 157 (2007 referrals)

Cumulative summed frequency			
Year	Referrals	Calculation	Cusum point
2007	157	157	0
2008	225	(225 − 157) + 157 = 225	+58
2009	249	(249 − 157) + 225 = 317	+160
2010	233	(233 − 157) + 317 = 393	+236
2011	227	(227 − 157) + 393 = 463	+306
2012	245	(245 − 157) + 463 = 551	+394
2013	323	(323 − 157) + 551 = 717	+560
2014	323	(323 − 157) + 717 = 883	+726
2015	328	(328 − 157) + 883 = 1054	+897
2016	340	(340 − 157) + 1054 = 1237	+1080

See Fig. 1.2

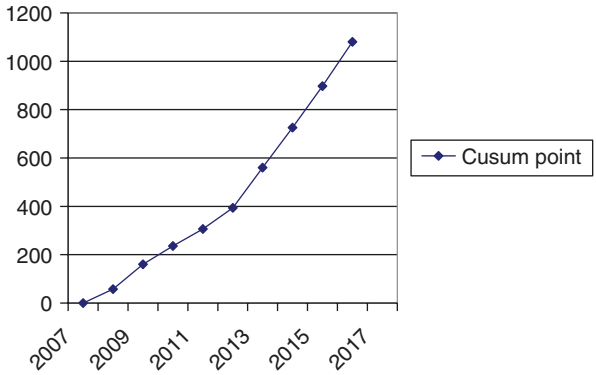

Fig. 1.2 Cusum plot: CFC referrals, 2007–2016

might have been anticipated to erode referrals to a neurology-led clinic. In fact, comparing the 2 years immediately before and after publication of the NICE/SCIE guidelines (Larner 2009a) there was a 79% increase in new referrals seen in CFC. Likewise, there was a 12% increase in the number of referrals comparing the 12-month periods immediately before and after the launch of the NDS (Larner 2010).

The fall off in numbers of follow-up appointments post 2008 (Fig. 1.1) was occasioned by the decommissioning of CFC prescriptions for cholinesterase inhibitors for financial reasons. It is possible that memory clinics may be no more effective than primary care practitioners for post-diagnosis treatment and coordination of care for dementia patients, as shown in a study from the Netherlands (Meeuwsen et al. 2012), although inevitably the cohort of patients readily available for clinical trials of novel drugs in the secondary care (Sect. 10.2.2) setting is reduced.

1.2 Referral Sources

The vast majority of referrals to CFC have come from three sources: primary care physicians (general practitioners), psychiatrists, and neurologists.

1.2.1 Primary Care

The majority of referrals to CFC have been initiated by general practitioners (GPs) working in primary care settings.

Initial studies examining referral sources found that around 50% came from primary care (Larner 2005a; Fisher and Larner 2007; Fearn and Larner 2009). This proportion increased to around 70% following publication of national directives (NICE/SCIE, NDS; Larner 2009a, 2010; Menon and Larner 2011; Table 1.2 penultimate row) and has remained consistently above this figure in subsequent studies (Ghadiri-Sani and Larner 2014; Wojtowicz and Larner 2015, 2016; Cannon and Larner 2016). These data suggest that awareness of the problem of dementia has increased amongst primary care clinicians over the past decade (see also Sects. 10.5.1 and 10.5.3).

A closer analysis of referrals has permitted referral source patterns to be addressed (Table 1.3; Fig. 1.3). In the 5-year period 2009–2013 the null hypothesis that the proportion of patients referred to CFC from primary care did not differ significantly was rejected ($\chi^2 = 22.1$, df = 4, $p < 0.001$; Larner 2014a). Extending the analysis to 8 years (2009–2016) resulted in the same outcome ($\chi^2 = 26.9$, df = 7, $p < 0.001$).

Table 1.2 Referral numbers, sources and diagnoses before and after launch of NICE/SCIE and NDS directives (adapted from Menon and Larner 2011; based on data from Larner 2005a; Fisher and Larner 2007; Menon and Larner 2011) reprinted with permission

	(Sept 2002 to August 2004)	Before NICE/SCIE launch (Oct 2004 to Sept 2006)	Before NDS launch (Feb 2008 to Feb 2009)	After NDS launch (Feb 2009 to Feb 2010)
New referrals seen	183	231	225	252
Dementia (% prevalence in cohort)	90 (49.2)	117 (50.6)	74 (32.9)	75 (29.8)
New referrals from primary care (% of total new referrals)	90 (49.2)	123 (53.2)	131 (58.2)	175 (70.2)
Primary care referrals with new diagnosis of dementia (% of primary care referrals)	36 (40.0)	45 (36.6)	28 (21.3)	42 (24.0)

Table 1.3 Referral numbers, sources and diagnoses, CFC 2009–2016 (adapted and updated from Larner 2014a; see Table 1.8 for a breakdown of sources of secondary care referrals)

Year	*N*	Referral source		Diagnosis		
		Primary care (%)	Secondary care (%)	Dementia (% of *N*)	No dementia (% of *N*)	MCI (% of *N*; % of no dementia)
2009	249	174 (70)	75 (30)	76 (31)	173 (69)	30 (12; 17)
2010	233	149 (64)	84 (36)	71 (30)	162 (70)	25 (11; 15)
2011	227	177 (78)	50 (22)	53 (23)	174 (77)	39 (17; 22)
2012	245	197 (80)	48 (20)	67 (27)	178 (73)	40 (16; 22)
2013	323	243 (75)	80 (25)	88 (27)	235 (73)	66 (20; 28)
2014	323	252 (78)	71 (22)	82 (25)	241 (75)	71 (22; 29)
2015	328	246 (75)	82 (25)	70 (21)	258 (79)	69 (21; 28)
2016	340	265 (78)	75 (22)	75 (22)	265 (78)	70 (21; 26)
Total (%)	2268	1703 (75.1)	565 (24.9)	582 (25.7)	1686 (74.3)	410 (18; 24)

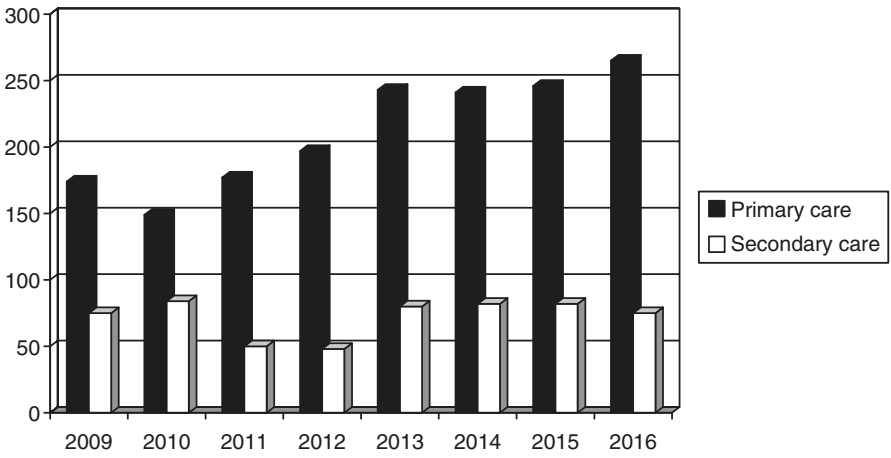

Fig. 1.3 Referral sources to CFC, 2009–2016

Cusum points (Kinsey et al. 1989; Sect. 1.1) for annual referrals to CFC from primary care were calculated and plotted with the 2009 datum selected as reference point (Table 1.4; Fig. 1.4). The upward trend of referrals to CFC from primary care in recent years is evident from the upward gradient of the cusum plot.

The frequency of dementia diagnosis has been consistently lower in the referral cohort from primary care than in patient groups referred from secondary care (Larner 2005a; Fisher and Larner 2007; Menon and Larner 2011; Table 1.2 bottom row). There is some evidence for increasing numbers of referrals of so-called "worried well" patients (for a discussion of this terminology, see Sect. 8.3) from primary care (Sect. 10.5.3). Whilst it is accepted that making a diagnosis of dementia or cognitive disorder is not the only function of CFC, and that reassurance of the "worried well" may be deemed an important clinical function, nonetheless establishing dementia diagnoses is key to the purposes of such clinics.

Table 1.4 Cusum points for annual referrals to CFC from primary care, 2009–2016: reference point = 174 (2009 referrals)

Cumulative summed frequency			
Year	Referrals from primary care	Calculation	Cusum point
2009	174	174	0
2010	149	(149 − 174) + 174 = 149	−25
2011	177	(177 − 174) + 149 = 152	−22
2012	197	(197 − 174) + 152 = 175	+1
2013	243	(243 − 174) + 175 = 244	+70
2014	252	(252 − 174) + 244 = 322	+148
2015	246	(246 − 174) + 322 = 394	+220
2016	265	(265 − 174) + 394 = 485	+311

See Fig. 1.4

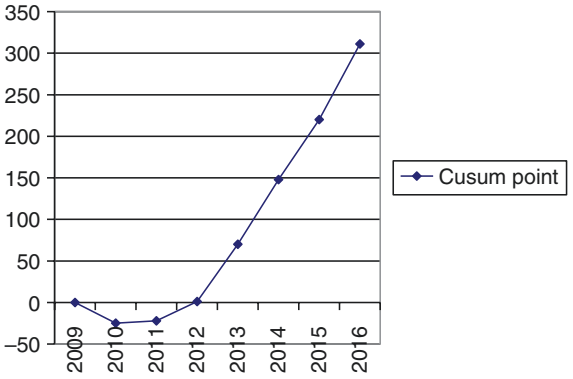

Fig. 1.4 Cusum plot: annual referrals to CFC from primary care, 2009–2016

Why should primary care referrals have the lowest "hit rate" for dementia diagnosis? It might be argued that with the possibility of longitudinal (i.e. intraindividual) patient assessment, GPs are well placed to detect cognitive change in their patients (Fisher and Larner 2006), unlike practitioners in secondary care who generally have to make a cross sectional (i.e. interindividual) assessment. Change in patient function might be suggested to primary care physicians by missed appointments, repeated phone calls on the same topic, and poor medication concordance. On the other hand, there has undoubtedly been a certain antipathy to making dementia diagnoses in primary care for various reasons, including therapeutic nihilism and lack of confidence related to inadequate training in this area (O'Connor et al. 1988; Audit Commission 2002) rather than any suggestion of intellectual turpitude. Failure to administer cognitive screening instruments (CSI; see Chap. 4) may also be a contributory factor.

Examination of referral letters from primary care physicians to CFC, looking for evidence of CSI use prior to referral, has been undertaken in several cohorts (Fisher and Larner 2007; Menon and Larner 2011; Cagliarini et al. 2013; Ghadiri-Sani and Larner 2014; Wojtowicz and Larner 2015, 2016; Cannon and Larner 2016;

Table 1.5 Cognitive screening instrument (CSI) use reported in primary care referrals to CFC (adapted from Wojtowicz and Larner 2015; based on data from Fisher and Larner 2007; Menon and Larner 2011; Cagliarini et al. 2013; Ghadiri-Sani and Larner 2014; Cannon and Larner 2016; Bharambe and Larner 2018)

Period	Oct 2004 to Sept 2006	Feb 2008 to Feb 2009	Feb 2009 to Feb 2010	July to Dec 2012	July to Dec 2013	Jan to Dec 2015	April to Oct 2017
N (% of all referrals to CFC)	123 (53.2)	131 (58.2)	175 (70.2)	99	140 (75.7)	246 (75.0)	127 (75.1)
Any CSI used (% of *N*)	25 (20.3)	34 (25.9)	47 (26.8)		44 (31.4)	93 (37.8)	65 (51.1)
CSI use:							
MMSE	17	31	29		13	30	27
AMTS	6	2	11		6	4	2
CDT	1	0	0		0	1	0
6CIT	1	0	2	7	8	38	24
GPCOG	0	0	1		13	22	10
MoCA	0	0	0		0	3	4
Equivocal	0	1	6 (NB: 2 tests reported in 2 patients)		4	1 (NB: 2 tests reported in 6 patients)	0 (NB: 2 tests reported in 2 patients)

N number of referrals from primary care, *MMSE* Mini-Mental State Examination, *AMTS* Abbreviated Mental Test Score, *CDT* Clock drawing test, *6CIT* Six-Item Cognitive Impairment Test, *GPCOG* General Practitioner Assessment of Cognition, *MoCA* Montreal Cognitive Assessment

Bharambe and Larner 2018). For example, in two 2-year cohorts, covering the periods October 2004 to September 2006 (Fisher and Larner 2007) and February 2008 to February 2010 (Menon and Larner 2011; Tables 1.2 and 1.5), the initial study found that in 20.3% of GP referrals (25/123) a specific CSI was mentioned, whereas in the second study this had risen to 26.5% (81/306), a change which did not permit rejection of the null hypothesis ($\chi^2 = 1.54$, df = 1, $p > 0.1$).

The latter 2-year cohort bridged the launch of the National Dementia Strategy (Department of Health 2009). Comparing the 12 month periods pre- and post-NDS launch there was a small increase in reported CSI use (34/131, 25.9% vs. 47/175, 26.8%; Table 1.5) but this did not reach statistical significance ($\chi^2 = 0.07$, df = 1, $p > 0.5$; Menon and Larner 2011).

The CSIs most commonly used in these observational surveys of primary care practice were initially the Mini-Mental State Examination (MMSE; Folstein et al. 1975) and the Abbreviated Mental Test Score (Hodkinson 1972). This practice may have reflected the longevity of these instruments, and/or their recommendation in *Understanding dementia. A resource pack for GPs and patients* which was issued in support of the NDS (Department of Health/Alzheimer's Society 2009).

There are, of course, a very large number of CSIs described in the literature (see, for example, Larner 2017), some of which have been developed specifically for use in primary care and are therefore recommended in this setting (Brodaty et al. 2006; Cordell et al. 2013). These include the Six-Item Cognitive Impairment Test (6CIT; Brooke and Bullock 1999; Gale and Larner 2017), the Memory Impairment Screen (MIS; Buschke et al. 1999), Mini-Cog (Borson et al. 2000), and the General Practitioner Assessment of Cognition (GPCOG; Brodaty et al. 2002; Seeher and Brodaty 2017). These CSIs were very seldom mentioned, if at all, in the initial CFC surveys (Larner 2005a; Fisher and Larner 2007; Menon and Larner 2011), suggesting they had not displaced the older tests (Table 1.5).

An audit of dementia referrals to a later life psychiatry service reported that only 13.2% of referral letters contained MMSE results (Hussey et al. 2009), commensurate with the empirical findings in CFC (Fisher and Larner 2007; Menon and Larner 2011), and in marked contrast with the (widely cited) findings reported from a postal survey which claimed 79% use of CSIs in three English Primary Care Trusts (Milne et al. 2008). Since it would seem unlikely that GPs fail to report MMSE or other CSI results in referral letters to dedicated dementia services if these tests have been undertaken in primary care (at least as a systematic, as opposed to an occasional, omission), the discrepancy might be accounted for by MMSE being too time consuming in primary care, and/or too difficult to interpret (Larner 2009b).

More recent surveys of primary care referrals to CFC (Cagliarini et al. 2013; Ghadiri-Sani and Larner 2014; Wojtowicz and Larner 2015, 2016; Cannon and Larner 2016; Bharambe and Larner 2018) have suggested increased use of CSIs appropriate for administration in primary care, specifically 6CIT and GPCOG (Table 1.5, three right-hand columns). However, despite an increase in overall CSI usage (approaching 40% in the 2015 cohort) the null hypothesis that the proportion of CSI use in primary care patients in the first four sequential cohorts did not differ significantly was not rejected ($\chi^2 = 3.94$, df = 3, $p > 0.1$; Ghadiri-Sani and Larner 2014). Looking specifically at use of GPCOG (Wojtowicz and Larner 2015), the null hypothesis that the proportion of GPCOG use in primary care referrals did not differ significantly between the 2015, 2013, and the summed previous cohorts was rejected ($\chi^2 = 41.1$, df = 2, $p < 0.001$).

Despite evidence of increasing CSI usage in primary care, this may not necessarily provide unequivocal and hence potentially useful diagnostic information, since errors in the scoring and reporting of CSIs administered in primary care were found in around one-quarter of cases. Both 6CIT and GPCOG, CSIs specifically recommended for use in primary care, were particularly liable to scoring errors (Cannon and Larner 2016; Wojtowicz and Larner 2016; Fig. 1.5).

Does primary care CSI use vary according to the final CFC diagnosis? In the study of Cannon and Larner (2016), the proportions of patients with diagnoses of dementia or no dementia (=mild cognitive impairment [MCI] + subjective memory complaint [SMC]) who had been assessed with CSIs in primary care were 16/52 (=30.8%) and 77/194 (=39.7%) respectively. The null hypothesis that the proportion

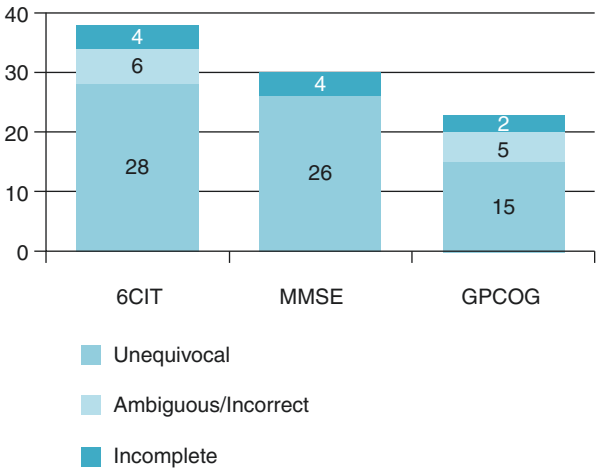

Fig. 1.5 Frequency of scoring/reporting errors for different CSIs administered in primary care (adapted from Wojtowicz and Larner 2016; error classification categories of Wojtowicz and Larner 2015)

Table 1.6 Comparison of primary care CSI use by final diagnosis in two patient cohorts

Period	July to December 2013	January to December 2015
Reference	Ghadiri-Sani and Larner (2014)	Cannon and Larner (2016)
N	140	246
Prevalence: Dementia; MCI	0.24, 0.13	0.21, 0.20
Proportion of dementia vs. non-dementia patients (MCI + SMC) assessed with CSI	12/34 (=35.3%) vs. 32/106 (=30.2%); $\chi^2 = 0.18$, df = 1, $p > 0.5$	16/52 (=30.8%) vs. 77/194 (=39.7%); $\chi^2 = 1.65$, df = 1, $p > 0.1$
Proportion of any cognitive impairment (dementia + MCI) vs. no cognitive impairment (SMC) patients assessed with CSI	17/52 (=32.7%) vs. 27/88 (=30.7%); $\chi^2 = 0.14$, df = 1, $p > 0.5$	35/100 (=35%) and 58/146 (=39.7%); $\chi^2 = 0.64$, df = 1, $p > 0.1$

of demented and non-demented patients assessed in primary care with a CSI did not differ significantly was not rejected ($\chi^2 = 1.65$, df = 1, $p > 0.1$). The proportions of cognitively impaired (dementia + MCI) and cognitively unimpaired (=SMC) patients who had been assessed with a CSI in primary care were 35/100 (=35%) and 58/146 (=39.7%) respectively. The null hypothesis that the proportion of cognitively impaired and cognitively unimpaired patients assessed in primary care with a CSI did not differ significantly was not rejected ($\chi^2 = 0.64$, df = 1, $p > 0.1$). These figures were similar to those observed in the prior study by Ghadiri-Sani and Larner (2014), as shown in Table 1.6. However, Bharambe and Larner (2018) found a trend towards patients with functional cognitive disorders (see Sect. 8.3) being more likely to have had a cognitive screening instrument administered prior to referral than those with a cognitive disorder ($\chi^2 = 3.41$, df = 1, $0.1 > p > 0.05$).

1.2.2 Psychiatry

Behavioural and neuropsychiatric symptoms (BPSD) are not uncommon in dementia syndromes (see Sect. 8.2.1). Dementia as a syndrome transcends the professional boundaries of neurology and psychiatry and it is therefore not surprising that both disciplines should be involved in patient diagnosis and management (see Sect. 10.6).

Analysis of referrals to CFC over a 5-year period (September 2002 to August 2007; Larner 2007a) showed that 21.3% of referrals (95% CI = 17.8–24.8%) came directly from either general or old age psychiatrists (Table 1.7, left hand column). Of these, 58.8% received a diagnosis of dementia (95% CI = 49.7–67.8%). The most common dementia subtypes were Alzheimer's disease (36) and frontotemporal lobar degenerations (FTLD; 20). Informal comparison of these data with an unselected (partially overlapping) cohort of consecutive patients previously reported from CFC (Table 1.7, right hand column; Larner 2005b) indicated that the patients referred by psychiatrists were of similar age but had a higher frequency of dementia (58.8% vs. 50.6%), particularly FTLD (29.8% vs. 12.5%). These data suggested that psychiatrists use neurological services to assist with the diagnosis of dementia, and hence presumably value this referral option, particularly in the case of individuals with suspected dementia of early-onset and of FTLD type.

The NICE/SCIE guidelines (2006) regarding the identification, treatment and care of people with dementia anticipated that psychiatrists, particularly old age psychiatrists, would manage the dementia care pathway in its entirety from diagnosis to end-of-life care. A "single point of referral" was specified in the guidelines. These recommendations apparently ignored the fact that some neurologists and geriatricians had developed significant specialist interests in dementia. Compliance with NICE/SCIE guidelines might have been anticipated to erode the number of general referrals to neurology-led memory clinics, and referrals to these clinics from psychiatrists in particular. However, a study in CFC (see Sect. 10.5.1; Table 10.2) in

Table 1.7 Referrals from psychiatrists to CFC: demography and diagnoses (adapted from Larner 2007a)

	Referrals from psychiatrists (September 2002 to August 2007)	All referrals (February 2002 to January 2004) (data from Larner 2005b)
N	114	158
Prevalence dementia	0.59	0.51
F:M (% female)	53:61 (46.5%)	69:89 (43.7%)
Age range in years	42–81 (mean 63.4 ± 8.6)	49–84 (mean 64.5 ± 8.2)
Dementia subtypes		
Alzheimer's disease	36	62
Frontotemporal dementias	20	10
Vascular dementias	4	4
Others	7	4

Table 1.8 Referral numbers from secondary care to CFC 2009–2016

Year	*N*	Referral source		
		Psychiatry (% of *N*)	Neurology (% of *N*)	Other (% of *N*)
2009	75	30 (40)	33 (44)	12 (16)
2010	84	36 (43)	37 (44)	11 (13)
2011	50	27 (54)	14 (28)	9 (18)
2012	48	22 (46)	11 (23)	15 (31)
2013	80	30 (38)	24 (30)	26 (32)
2014	71	22 (31)	26 (37)	23 (32)
2015	82	32 (39)	26 (32)	24 (29)
2016	75	36 (48)	19 (25)	20 (27)
Total (%)	565	235 (41.6)	190 (33.6)	140 (24.8)

fact showed a large increase in referral numbers to CFC comparing the 2-year periods immediately before (January 2005 to December 2006) and after (January 2007 to December 2008) publication of the NICE/SCIE document (Larner 2009a).

An analysis of referrals to CFC from secondary care also addressed this issue (Table 1.8). About 40% of such referrals come from psychiatrists. The null hypothesis that the proportion of patients referred from secondary care by psychiatrists to CFC over the 8-year period 2009–2016 did not differ significantly was not rejected ($\chi^2 = 9.14$, df = 7, $p > 0.1$); likewise, referrals from psychiatrists as a proportion of all referrals to CFC, although a trend was observed ($\chi^2 = 12.75$, df = 7, $0.1 > p > 0.05$).

1.2.3 Neurology

A sizeable number of secondary care referrals to CFC comes from other neurologists (Table 1.8), mostly colleagues at WCNN but sometimes from further afield. These neurological referrals have the highest percentage of dementia diagnoses, compared to referrals from primary care and from psychiatrists (Larner 2005a), a possible indication of the "added value" to be gained from neurological referral. (The added value of neurological referral has, perhaps counterintuitively from the perspective of neurologists, been difficult to demonstrate; Association of British Neurologists 2002.) Neurologists may also refer from their own area of subspecialist interest patients who may have cognitive impairment as one feature of their neurological illness (Larner 2008, 2013a; Larner et al. 2011).

1.3 Referral Demographics

1.3.1 Patient Age

With its historic focus on early-onset dementias (Ferran et al. 1996), it is inevitable that the patients referred to CFC are generally younger than those seen in old age psychiatry and geriatric memory clinics. (It is generally recognised that patients

with dementia included in clinical research studies are systematically younger than patients from the general population; Schoenmaker and Van Gool 2004.) Although dementia prevalence increases with age, the differential diagnosis of cognitive impairment in younger people is recognised to be much broader (Doran 1997; Rossor et al. 2010; Davies et al. 2011). Numbers of patients with early-onset dementia are thought to be higher than previously recognised (Alzheimer's Society 2014).

Typically the mean or median age of patients referred to CFC has been in the late 50s to early 60s, with a broad age range from around 20 to 90 years (e.g. see Table 1.7, and data from a number of pragmatic diagnostic test accuracy studies in consecutive new patient referrals detailed in Chap. 4). This age structure does not seem to have changed noticeably during the period over which these studies have been undertaken in CFC.

In a cohort of patients seen over a 1-year period (July 2012 to June 2013; $N = 269$; Price and Larner 2013), 177 (=65.8%) were aged ≤65 years, of whom 24 had dementia (=13.6%) and another 33 (=18.6%) had cognitive impairment but were not demented, whereas 78/92 (=84.7%) older patients had either dementia (57) or cognitive impairment but not dementia (21). Hence the relative risks or risk ratios of any cognitive impairment, of dementia, or of cognitive impairment short of dementia in young patients compared to old were 0.38 (95% CI = 0.17–0.59), 0.22 (95% CI = −0.12–0.56), and 0.82 (95% CI = 0.58–1.05) respectively.

Correlations between patient age and scores on a number of the CSIs examined in CFC (see Chap. 4) are shown in Table 1.9. Diagnostic performance of investigations may be influenced by patient age, for example some neurological signs (see Sect. 3.2.1, Fig. 3.2) and CSIs (Sect. 6.1.5; Wojtowicz and Larner 2017).

Table 1.9 Summary of correlation coefficients for selected cognitive screening instruments examined in CFC and patient age (adapted and updated from Larner 2015b:75)

	r	Performance	*t*	*p*
MMSE	−0.23	No	3.63	<0.001
MMP	−0.26	No	4.06	<0.001
ACE-R	−0.32	Low	4.47	<0.001
MACE	−0.31	Low	7.96	<0.001
6CIT	0.33	Low	5.55	<0.001
MoCA	−0.34	Low	5.84	<0.001
s-MoCA	−0.40	Low	7.01	<0.001
TYM	−0.30	Low	4.61	<0.001
H-TYM	−0.37	Low	2.37	<0.02
Free-Cog[a]	−0.31	Low	1.37	>0.1
AD8	0.02	No	0.28	>0.5

Negative correlation with age = lower test scores worse
Positive correlation with age = higher test scores worse (i.e. test negatively scored)
MMSE Mini-Mental State Examination, *MMP* Mini-Mental Parkinson, *ACE-R* Addenbrooke's Cognitive Examination-Revised, *MACE* Mini-Addenbrooke's Cognitive Examination, *6CIT* Six-Item Cognitive Impairment Test, *MoCA* Montreal Cognitive Assessment, *s-MoCA* Short Montreal Cognitive Assessment, *TYM* Test Your Memory test, *H-TYM* Hard Test Your Memory test
[a]Preliminary data

1.3.2 Patient Gender

Meta-analyses of dementia prevalence studies suggest that dementia is more prevalent in women, mostly due to the increasing prevalence of Alzheimer's disease with age, whilst vascular dementia is more common in men (Lobo et al. 2000). Local studies have also suggested the influence of female gender on Alzheimer's disease incidence (Copeland et al. 1999:435). The appropriate population for dementia screening might be anticipated to show a slight female predominance (hence all the CFC studies tabulated in this book give the proportion of female patients in each cohort).

Regarding patient gender in referrals to CFC, typically there has been a slight preponderance of males (Table 1.10; Fig. 1.6a), in contrast with general neurology clinics where females are in the majority (Larner 2011:27, 43–5; Fig. 1.6b). For example, in a 3-year study (September 2008 to August 2011), a total of 726 new patients was assessed in CFC of whom 52.8% were male (F:M = 343:383; Larner 2014b). Consistently, pragmatic diagnostic test accuracy studies of neurological signs and CSIs undertaken in consecutive patient cohorts (Chap. 4) have recruited more men than women, with only rare exceptions (e.g. Larner 2007b, 2012a).

Diagnostic performance of neurological signs may be influenced by patient gender (see Sects. 3.2.1 and 3.2.2, and Fig. 3.1).

1.3.3 Patient Ethnicity and Social Class

Details on patient ethnicity and social class have not been collected in CFC studies. However, using the 2001 UK Census groupings for ethnicity, the vast majority of patients referred (estimated to be >95% of total) fall within the White (British; Irish; Other) codes, with only small numbers (estimated to be <5% of total) falling within the Mixed, Asian or Asian British, Black or Black British, and Other ethnic groups codes.

Table 1.10 Referral numbers by patient gender, CFC 2009–2016

		Gender		
Year	*N*	Female	Male	% female
2009	249	110	139	44.2
2010	233	109	124	46.8
2011	227	117	110	51.5
2012	245	122	123	49.8
2013	323	141	182	43.7
2014	323	166	157	51.3
2015	328	156	172	47.6
2016	340	165	175	48.5
Total	2268	1086	1182	47.9

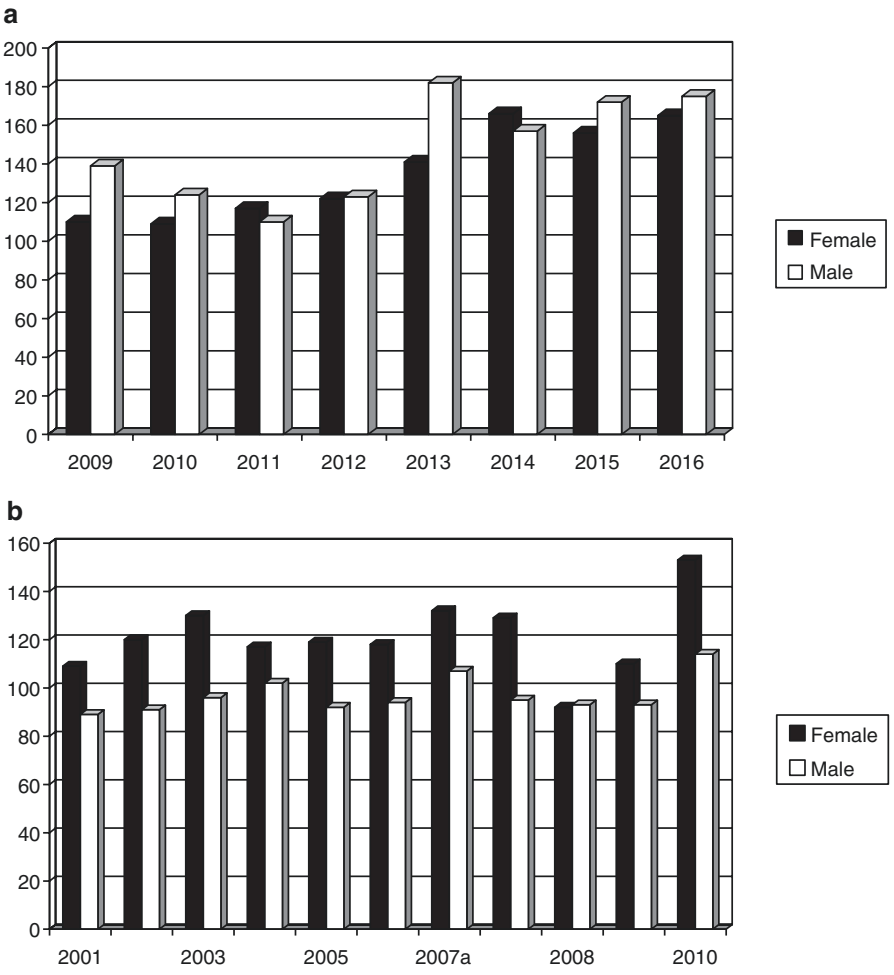

Fig. 1.6 Referrals by patient gender to (**a**) CFC, annual cohorts 2009–2016; and (**b**) the author's general neurology clinics, 3 month cohorts 2001–2010 (two cohorts in 2007). Graph b based on data in Larner 2011 "reprinted with permission"

1.3.4 Patient Handedness

Details on patient handedness have not been routinely collected in CFC studies, with the exception of the study on the mini-Addenbrooke's Cognitive Examination (MACE; Sect. 4.1.5.5; e.g. Larner 2015c).

Over a 3-year period, of 599 (F:M = 280:319) patients tested with MACE a total of 73 (=12.2%) were left-handed. Of these patients, 26/280 females were left-handed (=10.2%), and 47/319 males (=14.7%). These figures (Williamson and Larner 2018) are comparable with reference data: McManus (2009:45) reported an overall figure of 12.24% for left-handedness in the UK, and that

around 11–12% of men and 9–10% of women are typically left-handed in Western countries.

1.4 Casemix: Dementia Prevalence

The casemix of referrals to CFC shows marked clinical heterogeneity. This is, of course, the idiom of clinical practice, which is rather alien to the common methodology (Chap. 2) of assessing the utility of cognitive and non-cognitive screening instruments (Chaps. 4 and 5) which is usually based on the examination of selected diagnostic groups, and sometimes with normal control groups (see Sect. 2.3), so-called proof-of-concept (or phaseI/II; Sackett and Haynes 2002) studies.

There has been a decline over the years in the percentage of referred patients who have received a dementia diagnosis (see, for example, Table 1.2, row 2). Dementia prevalence was higher in the cohort assessed with the Addenbrooke's Cognitive Examination (n = 285; February 2002 to August 2005; 49%; Larner 2007c), compared to the cohort assessed with the Addenbrooke's Cognitive Examination-Revised (n = 243; August 2005 to August 2008; 35%; Larner 2009c, 2013b), and the cohort assessed with the Montreal Cognitive Assessment (n = 150; September 2009 to March 2011; 24%; Larner 2012b), and the cohort assessed with the mini-Addenbrooke's Cognitive Examination (n = 599; June 2014 to May 2017; 16.5%; Williamson and Larner 2018). A less rigorous comparison, but which nevertheless supports this conclusion, was provided by retrospective (2001–2002) and prospective cohorts (2010) evaluated with a test of visuoperceptual function, the Poppelreuter figure (Sect. 4.2.3), in which dementia prevalence was 56% and 28% respectively (Sells and Larner 2011).

This fall in dementia prevalence in clinic attenders may reflect increased referral of those non-demented individuals who may be variously described as "worried well", "subjective memory complainers", or be diagnosed with subjective memory complaint or impairment, particularly from primary care (see Sects. 1.2.1 and 10.5.3; also Sect. 3.2.1 for another example of the falling prevalence of dementia in clinic referrals over time). A similar pattern of increased referral of "benign memory complaints" has been reported from other clinics (Blackburn et al. 2014). However, it might also be reflective of earlier referral and identification of neurodegenerative disorders at the mild cognitive impairment stage before a dementia diagnosis is reached, a potentially important change in terms of case ascertainment and early deployment of disease-modifying therapy. Alternatively, many of these patients may have functional cognitive disorders (Stone et al. 2015; Bharambe and Larner 2018; see Sect. 8.3).

Analysis of referrals in the 8-year period 2009–2016 permitted diagnostic frequencies of dementia and mild cognitive impairment (MCI) to be examined (Table 1.3; Fig. 1.7). The null hypotheses that the proportions of all patients referred to CFC with either dementia ($\chi^2 = 12.45$, df = 7, $0.1 > p > 0.05$) or cognitive impairment (=dementia + MCI; $\chi^2 = 6.09$, df = 7, $p > 0.1$) over this period did not differ significantly were not rejected, confirming the findings of a prior 5-year analysis (Larner 2014a).

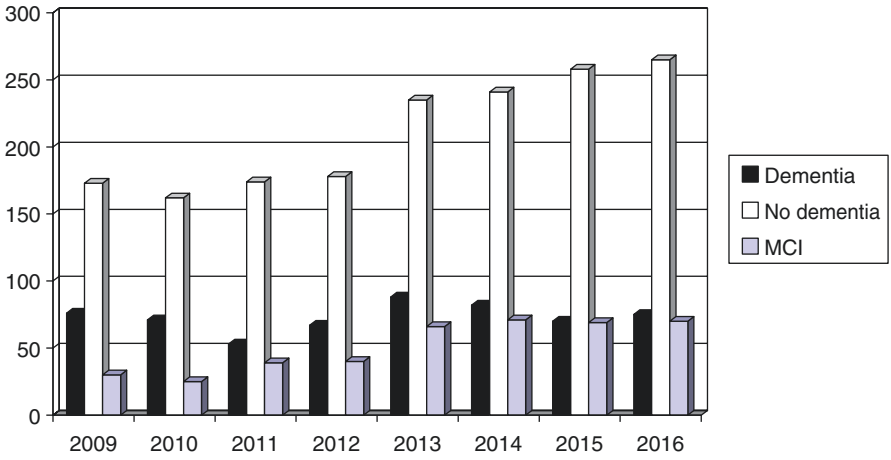

Fig. 1.7 Diagnostic frequencies of dementia, no dementia, and mild cognitive impairment, 2009–2016

Table 1.11 Cusum points for dementia diagnoses in CFC referrals, 2009–2016: reference point = 76 (2009 referrals)

Cumulative summed frequency			
Year	Dementia diagnoses	Calculation	Cusum point
2009	76	76	0
2010	71	(71 − 76) + 76 = 71	−5
2011	53	(53 − 76) + 71 = 48	−28
2012	67	(67 − 76) + 48 = 39	−37
2013	88	(88 − 76) + 39 = 51	−25
2014	82	(82 − 76) + 51 = 57	−19
2015	70	(70 − 76) + 57 = 51	−25
2016	75	(75 − 76) + 51 = 50	−26

See Fig. 1.8

Cusum points (Kinsey et al. 1989; Sect. 1.1) for dementia diagnoses in CFC referrals were calculated and plotted with the 2009 datum selected as reference point (Table 1.11; Fig. 1.8). The downward trend of referrals to CFC receiving a diagnosis of dementia is clearly seen from the downward gradient of the cusum plot.

Hence there is a paradox of more referrals (Figs. 1.1 and 1.2) but with fewer dementia diagnoses (Fig. 1.8) in CFC, and this despite rising numbers of dementia diagnoses nationally according to figures from the Health and Social Care Information Centre (http://www.hscic.gov.uk/article/4902/Number-of-patients-with-recorded-diagnosis-of-dementia-increases-by-62-per-cent-over-seven-years (last accessed 27/12/2017)).

Most dementia diagnoses have been of Alzheimer's disease and frontotemporal lobar degenerations (e.g. Table 1.7). Although cerebrovascular disease may be a recognised comorbidity in Alzheimer's disease, particularly in older patients,

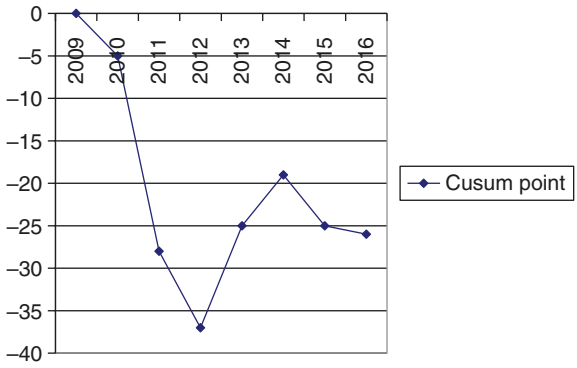

Fig. 1.8 Cusum plot: dementia diagnoses in CFC referrals, 2009–2016

patients with pure vascular dementia and vascular cognitive impairment have rarely been seen in CFC (see Sect. 9.4), likewise dementia with Lewy bodies and Parkinson's disease dementia (see Sect. 9.3). It may be that cases within the latter two categories are seen in dedicated stroke and movement disorder clinics respectively within WCNN, or may possibly be more likely to be referred directly to old age psychiatry and/or geriatric services.

1.5 Summary and Recommendations

Referrals to CFC of individuals with cognitive complaints have increased in number over the past decade, most particularly referrals from primary care. If this trend is mirrored in neurological services elsewhere, then it may well be that neurologists will be increasingly called upon to assess such patients, rather than relying on, or redirecting them to, old age psychiatry or geriatric services. The increase in referrals may reflect increased societal awareness of the problem of dementia and the importance of early diagnosis. However, there has been no increase in the proportion of patients diagnosed with dementia or cognitive impairment, and hence no evidence for closure of the dementia diagnosis gap (see Sects. 10.5.3, 10.5.4, and 10.5.5). Nevertheless, the retention and further development of neurology-led memory clinics, integrated with other services involved in the management of cognitive problems (see Sect. 10.6), would seem to remain both necessary and appropriate.

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Methods

2

Contents

Abstract

This chapter examines the methods used in the cognitive function clinic, in particular the methodology used to assess the diagnostic accuracy of clinical signs and cognitive and non-cognitive screening instruments to assist in the diagnosis of dementia. The relevance of pragmatic diagnostic test accuracy studies, compared to experimental or proof of concept studies, as a better reflection of the idiom of clinical practice, is emphasized.

Keywords

Dementia · Diagnosis · Diagnostic test accuracy studies · Diagnostic criteria

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2.1 Cognitive Clinic Logistics

For the optimal assessment of patients referred to a dedicated cognitive disorders clinic, such as the Cognitive Function Clinic (CFC) at the Walton Centre for Neurology and Neurosurgery (WCNN) in Liverpool, some thought needs to be given to available resources such as clinic location and personnel, time available for assessment (clinic template), as well as access to additional testing modalities (Chap. 7).

2.1.1 Clinic Location

A dedicated cognitive clinic should ideally be located in a quiet room, relatively sound-proofed from external noise (in my experience, significant distracting noises may include bantering clinic assistants, lawnmowers, and building works). Extraneous noise not only impairs clinical history taking but may also impact on the administration of and performance on screening instruments.

2.1.2 Clinic Personnel

Some clinics, particularly in research settings, may have access to numbers of personnel to undertake different tasks, such as clinical assessment (history taking and neurological examination; Chap. 3) and cognitive testing. Other clinics, less endowed with resources, may be single-handed. All the various clinical tasks can be undertaken by a solitary clinician, although issues may then arise in terms of the blinding of diagnostic test accuracy studies or clinical trials of therapeutic agents.

Because the casemix of a cognitive disorders clinic consists principally of forgetful people, a high patient "did not attend" (DNA) rate is to be anticipated. A clinic coordinator who can ring or text to remind patients or their relatives to attend is a boon. Certainly the number of new patient attendances to CFC increased from 2013 (see Table 1.3) when a de facto clinic coordinator was in place. During a 4 month period (February to May 2015 inclusive) when these duties were not undertaken, because the coordinator was seconded to administrative duties elsewhere, new patient attendances were observed to fall by 14.7% (95% CI = 8.22–21.1%) compared to the previous 4 months (October 2014 to January 2015), and in the 4 months after the end of the secondment and the coordinator's return to post (June to September 2015) the new attendances rose again by 21.2% (95% CI = 13.2–29.3%). The value of a clinic coordinator in reducing patient DNA rate is therefore evident.

2.1.3 Clinic Template

As well as number of available clinic personnel, time available will influence the clinic template. History taking from patient and collateral source, neurological

Box 2.1 Approximate Times to Complete Various Multidomain Cognitive Screening Instruments (See Chaps. 4 and 5 for More Details on Individual Tests)

Clock Drawing Test:	1 min
6CIT, Codex, AD8:	2–3 min
MMSE, MMP, MACE, s-MOCA:	5–10 min
TYM:	5–10 min (self-administered under medical supervision)
DemTect:	8–10 min
MoCA:	10–15 min
ACE, ACE-R, ACE-III:	15–20 min

examination (Chap. 3) and administration of cognitive screening instruments (CSIs; Chap. 4; Box 2.1), and possibly other screening instruments (Chap. 5) to ensure a comprehensive assessment prior to deployment of other investigations (Chap. 7) takes time, and is best done in an unhurried manner. Hence, unlike the situation in general neurological clinics, where 30 min slots are generally deemed appropriate (in the UK), cognitive clinic slots for new patients should ideally be longer, ranging from 45 to 60 min. An inevitable corollary is that cognitive clinics are likely to be low capacity (unless many personnel are available) for which reason they are often not popular with the managerial-bureaucratic complex, but this low capacity should not be confused with any managerial concept of "inefficiency".

Patient self-administered screening tests such as the Test Your Memory (TYM) test (Brown 2017) may be of particular value in situations where clinician time is limited, precluding performance of clinician-administered tests. However, patient self-administered tests may be more liable to drop outs (Sect. 4.1.9) and also omit the qualitative clinician-patient interaction in testing which may inform clinical judgements over and above any raw test scores.

Whereas brevity of cognitive tests may be paramount in primary care settings, a factor taken into account in the design of instruments suitable for primary care use, such as the Six-item Cognitive Impairment Test (6CIT; Sect. 4.1.6; Gale and Larner 2017) and the General Practitioner Assessment of Cognition (GPCOG; Seeher and Brodaty 2017), in secondary care settings time factors should be less pressing. Nevertheless, speed of test administration was one of the factors, along with effectiveness and ease of administration, which emerged in one survey documenting specialty clinicians' preferences (Ismail et al. 2013). Instruments such as the ADAS-Cog (Rosen et al. 1984; Mohs et al. 1997), the Mattis Dementia Rating Scale (Mattis 1976, 1992), and the Neuropsychological Assessment Battery (Stern and White 2003) are generally considered too long for routine clinical use, being largely reserved for research settings. However, there may be a trade-off between cognitive screening test accuracy and time of administration (Larner 2015a, b; see Sect. 6.1.3, Table 6.13, Figs. 6.2 and 6.3).

2.2 Diagnosis and Diagnostic Criteria

Neurological diagnosis is generally based on the clinical judgement of an experienced clinician, based on the findings elicited by history taking from the patient (and, where necessary, a reliable informant), neurological examination, and selected neurological investigations (Larner et al. 2011).

The same principles inform the diagnosis of cognitive disorders (Hodges 1994, 2007; Larner 2008, 2011a, 2013a, 2018). The general clinical assessment undertaken in CFC has been by means of semi-structured patient interview, collateral history (where available), administration of selected CSIs (Chap. 4), and structural neuroimaging (CT ± MRI; see Sect. 7.2.1). According to presentation and suspected diagnosis, this initial assessment battery may be supplemented with formal neuropsychological assessment (using instruments such as the Wechsler Adult Intelligence Scale Revised, National Adult Reading Test, Wechsler Memory Scale III, Graded Naming Test, Rey-Osterrieth Complex Figure, Stroop colour-word test, verbal fluency tests), and other investigations (Chap. 7). There has been only limited access to functional neuroimaging with HMPAO-SPECT or 1H-magnetic resonance spectroscopy (Sect. 7.2.2), and no dedicated access to measuring AD cerebrospinal fluid (CSF) biomarkers or amyloid PET imaging.

Diagnosis of dementia, specific dementia subtype, mild cognitive impairment (MCI), or subjective memory complaint (SMC) is based on clinician judgement which may be supplemented by the use of CSIs (Chap. 4) and the application of diagnostic criteria. The latter are generally developed by consensus of recognised experts in the field, and are updated from time to time in light of developments within the field. Various diagnostic criteria for cognitive disorders have been used in CFC studies, according to whichever has been widely accepted and/or validated at the time (Box 2.2).

Box 2.2 Diagnostic Criteria for Cognitive Disorders Used in Clinical Practice and Diagnostic Test Accuracy Studies (Adapted from Larner 2015c:28–9)

Dementia:

DSM iterations, e.g. DSM-IV-TR, DSM-5: American Psychiatric Association (2000, 2013)
ICD iterations, e.g. ICD-10, 2nd edition: World Health Organization (2004)

Alzheimer's disease (AD):

NINCDS-ADRDA: McKhann et al. (1984)
IWG: Dubois et al. (2007a)
NIA-AA: McKhann et al. (2011)
IWG-2: Dubois et al. (2014)

Mild cognitive impairment (MCI):

Petersen et al. (1999, 2005)
Winblad et al. (2004)
Portet et al. (2006)
NIA-AA: Albert et al. (2011), Sperling et al. (2011)

Posterior cortical atrophy (PCA):

Crutch et al. (2017)

Frontotemporal lobar degenerations:

Neary et al. (1998)
McKhann et al. (2001)
Behavioural variant frontotemporal dementia (bvFTD):
Rascovsky et al. (2011)
Primary progressive aphasias:
Gorno-Tempini et al. (2011): agrammatic, semantic variants
[IWG-2: Dubois et al. (2014): logopenic variant]
Frontotemporal dementia with motor neuron disease:
Strong et al. (2009)

Parkinsonian disorders:

Dementia with Lewy bodies (DLB):
McKeith et al. (1996, 1999, 2005, 2017)
Parkinson's disease dementia (PDD):
Emre et al. (2007)
Dubois et al. (2007b)
Parkinson's disease MCI:
Litvan et al. (2012)
Progressive supranuclear palsy (PSP):
Litvan et al. (1996)
Hoglinger et al. (2017)
Corticobasal degeneration (CBD):
Armstrong et al. (2013)
Corticobasal syndrome (CBS):
Mathew et al. (2012)

Vascular dementia (VaD), vascular cognitive impairment (VCI):

ADDTC: Chui et al. (1992)
NINDS-AIREN: Román et al. (1993), van Straaten et al. (2003)
Subcortical (ischaemic) vascular dementia (SIVD): Erkinjuntti et al. (2000), Gorelick et al. (2011), Kim et al. (2014)
VASCOG: Sachdev et al. (2014)

Prion disease:

Zerr et al. (2009)
Variant Creutzfeldt-Jakob disease (vCJD):
Heath et al. (2010)

Huntington's disease (HD):

Reilmann et al. (2014)

Generally there has been movement over the past 20–30 years from diagnostic criteria based purely or largely on clinical findings to criteria which are based on an understanding of disease biology, i.e. incorporating disease biomarkers. For example, the original NINCDS-ADRDA clinical diagnostic criteria for Alzheimer's disease (AD; McKhann et al. 1984) advocated a binary approach (i.e. Is there dementia? If yes, is it AD?). More recent diagnostic criteria (McKhann et al. 2011; Dubois et al. 2014) favour a clinico-biological approach to the diagnosis of AD, requiring more sophisticated investigation techniques (CSF and functional imaging biomarkers). A similar progression may be observed in DLB criteria (McKeith et al. 1996, 1999, 2005, 2017). It is recognised that these clinico-biological criteria are of particular relevance for research studies, but since the required investigations may not be easily available in many centres (including WCNN) less stringent criteria may be used pragmatically. There is a need to balance equity of access for expensive tests versus efficiency of diagnosis.

The term mild cognitive impairment (MCI) has been used somewhat variably by different authors (indeed some seek to abandon it altogether; Dubois et al. 2007a, 2014). Some reserve MCI strictly for a prodromal phase of AD, others use it more broadly for cognitive impairment without dementia from any cause. In CFC, a syndromic approach has been used (i.e. cognitive impairment, no dementia, relatively preserved activities of daily living) without implication about underlying pathology (i.e. MCI has not been used synonymously with prodromal AD), hence this is a broad and heterogeneous group. Clearly the precise choice of MCI definition may have important prognostic implications, regarding the rate of progression to dementia.

It should be recognised that diagnostic criteria have their shortcomings, in terms of sensitivity and specificity, such that disorders may be incorrectly classified because of overlap in criteria (e.g. Varma et al. 1999; Harris et al. 2015). The criteria

for primary progressive aphasia (Gorno-Tempini et al. 2011) may not classify some aphasic syndromes (Harris et al. 2013).

2.3 Diagnostic Test Accuracy Studies: Methodology

Because of the importance of screening instruments in the diagnostic process in CFC, a number of studies of their diagnostic test accuracy have been undertaken in this setting (Chaps. 3–6). Accordingly, some detail on the methodology of such studies is required.

A general account of diagnostic (or screening) test accuracy studies for dementia and cognitive impairment, based on studies undertaken in CFC, has already been presented (Larner 2015c), and hence only a brief account is given here. This is based in part on existing formulations of diagnostic test accuracy studies in general (Kraemer 1992; Sackett and Haynes 2002), the STAndards for the Reporting of Diagnostic accuracy studies (STARD) guidelines (Bossuyt et al. 2003, 2015; Cohen et al. 2017), and for studies of dementia in particular (Noel-Storr et al. 2014; Quinn and Takwoingi 2017).

2.3.1 Participants and Test Methods

Diagnostic (or screening) test accuracy studies compare an index test against a diagnostic reference ("gold") standard in a defined population of participants.

The study population may comprise participants with the target disorder and a control population of normals without the target disorder with whom they are compared. Such index, experimental, proof-of-concept studies, or phase I/II studies in the nomenclature of Sackett and Haynes (2002), are appropriate for the initial establishment of test validity (e.g. to show that the test does indeed identify patients with dementia and differentiate them from people without dementia). However, this approach is alien to day-to-day clinical practice in which a normal control group does not exist. At minimum, all patients attending a cognitive disorders clinic will have subjective memory complaints, a setting in which phase III (Sackett and Haynes 2002) or pragmatic diagnostic test accuracy studies are more appropriate (Larner 2012, 2015c; see Sect. 2.4). Clearly both approaches involve patient selection bias, and the particular paradigm chosen will depend, at least in part, on which type of selection bias is deemed preferable or least objectionable.

The method of patient recruitment is ideally prospective. Administration of both index test and reference standard should be applied to all participants, in a standardized manner, and in a blinded fashion (i.e. those administering the reference standard should not know the outcome of the index test and vice versa). Diagnoses should be made independent of the specific test instrument being examined in order to minimize review bias (Gifford and Cummings 1999; Whiting et al. 2004),

Aside from these logistical issues, a number of (interrelated) patient-related factors may bedevil any CSI diagnostic test accuracy studies. Test performance may be influenced not only by the target condition (e.g. dementia) but also by any underlying affective disorder (hence the exclusion of depressed patients in some experimental, as opposed to pragmatic, studies; see Sect. 2.3), sleep disturbance, fatigue, and effort.

Formal neuropsychological assessments now often include some measure of performance validity (or effort), for example using instruments such as the Test of Memory Malingering (Tombaugh 1996, 1997) or the Word Memory Test (Green et al. 2002), but in everyday clinical practice assessment of patient effort on cognitive screening tests may be simply a matter of clinical judgement. Frank malingering of memory symptoms is rare, and may be detected with tests such as the "coin-in-the-hand" test (Kapur 1994).

Test reproducibility or reliability may be assessed by measures such as intra- and inter-rater reliability. However this may be a problem for diagnostic test accuracy studies of cognitive screening instruments because of practice effects when repeating a CSI after a short period of time, which might result in an underestimate of reproducibility. Reproducibility of CSIs may also be assessed by examining independent patient cohorts, although this external validation is time consuming. Some studies recruit an initial validation cohort and then assess reproducibility with a separate cohort (Hancock and Larner 2008; Sect. 5.2.1), or use extant datasets (historical cohort) for a validation study and newly recruited patients for a reproducibility study (Larner 2017a; see Sect. 4.1.8.2).

2.3.2 Measures of Discrimination

The principles of evidence-based diagnosis are based upon the calculation of various parameters of diagnostic value, or measures of discrimination, based on a 2×2 data table (Fig. 2.1). Also sometimes known as a table of confusion or a confusion matrix, the 2×2 table shows binary index test results cross-classified with the binary diagnostic reference standard (e.g. clinician diagnosis based on diagnostic criteria; Sect. 2.2). This dichotomisation of test results/scores is useful for clinical and statistical interpretation, although it has been pointed out that studying cognition as a continuous variable affords greater statistical power (Altman and Royston 2006).

A large number of parameters may be calculated from the 2×2 table (Knottnerus and van Weel 2002; Larner 2013b, 2015c; Quinn and Takwoingi 2017; see Box 2.3 for details on calculation). Many of these measures are dependent on the precise test cut-off (also known as the cut-point, threshold, or dichotomisation point) used: this may be the cut-off defined in the index paper describing the test, or may be derived from the study data, although the latter risks introducing bias into the study results (Davis et al. 2013).

		True Status	
		Condition present	**Condition absent**
Test Outcome	**Positive**	True positive [TP] (a)	False positive [FP] (b)
	Negative	False negative [FN] (c)	True negative [TN] (d)

Fig. 2.1 2×2 table (table of confusion, confusion matrix)

Box 2.3 Some Measures of Test Utility Applicable to Diagnostic Test Accuracy Studies (See Also Fig. 2.1; Adapted from Larner 2015c:45–71)

Disease prevalence in the patient sample:

P = True positives + False negatives/Total number tested
= (a + c)/(a + b + c + d)
= pre-test probability

Pre-test odds:

= Prevalence (= pre-test probability)/(1 − prevalence)
= P/(1 − P)

Level of the test in the patient sample:

Q = True positives + False positives/Total number tested
= (a + b)/(a + b + c + d)

Correct classification accuracy (Acc):

Acc = True positives + True negatives/Total number tested
= (a + d)/(a + b + c + d)
= posterior probability

Net reclassification improvement (NRI):

NRI = posterior probability − pre-test probability
= Accuracy − Prevalence

Error rate or Inaccuracy:

= False positives + False negatives/Total number tested
= (b + c)/(a + b + c + d)
= (1 − Accuracy)

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

Se = True positives/True positives + False negatives
= a/(a + c)
= y axis (ordinate) of ROC curve

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

Sp = True negatives/False positives + True negatives
= d/(b + d)

Youden index (Y), or Youden J statistic:

Y = Sensitivity + Specificity − 1

Positive predictive value (PPV): a measure of the probability of disease in a patient with a positive test, or the proportion of individuals that do possess a positive test who do have the diagnosis:

PPV = True positives/True positives + False positives
= a/(a + b)
= post-test probability

Negative predictive value (NPV): a measure of the probability of the absence of disease in a patient with a negative test, or the proportion of individuals that do not have a positive test who do not have diagnosis:

NPV = True negatives/False negatives + True negatives
= d/(c + d)

Predictive summary index (PSI):

PSI = PPV + NPV − 1

False positive rate:

= False positives/False positives + True negatives
= b/(b + d)
= (1 − Specificity)
= x axis (abscissa) of ROC curve

False negative rate:

= False negatives/True positives + False negatives
= c/(a + c)
= (1 − Sensitivity)

False alarm rate:

= False positives/True positives + False positives
= b/(a + b)
= (1 − PPV)

False reassurance rate:

= False negatives/False negatives + True negatives
= c/(c + d)
= (1 − NPV)

Positive likelihood ratio (LR+): odds of a positive test result in an affected individual relative to an unaffected individual, hence a measure of diagnostic gain, more readily applicable in the setting of an individual patient:

LR+ = (True positives/(True positives + False negatives))/
(False positives/(False positives + True negatives))
= (a/(a + c))/(b/(b + d))
= Sensitivity/(1 − Specificity)
= Sensitivity/False positive rate

Negative likelihood ratio (LR−): odds of a negative test result in an affected individual relative to an unaffected individual, hence a measure of diagnostic gain, more readily applicable in the setting of an individual patient:

LR− = (False negatives/(True positives + False negatives))/
(True negatives/(False positives + True negatives))
= (c/(a + c))/(d/(b + d))
= (1 − Sensitivity)/Specificity
= False negative rate/Specificity

Diagnostic odds ratio (DOR) ***or cross-product ratio***:

= True positives × True negatives/False positives × False negatives
= ad/bc
= (Sensitivity/(1 − Sensitivity))/((1 − Specificity)/Specificity)
= (Sensitivity/False negative rate)/(False positive rate/Specificity)
= PPV × NPV/(1 − PPV) × (1 − NPV)
= PPV × NPV/False alarm rate × False reassurance rate
= LR+/LR−

Error odds ratio (EOR):

= True positives × False positives/False negatives × True negatives
= ab/cd
= (Sensitivity/(1 − Sensitivity))/(Specificity/(1 − Specificity))
= (Sensitivity/False negative rate)/(Specificity/False positive rate)

Post-test odds*:*

= Pre-test odds × Likelihood ratio (by Bayes' theorem)
= PPV/(1 − PPV)

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

CUI+ = Se × PPV (ruling in a diagnosis)
CUI− = Sp × NPV (ruling out a diagnosis)

Receiver operating characteristic (ROC) curve: plot of false positive rate (1 − Specificity) on the x axis (abscissa) against sensitivity ("hit rate") on the y axis (ordinate); 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. Q* index is defined as the point where sensitivity and specificity are equal, that being the point closest to the ideal top left ("northwest") corner of the ROC curve.

Those measures which are in most common usage, and/or which have been selected for routine use and to facilitate comparison between studies undertaken in CFC, include both paired and unitary measures.

Paired measures (see Box 2.3) include:

- sensitivity (Se) and specificity (Sp)
- positive and negative predictive values (PPV, NPV)
- positive and negative likelihood ratios (LR+, LR−; Deeks and Altman 2004)
- positive and negative clinical utility index (CUI+, CUI−; Mitchell 2011)

All these measures may range in value from 0 to 1 (higher values better). Sensitivity, specificity, and predictive values are sometimes expressed as percentages. Because presenting probabilities as percentages, although a standard practice, may lead to confusion in interpretation (e.g. Bodemer et al. 2014), in the studies described in this volume percentages have been eschewed in favour of decimal fractions when reporting measures of discrimination. Some of these measures have specific classifications (Boxes 2.4 and 2.5) which have been used in studies in CFC:

Box 2.4 Classification of Likelihood Ratios (LR)

	Large	Moderate	Small	Unimportant
LR+	>10	5–10	2–5	1–2
LR−	<0.1	0.1–0.2	0.2–0.5	0.5–1

Box 2.5 Classification of Clinical Utility Indexes (CUI)

	Excellent	Good	Adequate	Poor	Very poor
CUI+, CUI−	≥0.81	≥0.64	≥0.49	≥0.36	<0.36

There is always a balance or trade-off to be struck between test sensitivity and specificity (and predictive values), dependent upon the selected test cut-off. If the aim is to identify as many cases as possible (i.e. case finding, or rule-in: Mitchell and Malladi 2010a, b), tests of high sensitivity but low specificity might be used, accepting that this will entail many false positives or "overcalls". Conversely, if the aim is to exclude as many normals as possible (i.e. screening, or rule-out: Mitchell and Malladi 2010a, b) then tests of high specificity but low sensitivity might be used, which minimise false positives and accept more false negatives.

Clinicians may prefer tests with high sensitivity, whereas researchers may prefer high specificity (Tate 2010:250). In other words, when looking for cognitive impairment clinicians may be prepared to accept false positives which inevitably come with highly sensitive screening tests, in preference to tests with high specificity and hence with false negatives (i.e. missed diagnoses). The chosen test cut-off may be determined by the needs of the particular clinical situation; various methods to set the test cut-off may be used.

Unitary measures (see Box 2.3) include:

- correct classification accuracy, also sometimes referred to as "efficiency" (Kraemer 1992:27)
- Youden index (Y; Youden 1950)
- predictive summary index (PSI; Youden 1950)
- diagnostic odds ratios (DOR) or cross-product ratio (Glas et al. 2003)
- area under the receiver operating characteristic (ROC) curve (Zweig and Campbell 1993)
- Q* index (Walter 2002)

Most of these measures also range in value from 0 to 1 (higher values better), the exception being the diagnostic odds ratio which is desirably as large as possible; DOR = 1 is a useless test. If either cell b or c in the 2×2 table (False positive or False negative) is zero then DOR is infinite, denoted by a lemniscate (∞).

Box 2.6 Classification of Area Under ROC Curve (AUC ROC) After Metz (1978)

	Excellent	Good	Fair	Poor	Failed
AUC ROC	0.9–1.00	0.8–0.9	0.7–0.8	0.6–0.7	0.5–0.6

Box 2.7 Classification of Area Under ROC Curve (AUC ROC) After Swets (1988)

	High accuracy	Moderate accuracy	Low accuracy
AUC ROC	≥0.91	0.71–0.90	0.50–0.70

For ROC curves, AUC ROC = 0.5 indicates that a test provides no added information, and AUC = 1 indicates a test providing perfect discrimination. Classification of intermediate AUC ROC values may follow the schemes suggested by either Metz (1978) or Swets (1988) (Boxes 2.6 and 2.7 respectively):

Other metrics which may be used for assessment include measures of weighted comparison of tests (Larner 2013c; see Chap. 6 for discussion), as more meaningful than AUC ROC (Mallett et al. 2012). Effect size (e.g. Cohen's d; Cohen 1988) is of interest since it is independent of test cut-off, being based solely on the reference standard (Fig. 2.2; Larner 2014).

2.3.3 Measures of Association

Other (non-diagnostic) metrics which are sometimes used for assessing tests include measures of association, such as:

- Correlation
- Test of agreement (Cohen's kappa statistic)
- Bland-Altman limits of agreement

(See Chap. 6 for discussion of these measures).

Calculation of a correlation coefficient (e.g. Pearson's product moment correlation coefficient, *r*) between the scores of different tests applied to the same

Cohen's d formula:

$$d = \frac{\overline{X}_1 - \overline{X}_2}{\sqrt{\frac{s_1^2 + s_2^2}{2}}}$$

Where d = Cohen's d effect size
X_1 and X_2 = means of two groups
s_1 and s_2 = standard deviations of two groups

Fig. 2.2 Cohen's d formula

Box 2.8 Classification of Correlation Coefficients (After Hinkle et al. 1998)

	Low	Moderate	High
r	±0.30–0.49	±0.50–0.69	±0.70–0.89

Box 2.9 Classification of Kappa Statistic (After Landis and Koch 1977)

	No agreement	Slight agreement	Fair agreement	Moderate agreement	Substantial agreement	Almost perfect agreement
κ	<0	0–0.2	>0.2–0.4	>0.4–0.6	>0.6–0.8	>0.8–1.0

population is often performed without any implication of causation. Correlation is a measure of the strength of association between datasets, and may therefore be an indication of concurrent validity (Box 2.8) but it is not a measure of how well tests agree.

Tests of agreement, such as Cohen's kappa statistic (κ; Cohen 1960) are used to measure concordance beyond chance, or chance corrected agreement, for example inter-rater and intra-rater reliability. Kappa is thus a measure of precision, not of accuracy. For Cohen's kappa statistic, $\kappa = 1$ is perfect agreement between tests, and $\kappa = 0$ is agreement due to chance alone (Cohen 1960). Kappa statistic interpretation may be based on the convention of Landis and Koch (1977; Box 2.9).

Measures may correlate but not agree, and high correlation may in fact mask lack of agreement. Bland and Altman (1986) suggested a method which provides a measure of agreement between tests by estimating how far apart the two values are on average and putting an interval around this. The limits of agreement thus defined indicate how closely the two methods agree, but what is accepted as "close" remains a clinical rather than a statistical judgement. Some commonly used brief CSIs may have broad limits of agreement, between 10 and 15 points in 30-point scales (Larner 2016).

2.4 Pragmatic Diagnostic Test Accuracy Studies

Because patients attending a cognitive disorders clinic will at minimum have subjective memory complaints, this is a setting which is suited to Phase III (Sackett and Haynes 2002) or pragmatic diagnostic test accuracy studies (Larner 2012, 2015c), since the tests are being used to try to distinguish those with and without the target disorder among those in whom it is clinically sensible to suspect the target disorder (older people with subjective memory complaints are more likely than those without to progress to dementia; Mitchell et al. 2014).

A standardised methodology for the pragmatic study of the diagnostic utility of neurological signs, cognitive, and non-cognitive screening instruments, and their comparison and combination, has been used in the CFC (see Chaps. 3, 4, 5 and 6 respectively). Generally, consecutive new patient referrals have been examined for the sign or have been administered the screening instrument being studied. Hence, in accordance with the idiom of clinical practice, a passive case finding strategy has been pursued (as in other long-term clinic-based studies, e.g. Larner 2011b, c, 2017b; Williamson and Larner 2015). No case-control studies have been undertaken. All tests which have been examined (neurological signs, cognitive, and non-cognitive screening instruments) have been operator (i.e. clinician) dependent; computerised tests or batteries have not been used, with one minor exception (Hancock et al. 2007).

Occasionally tests have been applied to non-consecutive patient cohorts, for example when a specific diagnostic question is being addressed. This is based on the fact that tests are essentially used to provide arguments for a given diagnosis that is suspected by a clinical assessment (e.g. use of the Frontal Assessment Battery in patients whose differential diagnosis encompassed behavioural variant frontotemporal dementia, and of the Fluctuations Composite Scale in patients whose differential diagnosis encompassed a synucleinopathy; see Sects. 4.2.1 and 5.4.3 respectively). Otherwise, no enriched sampling methods have been performed. Informant-based assessments (Sect. 5.4) may be applied only to those patients attending with a knowledgeable informant. Clearly all clinic-based patient cohorts show selection bias in comparison to community-based samples, but nonetheless such samples still have a large clinical variability which will reduce test power.

The standard clinical paradigm is cross-sectional (i.e. interindividual) patient assessment. However, cognitive disorders, being usually processes rather than events, often require longitudinal (i.e. intraindividual) patient assessment in order to establish a diagnosis. Longitudinal use of some screening instruments has been undertaken (Larner 2006, 2009a, b).

A pragmatic approach to sample size estimates has suggested that normative ranges for sample sizes may be calculated for common research designs, with anything in the range of 25–400 being acceptable (Norman et al. 2012).

Proof-of-concept (phase I/II) studies may establish test cut-offs which are too stringent for day-to-day clinical practice, and hence may overdiagnose dementia or cognitive impairment (false positives). Revision of published test cut-offs may therefore be desirable in order to optimise diagnostic accuracy in the pragmatic clinical situation (e.g. Larner 2007; Jefferis et al. 2015), and there are various ways to do this (e.g. based on maximal correct classification accuracy or Youden index; Larner 2015d). However, this definition of optimal cut-offs post-hoc, based on the study data, may incur the introduction of bias into the study results (Davis et al. 2013). Examples of test cut-off revision will be encountered in studies of various screening instruments undertaken in CFC (e.g. ACE, ACE-R, MoCA, TYM; see Chap. 4).

A standardized tabulation of test demographic and diagnostic parameters has been used to summarize the outcomes of pragmatic diagnostic test accuracy studies undertaken in CFC (Box 2.10).

Box 2.10 Demographic and Diagnostic Parameters Summarizing Pragmatic Test Accuracy Studies Undertaken in CFC

Demographics
N
Gender: F:M (% female)
Age range (years), + median
Prevalence of dementia/MCI/cognitive impairment (= pre-test probability)
Pre-test odds
Diagnostics
Test cut-off
Accuracy
Net Reclassification Improvement (NRI)
Sensitivity (Se)
Specificity (Sp)
Youden index (Y)
Positive predictive value (PPV; = post-test probability)
Negative predictive value (NPV)
Predictive summary index (PSI)
Positive likelihood ratio (LR+)
Negative likelihood ratio (LR−)
Diagnostic odds ratio (DOR)
Post-test odds (= pre-test odds × LR+)
Positive clinical utility index (CUI+)
Negative clinical utility index (CUI−)
Area under the receiver operating characteristic curve (AUC ROC)

Other factors may also need to be taken into account, for example the feasibility of test administration. Disease-related motor and/or language deficits (e.g. post stroke) may impact on test performance, independent of cognitive function, and how any missing data are handled may influence test outcomes and interpretation, and therefore require to be made explicit (Lees et al. 2017).

2.5 Summary and Recommendations

A standardized methodology should be used to generate meaningful data about the value of neurological signs and investigations in the cognitive disorders clinic. Pragmatic study design may be readily adopted even in non-academic, non-tertiary care settings.

Finally, it should be remembered that practical medical knowledge also has a narrative structure (Hunter 1991), since this is the idiom of clinical practice, hence the inclusion in this volume of case material, considerable experience in the writing up of which has been gained (Ghadiri-Sani and Larner 2014; Larner 2017c).

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Clinical History and Neurological Examination

3

Contents

Abstract

This chapter considers important aspects in the clinical history, including single item cognitive screening questions and family history, in the diagnosis of cognitive disorders, and also examines the diagnostic utility of various "non-canonical" neurological signs (attended alone, head turning, applause, *la maladie du petit papier*).

Keywords

Dementia · Diagnosis · History · Neurological signs

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3.1 History Taking

Guides to cognitive assessment which are accessible to, and designed for use by, all clinicians are available (e.g. Hodges 2007). History taking and physical examination are the touchstone of all neurological assessments and the first step in all diagnostic pathways (Larner et al. 2011). This is as true for individuals with cognitive complaints as for those with elemental neurological (sensory and/or motor) problems. History taking ("anamnesis") is by far the most important method of assessment.

A semi-structured approach to the history, sufficiently flexible to accommodate the variety of clinical presentation, is required. Application of Kipling's "six honest serving men" (what, why, when, how, where, who) may be useful (Fisher and Larner 2006; Larner 2007a; Box 3.1). This may also flesh out the social, occupational, and past medical history which will contextualise the current problems.

Box 3.1 One Suggested Approach to the History Taking in the Cognitive Clinic (Adapted from Larner 2007a)

What are the problems? Frequent repetition of questions or comments suggests organic amnesia. Impairment in instrumental activities of daily living, such as handling finances or medications, travelling by public or private transport, and using the telephone, should arouse concern since epidemiological studies show them to be predictive of dementia.

Why has the patient presented now? Have problems been worsening over some months? Or has some particular incident triggered patient decline? An acute episode of confusion (delirium) occurring during febrile illness or postoperatively may be the harbinger of progressive cognitive decline.

When did this happen? Many years of forgetfulness are less alarming than a history of 6–12 months of progressive decline. Also, when in the lifespan: pathological causes of memory complaint are much more common in later life, although around 5% of dementia cases occur before the age of 65 years (in the UK; Alzheimer's Society 2014).

How do the patient and family cope with the situation? Have there been work or domestic repercussions because of forgetfulness, e.g. complaints that work is not being done or even dismissal from work, others needing to take over the patient's usual household chores?

Where do the problems occur? Are they more noticeable in new or unusual situations? Does the patient prefer to be at home, to the extent that social withdrawal has occurred? Has occupational function been impaired?

Who makes the complaint of forgetfulness? Does it emanate primarily from the patient, or from relatives, friends and carers? If the latter, whilst the patient makes little of the difficulties, the clinical index of suspicion should be increased, likewise if patients are unable to give examples of memory lapses. Patients attending alone very seldom have dementia.

Some centres use a history proforma to ensure that all potentially relevant issues are addressed, including not only cognitive symptoms but also behavioural and psychiatric features. Key history points (Larner 2011a) will include:

- The specific complaint: if memory problems, ask for some examples of how the patient's memory lets her/him down.
- Age at onset (and hence duration) of the problem.
- Onset and course of the problem: sudden or gradual onset? Fluctuating or steadily progressive course?

In addition, the importance of obtaining collateral history from a knowledgeable informant cannot be overemphasized. In some centres a provisional diagnosis of Alzheimer's disease (AD) in pre-dementia stage is based largely on informant report (Burns and Morris 2008:7, 39–41).

Enquiries about the impact of cognitive problems on occupational and/or social functions should be made, since impairment in these domains is a *sine qua non* for a diagnosis of dementia in some criteria (e.g. DSM-IV; American Psychiatric Association 2000). Further insights may be gained by enquiring about the impact of symptoms on activities of daily living (ADL), both instrumental and basic activities (Box 3.2). Dedicated screening instruments for the assessment of ADLs are available (see Sect. 5.1).

Additional points worth enquiring about in the history include:

- Education and employment: extent of education and employment history may give some pointers to premorbid cognitive function, and hence expectations about appropriate performance on cognitive screening instruments.
- Appetite: may be poor, and associated with some weight loss, in the early stages of some dementias (e.g. Alzheimer's disease); change in dietary habit with a predilection for sweet foods may occur in behavioural variant frontotemporal dementia (bvFTD).

Box 3.2 History Taking in the Cognitive Clinic: Activities of Daily Living (ADLs)

Instrumental activities:

- Ability to use public and private transport
- Handling monetary transactions
- Using the telephone, e.g. recalling messages
- Managing medications

Basic activities:

- Feeding
- Dressing
- Toileting

- Mood: anxiety and depression can impact on memory function, and may be potentially reversible with appropriate medication (see Sect. 5.2).
- Sleep pattern: disturbed sleep may impair memory, for example in depression or specific sleep-related disorders such as obstructive sleep apnoea syndrome or restless legs syndrome (see Sect. 5.3).
- Drug use: both prescription and recreational drugs may impair cognition, for example due to anticholinergic or soporific effects.

Specific aspects of the history may have positive predictive value for specific dementia disorders (see Chap. 9). These include:

- Motor slowing, visual hallucinations, REM sleep behaviour disorder in dementia with Lewy bodies and Parkinson's disease dementia.
- Early speech production problems or impaired comprehension in the linguistic variants of frontotemporal lobar degeneration (FTLD).
- Personality change, either apathy or disinhibition; increased tendency to routines; development of sweet tooth; wandering without getting lost in bvFTD.
- Getting lost early; lack of confidence; early amnesia in Alzheimer's disease.
- Prior transient ischaemic attacks/strokes, emotional incontinence in vascular cognitive impairment and vascular dementia.

Analysis of conversational profile may also have diagnostic potential (Elsey et al. 2015).

History taking may be envisaged as a conversion of the patient (and collateral) episodic account into a semantic formulation. The key question which history taking should seek to answer is whether the account is one of self-reported lapses in memory retrieval in the absence of collateral verification, or an informant report of memory impairment with loss of self-appreciation by the patient, the latter being more in keeping with a neurodegenerative disorder (Burns and Morris 2008:53; Larner 2011a).

Pattern recognition and deductive skills, perhaps akin to the methodology used by the fictional detective Sherlock Holmes, who encountered various neurological disorders in his practice (Larner 2011b), and whose skills have been adduced to the service of interpretive (Hunter 1991) and evidence-based medicine (Nordenstrom 2007), are central to diagnostic formulation, supplemented where necessary by further investigations (discussed in Chaps. 4–7).

3.1.1 Single Item Cognitive Screening Questions

Do single specific questions have particular utility in either screening for or the diagnosis of dementia and cognitive disorders? The validity of this single question approach has been illustrated in other areas of neurology, for example by the finding that a single question ("When you try to relax in the evening or sleep at night, do you ever have unpleasant, restless feelings in your legs that can be relieved by

walking or movement?") had very high sensitivity (1.00) and specificity (0.968) for the diagnosis of restless legs syndrome (Ferri et al. 2007). Clearly such single item screening questions may be subjected to pragmatic screening/diagnostic test accuracy studies (as outlined in Chap. 2).

In a prospective study, Creavin et al. (2015) found that three simple questions had high utility for dementia diagnosis: learning how to use new gadgets; problems handling personal finances; and problems with planning (commentary in Larner 2016a). A systematic review of single screening questions for cognitive impairment in older people found 11 eligible studies from 884 titles, with sensitivity range 26–96% and specificity range 45–100%, suggesting promise in informant-based single item screening questions for cognitive impairment, but insufficient evidence to support routine use (Hendry et al. 2015). Nevertheless, some have advocated the adoption of this approach.

3.1.1.1 Dementia CQUIN Question

The Dementia Commissioning for Quality and Innovation (Dementia CQUIN) policy document, a UK Government directive (Department of Health 2012), advocated a single screening question for cognitive impairment to be addressed to all individuals aged 75 years or over irrespective of the reason(s) for clinical presentation: "Have you been more forgetful in the past 12 months to the extent that it has significantly affected your life?". If answered in the affirmative, the CQUIN advised initiation of a "dementia risk assessment", exact nature unspecified (see Sect. 10.5.5).

No data on the sensitivity, specificity or other measures of discrimination for this screening question were presented in the Dementia CQUIN. Hence although it may have face validity, its ability to identify patients with and without dementia was unknown. Aji and Larner (2015) investigated this by asking the screening question to 100 consecutive patients attending a dedicated epilepsy outpatient clinic, on the grounds that subjective memory complaints are common in this patient population, variously related to underlying diagnosis, seizure frequency, medication effects, and comorbid affective disorder. They suspected that the sensitivity would be very high, with risk of identifying many false positives. In the event, nearly half of the patients questioned (48%) answered the screening question in the affirmative, although only one was aged greater than 75 years. None of these patients was judged to have dementia on clinical grounds.

3.1.1.2 Subjective Memory Complaints Likert Scale

Another single item cognitive screening question was described by Paradise et al. (2011), a five-point Likert scale for subjective memory complaints (SMC). Participants are asked "In general, how would you rate your memory?" with a choice of the following five responses: 1 = poor; 2 = fair; 3 = good; 4 = very good; or, 5 = excellent. The scale defined those rating their memory as either fair or poor (2 or 1) as experiencing SMC (SMC+). This Likert scale has been used as a screen for SMC in diagnostic test accuracy studies of cognitive screening instruments for mild cognitive impairment (O'Caoimh et al. 2016).

Aji and Larner (2017) administered the SMC Likert scale to 100 consecutive follow-up patients attending a dedicated epilepsy outpatient clinic. This study found a much lower self-rating of memory impairment using the Likert scale (20%) than the previous study (Sect. 3.1.1.1) which used a single yes/no screening question (48%). Using a Likert scale screening question may provide greater diagnostic discrimination than a simple yes/no question.

3.1.1.3 Metamemory

Metamemory may be defined as introspective knowledge or self-awareness of ones memory capabilities. Both the Dementia CQUIN screening question (Sect. 3.1.1.1) and the five-point SMC Likert scale (Sect. 3.1.1.2) may be judged to access the construct of metamemory, in that they address subjective memory judgements.

Both questions were administered (sequentially in counter-balanced order to avoid bias) to 50 consecutive new outpatients attending a dedicated cognitive disorders clinic (Larner 2018) along with a standard multidomain cognitive screening instrument, the mini-Addenbrooke's Cognitive Examination (MACE; see Sect. 4.1.5.5). Results (Table 3.1) showed that SMC Likert and MACE were highly sensitive for cognitive impairment (>0.95), but all the tests had low specificity (≤0.5). For the metamemory questions the accuracy, positive and negative predictive values were all around 0.5, with the exception of negative predictive value of 0.80 for SMC Likert, whereas MACE achieved better scores for all these parameters.

Since the standard patient assessment cognitive screening instrument, MACE, outperformed both the metamemory questions on all the measures of discrimination examined, this may cast doubt on the diagnostic utility of the metamemory construct, although further larger studies are required.

3.1.2 Family History of Dementia

Taking a family history is an integral part of the history taking process in all domains of medicine, not only neurology.

Many individuals attending cognitive disorders clinics with complaints of poor memory prove, following clinical and cognitive testing, to have no evidence for underlying cognitive impairment indicative of a neurodegenerative disorder, prompting diagnostic labels such as "worried well" and "subjective memory complainers" (see Sects. 1.4 and 8.3). What prompts these individuals to be sufficiently concerned about memory function to consult medical opinion is not entirely clear. Factors which may contribute to subjective memory complaint include affective disorders, such as anxiety and depression (Sect. 5.2.2; Hancock and Larner 2009a), sleep disturbance (Sect. 5.3.1; Hancock and Larner 2009b), and self-perception of impaired self-efficacy (Sect. 8.3).

Another possible factor is the presence of a family history of a dementing disorder (see Case Study 3.1). It has been reported that the occurrence of dementia in a close relative is a strong predictor of subjective forgetfulness (Commissaris

Table 3.1 Demographic and diagnostic parameters for single item cognitive screening (metamemory) questions (adapted from Larner 2018)

	Metamemory questions		
N	50		
F:M (% female)	26:24 (52)		
Age range (years)	26–84 (median 60.5)		
Prevalence of cognitive impairment (dementia + MCI) (= pre-test probability)	0.24		
Pre-test odds = prevalence/(1 − prevalence)	0.32		
Test	**CQUIN**	**SMC Likert**	**MACE**
Cut-off	**Yes/no**	**+/−**	**≤25/>25**
N	**30:20**	**45:5**	**37:13**
Accuracy	0.52 (0.38–0.66)	0.54 (0.40–0.68)	0.74 (0.62–0.86)
Net Reclassification Improvement (NRI)	0.28	0.30	0.50
Sensitivity (Se)	0.63 (0.43–0.82)	0.96 (0.88–1.00)	1.00
Specificity (Sp)	0.42 (0.23–0.61)	0.15 (0.02–0.29)	0.50 (0.31–0.69)
Y	0.05	0.11	0.50
PPV (= post-test probability)	0.50 (0.32–0.68)	0.51 (0.37–0.66)	0.65 (0.49–0.80)
NPV	0.55 (0.33–0.77)	0.80 (0.45–1.00)	1.00
PSI	0.05	0.31	0.65
LR+	1.08 (0.69–1.70) = unimportant	1.13 (0.94–1.36) = unimportant	2.0 = small
LR−	0.89 (0.56–1.39) = unimportant	0.27 (0.23–0.33) = small	∞
DOR	1.22 (0.78–1.92)	4.18 (3.48–5.03)	∞
Post-test odds (= pre-test odds × LR+)	0.35	0.36	0.64
CUI+	0.31 (very poor)	0.489 (poor)	0.65 (good)
CUI−	0.23 (very poor)	0.12 (very poor)	0.50 (adequate)

CQUIN Commissioning for Quality and Innovation, *SMC* subjective memory complaints, *MACE* mini-Addenbrooke's Cognitive Examination

et al. 1998). Concern based on the family history may be well justified in light of the increasing number of recognised genetically determined causes of dementia (Sect. 7.3). Although the family history may emerge or be volunteered during history taking, specific questions about this aspect may need to be addressed to the patient.

To investigate what effect positive family history of dementia might have on referrals to the Cognitive Function Clinic (CFC), a prospective observational study was undertaken, based on a clinical impression that a positive family history of

Case Study 3.1 Family History of Dementia

A 43 year-old lady was referred to the clinic by her general practitioner with memory complaints. She attended alone. Her specific complaints were of difficulty with peoples' names and forgetting ongoing tasks if distracted. There was a prior history of a seizure disorder, exact nature unspecified, but she was receiving neither antiepileptic nor any other medication. On direct questioning, she admitted to poor sleep, with sleep maintenance insomnia resulting in an estimated 4 h sleep per night, leaving her tired during the day. She was not working, and had lost interest in hobbies, but activities of daily living were preserved.

Her family history was positive for dementia. The patient (see Fig. 7.4, patient III.7) was one of seven siblings, all brothers, the three eldest of whom were affected, all with onset in their early 40s. Their mother was also affected. The brothers had been diagnosed with probable Alzheimer's disease (AD) on the basis of their clinical phenotype.

The patient's neurological examination was normal. Cognitive status was examined with the Mini-Mental State Examination (see Sect. 4.1.1) on which she scored 29/30 (1 point dropped out of 3 on delayed recall) and with the Montreal Cognitive Assessment (see Sect. 4.1.8) on which she scored 27/30 (normal ≥26/30; 1 point dropped out of 5 on delayed recall). Structural brain imaging was normal. In the absence of an objective measure of cognitive impairment, the patient was diagnosed with subjective memory complaint.

Following the death of one of her brothers, it became evident from post-mortem examination that he in fact had a tauopathy and not AD. Further investigation with neurogenetic testing showed that this was due to a splice site mutation in the gene encoding the microtubule associated protein tau on chromosome 17 (IVS10 + 16C > T), and hence his diagnosis was frontotemporal dementia with parkinsonism linked to chromosome 17 (FTDP-17; Doran et al. 2007). A cousin later presented with a clinical phenotype more typical of behavioural variant frontotemporal dementia but with the same tau gene mutation (Larner 2009a). In light of this information, the patient was offered referral to clinical genetics services for consideration of counselling prior to predictive genetic testing, but she declined this in light of her reassuring cognitive screening and neuroradiological findings.

dementia might be more common in clinic attenders without dementia (Larner 2013a). As part of clinical history taking, enquiry for a family history of dementia and/or AD was made in consecutive new patients attending the clinic over a 6-month period (April to September 2011 inclusive). The following definitions were used (after Cruts et al. 1998):

- "Autosomal dominant disease": ≥3 affected family members in at least two generations.
- "Familial disease": at least one first degree family relative affected.
- "Sporadic disease": no family history.

Of the 139 patients assessed (F:M = 73:66, 53% female; age range 18–88 years, median 61 years), 63 were judged to be either demented by DSM-IV criteria (American Psychiatric Association 2000) or to have mild cognitive impairment (MCI) by Petersen criteria (Petersen et al. 1999), hence the prevalence of cognitive impairment was 45%; 76 patients were not demented. Forty-three patients reported a positive family history of dementia. In only four instances were the criteria for "autosomal dominant disease" fulfilled, the remainder (39) having only "familial disease".

Of the 63 patients who received a diagnosis of dementia or MCI, 14 had a positive family history (all "familial disease"). Of the 76 patients who were judged to have neither dementia nor MCI, 29 had a positive family history (either "autosomal dominant disease", 4, or "familial disease", 25). Hence the frequencies of a positive family history in the two groups were 14/63 (=22.2%) and 29/76 (=38.2%) respectively. The relative risk or risk ratio of a patient with neither dementia nor MCI having a positive family history of dementia was 1.72 (95% confidence interval [CI] = 1.00–2.96). The null hypothesis that the proportion of patients with a positive family history of dementia was the same in the cognitively impaired and non-impaired groups was not rejected, although a trend was observed ($\chi^2 = 3.41$, df = 1; $0.1 > p > 0.05$). Using the Z test, the null hypothesis was rejected ($Z = 2.02$, $p < 0.05$).

As the data on family history of dementia in this study were based on patient report, with or without input from other family member, friend or carer, they are obviously subject to recall bias, which might be deemed a shortcoming. Nonetheless, since this reported family history is the one with which the patient operates, the data have ecological validity. (Note that this history may not be suitable for measuring heritability, where a metric such as the Goldman score may be required, from Goldman et al. 2005, modified by Rohrer et al. 2009; for an example of the use of the modified Goldman score, see Larner 2012a.) They suggest that a positive family history of dementia may be one stimulus for concerns about memory leading to consultation and onward referral.

A potential confounder of this result may be that patients with cognitive impairment might underreport a positive family history, for example as a consequence of an amnesic syndrome. However, since these individuals almost invariably attend the clinic with a relative, friend or carer (see Sect. 3.2.1), the risk of this confound may be minimised by the availability of collateral report.

It might be argued that using a more stringent definition of autosomal dominant disease (e.g. >3 affected family members in three generations, and/or disease age at onset <61 years) might alter the study conclusions (certainly this increases the chances of finding deterministic genetic mutations, e.g. Cruts et al. 1998; Campion

et al. 1999; Janssen et al. 2003). However, experience of eight families with deterministic genetic mutations for dementia seen in CFC (four with tau gene mutations, four with presenilin 1 gene mutations) found that in only three of these families was there a clear autosomal dominant pattern of disease transmission (using the same definition as used in this study); in four others there was familial disease, and one case was apparently sporadic, possibly due to *de novo* mutation. All but one of these families had early-onset (i.e. before 65 years of age) dementia (Doran and Larner 2009; see Sect. 7.3 for further details). All four of the patients in the family history study with a reported family history suggestive of autosomal dominant disease did not have cognitive impairment (Larner 2013a).

A study of first-degree relatives of patients with AD reported more subjective memory complaints than in the spouses of AD patients, especially in those with a prior history of depression (Tsai et al. 2006). Another study found this relationship only in the relatives of patients with early-onset AD, suggesting that increased monitoring of memory performance might occur when relatives enter the age range in which parents or siblings developed dementia (McPherson et al. 1995). It may be that these individuals are sensitized to the symptoms of memory impairment, or over-attend to apparent signs of cognitive loss, including memory lapses, as a consequence of their family history.

3.2 Neurological Examination

Neurological examination is guided by diagnostic hypotheses generated by history taking, which contextualise and give meaning (relevant, irrelevant) to the many signs which may be detected on neurological examination (Larner 2014a, 2016b). There are no neurological signs which are pathognomonic of dementia, in part because there is overlap with signs which may emerge with normal ageing (Larner 2006, 2012b, 2016b:6–7). In the appropriate setting certain features may be suggestive of the diagnosis, such as carphologia or floccillation (Larner 2007b).

A normal neurological examination may be anticipated in those with subjective memory complaint, but this is also the norm in neurodegenerative disorders such as Alzheimer's disease in its early stages. A number of neurological signs should be specifically looked for (Box 3.3; Larner 2011a, 2014a), since they may suggest specific disorders (also known as "secondary" dementias; Kurlan 2006) and/or broaden the differential diagnosis to the many neurological disorders which may have cognitive impairment as part of their phenotype (Larner 2013b). Measurement of blood pressure and auscultation for cardiac sounds and possible carotid bruits may be indicated if vascular dementia or vascular cognitive impairment is suspected.

The methodology used for assessing the diagnostic utility of neurological signs is similar to that used for cognitive and non-cognitive screening instruments (see Chap. 2).

Box 3.3 Neurological Signs to Look for in Patients Attending the Cognitive Clinic (Adapted from Larner 2011a, 2014a)

- Parkinsonism: Parkinson's disease dementia, dementia with Lewy bodies, progressive supranuclear palsy, corticobasal syndrome; may also be seen in Alzheimer's disease.
- Muscle wasting ± fasciculation; cachexia may be common to many dementias in their later stages, but concurrent fasciculation in the tongue or around the shoulder girdle suggests frontotemporal lobar degeneration with motor neurone disease (FTD/MND).
- Myoclonus: occurs early in sporadic Creutzfeldt-Jakob disease, late in Alzheimer's disease.
- Chorea: Huntington's disease.
- Sensory complaints: prion disease, especially variant CJD; multiple sclerosis.

3.2.1 "Attended Alone" Sign

The importance of collateral history from a knowledgeable informant when assessing individuals complaining of memory problems and in the diagnosis of dementia syndromes, particularly AD, has been emphasized in diagnostic guidelines (e.g. Knopman et al. 2001; Waldemar et al. 2007). Formalised input to the diagnostic process from a caregiver may be achieved through the use of structured interviews of informants, or informant scales (see Sect. 5.4).

Because of the importance of collateral history in the assessment of cognitive problems, all patients referred to CFC are sent written instructions, printed in bold type, requesting them to attend the clinic with someone who knows them well and can give information about them. These instructions are included with the letter giving the details of the clinic appointment (date, time, location).

Failure to attend CFC consultation with an informant, despite the prior provision of written instructions to do so, has been examined as a possible sign of absence of dementia in two consecutive studies over a 6-year period (September 2002 to August 2008) (Larner 2005a, b, 2009b). The results (Table 3.2) showed that the "attended alone" sign was a robust marker of the absence of dementia, with very high sensitivity, negative predictive value and negative likelihood ratio, but low specificity, positive predictive value and positive likelihood ratio, and clinical utility indices which were only adequate (rule in) or poor (rule out).

The utility of the attended alone sign may be dependent in part on the location in which patients are seen. In the study of the Instrumental Activities of Daily Living (IADL) Scale (see Sect. 5.1.1; Hancock and Larner 2007), of the patients completing the instrument without an informant present ($n = 63$), most did not have dementia (56, of whom 5 had mild cognitive impairment). Six of the seven patients adjudged to have dementia but attending the clinic alone lived close to the hospital,

Table 3.2 Demographic and diagnostic parameters of the "attended alone" sign for the absence of dementia (pooled data from Larner 2005a, 2009b, adapted)

	"Attended alone"
N	735
Prevalence of dementia (= pre-test probability)	0.45
Pre-test odds = prevalence/(1 − prevalence)	0.81
Accuracy	0.66 (0.61–0.72)
Net Reclassification Improvement (NRI)	0.21
Sensitivity (Se)	0.99 (0.91–1.07)
Specificity (Sp)	0.40 (0.37–0.43)
Y	0.39
PPV (= post-test probability)	0.57 (0.53–0.62)
NPV	0.98 (0.90–1.06)
PSI	0.55
LR+	1.65 (1.52–1.78) = unimportant
LR−	0.030 (0.027–0.033) = large
DOR	54.3 (50.1–58.9)
Post-test odds (= pre-test odds × LR+)	1.34
CUI+	0.56 (adequate)
CUI−	0.39 (poor)

the only medical institution in the town (Runcorn, Cheshire) where they were seen; the other patient travelled by ambulance arranged by his primary care practitioner.

A subsequent study of the "attended alone" sign in a large, independent outpatient cohort was undertaken to evaluate its utility as a simple screening test for the absence of dementia (Larner 2014b), as previously reported. Since "absence of dementia" may include individuals with MCI, the utility of the "attended alone" sign for identification of cognitively healthy individuals within the "absence of dementia" group was also examined, by excluding MCI patients. Over the 3-year study period (September 2008 to August 2011), a total of 726 new patients were assessed. The majority of referrals came from primary care physicians (500/726, =68.9%), the other major sources being psychiatry services (106/726, =14.6%) and other neurologists (88/726, =12.1%). Compared with the prior 6 year-period (September 2002 to August 2008), this suggested an increased (approximately doubled) referral rate (see Sect. 1.1).

Of the 726 patients, 480 (=66.1%) attended with an informant as requested, of whom 216 were diagnosed with either dementia or MCI, and 264 were diagnosed as cognitively healthy. In the attended alone group (n = 246), no patient was diagnosed as suffering from dementia but 16 patients were diagnosed with MCI and hence at possible risk of progressing to dementia, leaving 230 individuals diagnosed as cognitively healthy in this group. Prevalence of dementia/MCI (i.e. cognitive impairment) in the study population was therefore 31.9% (232/726). Dementia prevalence in previous studies (2002–2008) was 45.0% (331/735; MCI diagnoses not recorded). The null hypothesis that the proportion of patients with dementia/MCI in the study period versus the proportion with

dementia in the historical cohort was the same was rejected ($\chi^2 = 26.6$, df = 1; $p < 0.001$; see Sect. 1.4).

Diagnostic parameters for the "attended alone" sign for the absence of dementia (Table 3.3, left hand column) showed excellent sensitivity, negative predictive value, and negative likelihood ratio, as previously found (compare Table 3.2).

The sensitivity of the "attended alone" sign for identifying cognitively healthy individuals (i.e. excluding the MCI patients attending alone) was also examined (Table 3.3, right hand column). Again sensitivity, negative predictive value, and negative likelihood ratio were good. The relative risk or risk ratio of a patient with neither dementia nor MCI attending alone was 6.75 (95% confidence interval [CI] = 4.17–10.9). The null hypothesis that the proportion of patients attending alone was the same in the cognitively impaired and non-impaired groups was rejected ($\chi^2 = 112.1$, df = 1; $p < 0.001$).

Table 3.3 Demographic and diagnostic parameters of the "attended alone" sign for the absence of dementia or any cognitive impairment (adapted from Larner 2014b)

	"Attended alone"	
N	726	
F:M (% female)	343:383 (47.2)	
Age range	16–92 (median 61)	
Prevalence of cognitive impairment (dementia + MCI) (= pre-test probability)	0.32	
Pre-test odds = prevalence/(1 − prevalence)	0.47	
	Diagnosis of no dementia (i.e. presence of MCI or subjective memory complaint)	**Diagnosis of no dementia or MCI (i.e. presence of subjective memory complaint only)**
Accuracy	0.64 (0.60–0.67)	0.61 (0.58–0.65)
Net Reclassification Improvement (NRI)	0.32	0.29
Sensitivity (Se)	1.00	0.93 (0.90–0.97)
Specificity (Sp)	0.45 (0.41–0.49)	0.45 (0.41–0.49)
Y	0.45	0.38
PPV (= post-test probability)	0.48 (0.44–0.53)	0.47 (0.42–0.51)
NPV	1.00	0.93 (0.90–0.96)
PSI	0.48	0.40
LR+	1.82 (1.68–1.97) = unimportant	1.70 (1.56–1.86) = unimportant
LR−	0 = large	0.14 (0.13–0.16) = moderate
DOR	∞	11.8 (10.8–12.8)
Post-test odds (= pre-test odds × LR+)	0.86	0.80
CUI+	0.48 (poor)	0.44 (poor)
CUI−	0.45 (poor)	0.42 (poor)

Table 3.4 "Attended alone" sign, analysis by patient gender; cognitive impairment = dementia + MCI cases (adapted from Abernethy Holland and Larner 2013a)

	N	Cognitive impairment (% of N)	Attended alone (% of N)	Attended with (% of N)
Female	343	96 (28.0)	117 (34.1)	226 (65.9)
Male	383	136 (35.5)	129 (33.7)	254 (66.3)
Total	726	232 (32.0)	246 (33.9)	480 (66.1)

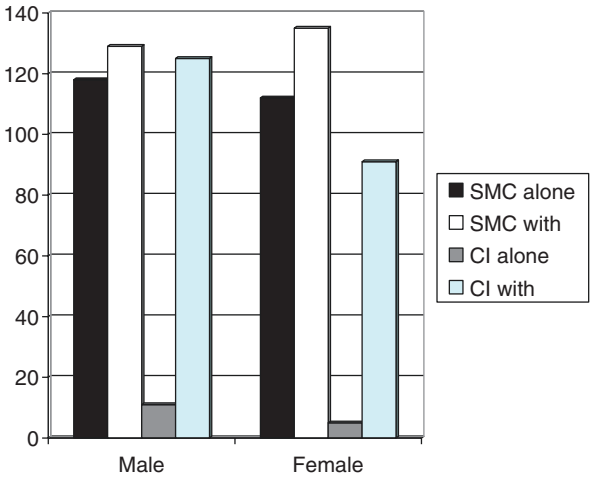

Fig. 3.1 "Attended alone" sign, analysis by patient gender; *SMC* subjective memory complaint, *CI* cognitively impaired (dementia + MCI) (adapted from Abernethy Holland and Larner 2013a)

Most neurological signs are evident in both men and women, but because there may be a behavioural component to the attended alone sign, analysis of the sign according to gender was undertaken (Table 3.4, Fig. 3.1; Abernethy Holland and Larner 2013a). The null hypothesis that the proportion of patients attending alone did not differ significantly by gender was not rejected ($\chi^2 = 0.02$, df = 1, $p > 0.5$). Looking at the diagnostic accuracy data by gender (Table 3.5) there was no obvious difference in the utility of the attended alone sign between the sexes.

Analysis of the attended alone sign by patient age was also performed (Table 3.6, Fig. 3.2), accepting that the age structure of the CFC population is unusual with a bias towards younger individuals (Sect. 1.3.1). The null hypothesis that the proportion of patients attending alone did not differ significantly by patient age was, unsurprisingly, rejected ($\chi^2 = 66.5$, df = 7, $p < 0.001$).

The attended alone sign is an easily observed and categorised clinical sign. As shown in these pragmatic studies of unselected new outpatient clinic cohorts it has good sensitivity for the absence of cognitive impairment. It may therefore be a useful screening observation, indicating in many cases that reassurance rather than intensive further investigation may be appropriate clinical management. Another

Table 3.5 Diagnostic parameters for "attended alone" sign analysed by patient gender (adapted from Abernethy Holland and Larner 2013a)

	Attended alone	
N	726	
F:M (% female)	343:383 (47.2)	
Prevalence of cognitive impairment (dementia + MCI) (= pre-test probability)	0.32	
Pre-test odds = prevalence/(1 − prevalence)	0.47	
	Female (*n* = 343)	**Male (*n* = 383)**
Accuracy	0.59 (0.54–0.64)	0.63 (0.59–0.68)
Net Reclassification Improvement (NRI)	0.27	0.31
Sensitivity (Se)	0.96 (0.92–0.99)	0.91 (0.87–0.96)
Specificity (Sp)	0.40 (0.34–0.47)	0.49 (0.43–0.55)
Y	0.36	0.40
PPV (= post-test probability)	0.45 (0.39–0.52)	0.48 (0.42–0.54)
NPV	0.95 (0.90–0.99)	0.92 (0.87–0.96)
PSI	0.40	0.40
LR+	1.60 (1.43–1.80) = unimportant	1.80 (1.58–2.06) = unimportant
LR−	0.11 (0.09–0.12) = moderate	0.17 (0.15–0.20) = moderate
DOR	15.1 (13.5–16.9)	10.4 (9.11–11.9)
Post-test odds (= pre-test odds × LR+)	0.75	0.85
CUI+	0.43 (poor)	0.47 (poor)
CUI−	0.38 (poor)	0.45 (poor)

Table 3.6 "Attended alone" sign, analysis by patient age; *SMC* subjective memory complaint, *CI* cognitive impairment (= dementia + MCI cases)

Age	N	SMC alone	SMC with	CI alone	CI with
16–20[a]	4	1	2	0	1
21–30	8	2	1	0	5
31–40	32	18	1	2	11
41–50	93	52	10	0	31
51–60	216	88	46	2	80
61–70	207	51	106	3	47
71–80	127	16	82	8	21
80+	39	2	16	1	20
Total	726	230	264	16	216

[a]Lower age limit of adult neurology outpatient clinics is 16 years

study has also reported that patients with functional memory disorders are less likely to be accompanied to the memory clinic than patients with dementia (40% vs 91%; Elsey et al. 2015).

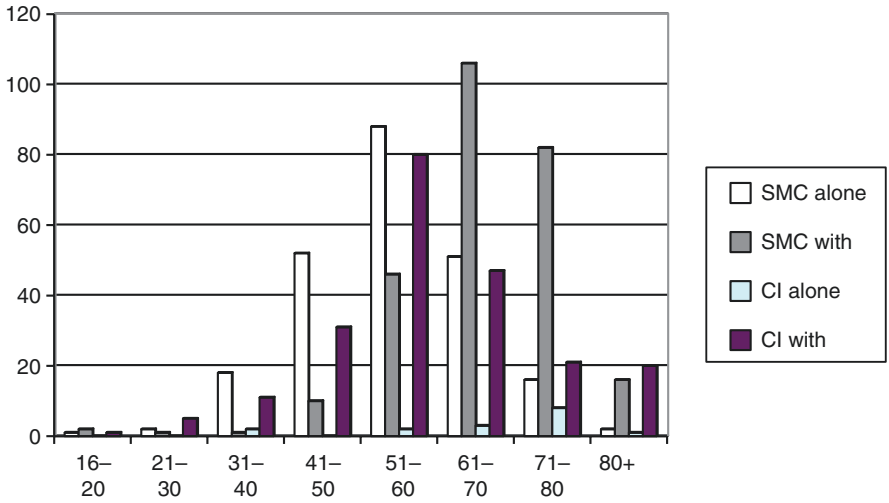

Fig. 3.2 "Attended alone" sign, analysis by patient age; *SMC* subjective memory complaint, *CI* cognitively impaired (dementia + MCI)

3.2.2 Head Turning Sign

Whilst taking the history from a patient with possible cognitive impairment.

> "the physician may observe that the patient exhibits the head turning sign (looking at his care-giver when asked a question), which is a common sign in A[lzheimer's] D[isease]" (Bouchard and Rossor 1996:37).

This phenomenon had probably been noted by earlier physicians, for example as a patient's tendency during case-taking to refer any questions to the person accompanying them (Allison 1962:14, 127). The phenomenon has also been described as a "positive head tilt" (Lipton and Marshall 2013:46), which might perhaps be confused with the head tilt observed in patients with some forms of diplopia or cervical dystonia (Larner 2016b:148). This clinically observed head turning sign is entirely different from the "head turn test" or head tracking test, a computerized measure of complex motor function requiring subjects to follow a moving object by moving their head, previously suggested to be of diagnostic use in Alzheimer's disease (Kluger et al. 1997).

Two prospective observational studies of day-to-day clinical practice have been undertaken to examine the utility of the head turning sign (HTS; Larner 2012c; Ghadiri-Sani and Larner 2013). HTS was operationalised thus: following introductions and initial pleasantries, HTS was adjudged to be present (HTS+) if the patient turned her/his head away from the interlocutor and towards the accompanying person(s) when first invited to describe symptoms (e.g. "Tell me about the problems you are having with your memory") or when specifically asked about them (e.g. "What problems are you having with your memory?" or "Can you give me an

example of how your memory lets you down?"). A verbal request for assistance from the patient to the caregiver was not required. Head turning later in the consultation, for example during administration of cognitive screening instruments, was not deemed HTS+ (cf. the operationalisation used by other authors: Fukui et al. 2011).

Over a 10-month period (January to October 2011), 207 consecutive new referrals were observed for the presence of HTS, of whom 82 (=39.6%) were judged to have cognitive impairment (Larner 2012c). This was a heterogeneous group, including cases of AD and mixed AD/cerebrovascular disease (26), amnestic MCI (28), frontotemporal lobar degenerations (FTLD; 8), dementia with Lewy bodies (DLB; 7), subcortical ischaemic vascular dementia (2), and miscellaneous others (11; see Case Study 7.2).

For the whole cohort, 52 (=25.1%) were HTS+ and 155 (=74.9%) were HTS−.

HTS+ was found to be very specific for the presence of cognitive impairment (0.98) but not very sensitive (0.60), with correspondingly excellent positive predictive value (0.94; Table 3.7, left hand column).

Of the HTS− group, 74 attended the clinic alone. Very few of those who attend memory disorders clinics alone have evidence of cognitive impairment (the

Table 3.7 Demographic and diagnostic parameters for head turning sign (adapted from Larner 2012c)

	HTS	
N	207	
F:M (% female)	109:98 (52.7)	
Age range (years)	18–91 (median 60)	
Prevalence of cognitive impairment (dementia + MCI) (= pre-test probability)	0.40	
Pre-test odds = prevalence/ (1 − prevalence)	0.67	
	Whole cohort (*N* = 207)	**Cohort minus "attended alone" (*n* = 133)**
Accuracy	0.83 (0.77–0.88)	0.76 (0.69–0.83)
Net Reclassification Improvement (NRI)	0.43	0.36
Sensitivity (Se)	0.60 (0.49–0.70)	0.63 (0.52–0.74)
Specificity (Sp)	0.98 (0.95–1.00)	0.95 (0.89–1.00)
Y	0.58	0.58
PPV (= post-test probability)	0.94 (0.88–1.00)	0.94 (0.88–1.00)
NPV	0.79 (0.72–0.85)	0.64 (0.54–0.75)
PSI	0.73	0.58
LR+	24.9 (8.0–77.2) = large	11.5 (3.78–35.1) = large
LR−	0.41 (0.13–1.28) = small	0.39 (0.13–1.20) = small
DOR	60.4 (19.5–187.3)	29.3 (9.62–89.2)
Post-test odds (= pre-test odds × LR+)	16.6	7.7
CUI+	0.56 (adequate)	0.59 (adequate)
CUI−	0.77 (good)	0.61 (adequate)

"attended alone" sign; see Sect. 3.2.1; Larner 2005a, b, 2009b, 2014b), and this was also the case in this cohort (four with MCI, none with dementia). The absence of an accompanying person to whom to turn their head might be deemed to disqualify these individuals from a study of HTS. Eliminating these patients, the diagnostic utility of HTS was recalculated ($n = 133$; Table 3.7, right hand column), again showing the sign to have good specificity (0.95) and positive predictive value (0.94). The null hypothesis that the proportion of HTS+ patients was the same in the cognitively impaired and non-impaired groups was rejected ($\chi^2 = 46.9$, df = 1; $p < 0.001$).

In a further, similar, study over a 10-month period (February to December 2012; Ghadiri-Sani and Larner 2013), 191 consecutive new outpatients were seen; 85 had cognitive impairment (55 with dementia by DSM-IV-TR criteria, 30 with MCI). Considering the whole cohort, HTS+ had sensitivity 0.61 and specificity 0.98 for the diagnosis of cognitive impairment (Table 3.8, left hand column). Considering only those patients who attended with an informant ($n = 113$), HTS+ had sensitivity 0.68 and specificity 0.94 for diagnosis of cognitive impairment, (Table 3.8, right hand column). All figures were comparable with the previous cohort (compare

Table 3.8 Demographic and diagnostic parameters for head turning sign (adapted from Ghadiri-Sani and Larner 2013)

	HTS	
N	191	
F:M (% female)	91:100 (47.6)	
Age range (years)	20–89 (median 60)	
Prevalence of cognitive impairment (dementia + MCI) (= pre-test probability)	0.45 (0.29 + 0.16)	
Pre-test odds = prevalence/(1 − prevalence)	0.82	
	Whole cohort (*N* = 191)	**Cohort minus "attended alone" (*n* = 113)**
Accuracy	0.82 (0.76–0.87)	0.76 (0.68–0.84)
Net Reclassification Improvement (NRI)	0.37	0.31
Sensitivity (Se)	0.61 (0.51–0.72)	0.68 (0.57–0.78)
Specificity (Sp)	0.98 (0.96–1.00)	0.94 (0.87–1.00)
Y	0.59	0.62
PPV (= post-test probability)	0.96 (0.91–1.00)	0.96 (0.91–1.00)
NPV	0.76 (0.69–0.83)	0.58 (0.45–0.70)
PSI	0.72	0.54
LR+	32.4 (8.13–129.3) = large	12.2 (3.13–47.2) = large
LR−	0.40 (0.10–1.58) = small	0.34 (0.09–1.33) = small
DOR	81.9 (20.5–326.7)	35.4 (9.11–137.2)
Post-test odds (= pre-test odds × LR+)	26.5	10.0
CUI+	0.59 (adequate)	0.65 (good)
CUI−	0.74 (good)	0.54 (adequate)

Table 3.9 Head turning sign, analysis by patient gender; cognitive impairment = dementia + MCI cases (adapted from Abernethy Holland and Larner 2013a)

	N	Cognitive impairment (% of N)	HTS+ (% of N)	HTS− (% of N)
Female	123	79 (64.2)	58 (47.2)	65 (52.8)
Male	123	76 (61.8)	48 (39.0)	75 (61.0)
Total	246	155 (63.0)	106 (43.1)	140 (56.9)

Tables 3.7 and 3.8), confirming that the head turning sign is very specific but not very sensitive for the diagnosis of cognitive impairment, with a high positive predictive value.

The relative risk or risk ratio of a patient with neither dementia nor MCI ($n = 113$) demonstrating HTS+ was 0.08 (95% confidence interval [CI] = 0.02–0.32). The null hypothesis that the proportion of HTS+ patients was the same in the cognitively impaired and non-impaired groups was rejected ($\chi^2 = 36.8$, df = 1; $p < 0.001$).

The exact neuropsychological correlates of HTS remain to be defined, although the impression gained from the CFC studies was that it might be a somatic marker of amnesia. Fukui et al. (2011) thought it might be the consequence of an imbalance between memory impairment and relatively preserved executive function, but it is of note that their cohort, unlike the CFC studies, did not include cases of FTLD. Patients with both behavioural and linguistic presentations of FTLD were observed to be HTS+ (Larner 2012c).

As with the attended alone sign (Sect. 3.2.1), there may be a behavioural component to the head turning sign. Analysis of HTS according to gender was undertaken by pooling the data from the two studies described above ($n = 398$, of whom 246, =62%, did not attend alone and hence could be assessed for HTS; Table 3.9; Abernethy Holland and Larner 2013a). In this selected subgroup, the null hypothesis that the proportion of patients with the head turning sign did not differ significantly by gender was not rejected although a trend was observed ($\chi^2 = 3.26$, df = 1, $0.1 > p > 0.05$). Looking at the diagnostic accuracy data by gender (Table 3.10) gave an impression that HTS may be of greater diagnostic utility in female patients.

HTS is an easily observed and categorised clinical sign. As shown in these pragmatic studies of unselected new outpatient clinic cohorts it has good specificity, i.e. is reliably absent in those without cognitive impairment. It may therefore be a useful screening observation, its presence indicating the need for further investigation of cognitive function, just as attending alone suggests that reassurance rather than further investigation is indicated.

The neurobiological correlates of HTS have been investigated, and correlation shown with CSF biomarkers of neurodegeneration (Tabuas-Pereira et al. 2016).

3.2.3 Applause Sign

The applause sign (*signe d'applause*, clapping test, three clap test) is elicited by asking a patient to clap their hands three times as quickly as possible, as

Table 3.10 Diagnostic parameters for head turning sign analysed by patient gender (adapted from Abernethy Holland and Larner 2013a)

	HTS	
N	246	
F:M (% female)	123:123 (50)	
Age range (years)	18–91	
Prevalence of cognitive impairment (dementia + MCI) (= pre-test probability)	0.63	
Pre-test odds = prevalence/(1 − prevalence)	1.70	
	Female (*n* = 123)	**Male (*n* = 123)**
Accuracy	0.81 (0.74–0.88)	0.71 (0.63–0.79)
Net Reclassification Improvement (NRI)	0.18	0.08
Sensitivity (Se)	0.72 (0.62–0.82)	0.58 (0.47–0.69)
Specificity (Sp)	0.98 (0.93–1.00)	0.91 (0.84–0.99)
Y	0.70	0.49
PPV (= post-test probability)	0.98 (0.95–1.00)	0.92 (0.84–0.99)
NPV	0.66 (0.55–0.78)	0.57 (0.46–0.69)
PSI	0.64	0.49
LR+	31.7 (4.55–221.5) = large	6.80 (2.61–17.7) = large
LR−	0.28 (0.04–1.99) = small	0.46 (0.18–1.20) = small
DOR	111.4 (16.0–777.2)	14.8 (5.68–38.5)
Post-test odds (= pre-test odds × LR+)	54.0	11.6
CUI+	0.71 (good)	0.53 (adequate)
CUI−	0.65 (good)	0.52 (adequate)

demonstrated by the examiner (Larner 2016b:32). Clapping more than three times, deemed abnormal, was first demonstrated in progressive supranuclear palsy (PSP) but not in FTLD by Dubois et al. (2005). The applause sign was subsequently reported in other parkinsonian disorders such as Parkinson's disease, DLB, corticobasal degeneration, and multiple system atrophy (e.g. Abdo et al., 2007; Wu et al. 2008; Somme et al. 2013) suggesting that it reflected basal ganglia pathology. An experimental study by Luzzi et al. (2011) looked at the applause sign in cortical dementias, AD and FTLD, as well as in PSP, and found it to be present in all three conditions, with highest sensitivity in PSP (0.80), followed by FTLD (0.60) and AD (0.31), but with poor specificities (respectively 0.59, 0.56, 0.32) and low positive predictive values (respectively 0.31, 0.35, 0.35). It was concluded that the applause sign was a motor perseveration indicative of frontal lobe dysfunction. Isella et al. (2013) reported similar findings, with the sign more likely to be observed in corticobasal syndrome and DLB (prevalence around 40%) than in AD and posterior cortical atrophy (prevalence around 10%). In AD the applause sign may be independent of disease severity (reported prevalence in severe, moderate and mild AD of 0.60, 0.37, and 0.38 respectively) and does not correlate with cognitive functions other than frontal lobe dysfunction (Luzzi et al. 2013).

Two prospective observational studies of day-to-day clinical practice have been undertaken to examine the utility of the applause sign in CFC (Abernethy Holland and Larner 2013b; Bonello and Larner 2016). Patients were asked by the examiner to clap three times, and the number of claps was recorded. The results were categorized and scored according to the method of Luzzi et al. (2011):

- 3 claps = score 3 (normal)
- 4 claps = score 2 (abnormal)
- 5–10 claps = score 1 (abnormal)
- >10 claps = score 0 (abnormal)

Hence, applause sign score ranged from 0 to 3, impaired to normal (i.e. number of claps inversely related to applause sign score).

Of 100 consecutive new outpatients (F:M = 37:63; age range 20–88 years, median 59.5 years) seen over a 5-month period (September 2012 to January 2013), 37 were demented by DSM-IV criteria and 20 had MCI by Petersen criteria. Nineteen had the applause sign, of whom 9 had a dementia syndrome and 6 had MCI. Of patients with a synucleinopathy (PD-MCI, PDD, DLB; $n = 9$), 5 (=55%) had the applause sign, which was also seen in patients with AD, alcoholic dementia, and in 4 subjective memory complainers. Applause sign had poor sensitivity for the diagnosis of dementia (0.24) or cognitive impairment (0.26), but better specificity for these diagnoses (0.84 and 0.91 respectively; Table 3.11). Thus, unlike the situation in experimental studies of selected patient groups, in this pragmatic study of consecutive new outpatients the applause sign was specific (i.e. its absence effectively ruled out dementia or MCI) but not sensitive for a dementia or MCI diagnosis. As in previous studies, the applause sign was not found to be specific to a particular disease (Abernethy Holland and Larner 2013b).

Over a subsequent, non-overlapping, 12-month study period (January 2014 to January 2015), a total of 275 new patients was assessed with the applause sign (Bonello and Larner 2016). Final diagnoses were dementia (52), MCI (71), and subjective memory complaint only (SMC; 152). The null hypothesis that the proportion of patients with cognitive impairment did not differ significantly between applause sign score groups was rejected ($\chi^2 = 27.4$, df = 3, $p < 0.001$).

The results of this study (Table 3.12; Fig. 3.3) were very similar to those observed in the previous study, suggesting that the test is reproducible. The results showed an evident floor effect (211/272 assessable = 77.6% of the whole cohort scored at floor) and hence the applause sign lacks sensitivity (64% of patients with dementia or MCI had a normal applause sign score). Nevertheless, the applause sign was specific ($\geq$0.85) for each of the differentials assessed, meaning that the false positive rate was low in this high prevalence setting. An abnormal applause sign score is therefore supportive of a diagnosis of dementia or cognitive impairment, and may be useful as an indicator of the need for the administration of other screening tests to further investigate cognitive function when pre-test probability for cognitive dysfunction is high.

Table 3.11 Demographic and diagnostic parameters for applause sign (adapted from Abernethy Holland and Larner 2013b)

	Applause sign	
N	100	
F:M (% female)	37:63 (37)	
Age range (years)	20–88 (median 59.5)	
Prevalence of cognitive impairment (dementia + MCI) (= pre-test probability)	0.57 (0.37 + 0.20)	
Pre-test odds = prevalence/(1 − prevalence)	1.33	
	Dementia vs no dementia	**Any cognitive impairment (dementia + MCI) vs no cognitive impairment**
Accuracy	0.62 (0.52–0.72)	0.54 (0.44–0.64)
Net Reclassification Improvement (NRI)	0.25	−0.03
Sensitivity (Se)	0.24 (0.10–0.38)	0.26 (0.15–0.38)
Specificity (Sp)	0.84 (0.75–0.93)	0.91 (0.82–0.99)
Y	0.08	0.17
PPV (= post-test probability)	0.47 (0.25–0.70)	0.79 (0.61–0.97)
NPV	0.65 (0.55–0.76)	0.48 (0.37–0.59)
PSI	0.13	0.27
LR+	1.53 (0.69–3.42) = unimportant	2.82 (1.01–7.92) = small
LR−	0.90 (0.40–2.01) = unimportant	0.81 (0.29–2.27) = unimportant
DOR	1.70 (0.76–3.81)	3.48 (1.24–9.75)
Post-test odds (= pre-test odds × LR+)	2.03	3.74
CUI+	0.12 (very poor)	0.21 (very poor)
CUI−	0.55 (adequate)	0.44 (poor)

3.2.4 *La Maladie Du Petit Papier*

La maladie du petit papier is a name sometimes applied when patients present to consultations with a written list of their symptoms, sometimes extensive, a phenomenon encountered by every neurologist from time to time. However, the diagnostic significance of such notes is uncertain (Grover 2015).

Over a 6-month period (April to September 2015), *la maladie du petit papier* was observed in 17/508 (3.35%) consecutive new patient referrals (16 handwritten examples, 1 ipad). It was seen more often in referrals to cognitive disorders clinics (8/169 = 4.73%) than to general neurology clinics (9/339 = 2.65%) but there was no significant frequency difference ($\chi^2 = 1.07$, $p > 0.1$; Randall and Larner 2016).

Table 3.12 Demographic and diagnostic parameters for applause sign (adapted from Bonello and Larner 2016)

	Applause sign	
N	275 (272 assessable)	
F:M (% female)	138:137 (50.2)	
Age range (years)	18–91 (median 61)	
Prevalence of cognitive impairment (dementia + MCI) (= pre-test probability)	0.45 (0.19 + 0.26)	
Pre-test odds = prevalence/ (1 − prevalence)	0.81	
	Dementia vs no dementia	**Any cognitive impairment (dementia + MCI) vs no cognitive impairment**
Accuracy	0.79 (0.74–0.84)	0.65 (0.59–0.71)
Net Reclassification Improvement (NRI)	0.60	0.20
Sensitivity (Se)	0.54 (0.40–0.67)	0.36 (0.28–0.45)
Specificity (Sp)	0.85 (0.70–0.99)	0.89 (0.84–0.94)
Y	0.39	0.25
PPV (= post-test probability)	0.46 (0.33–0.58)	0.72 (0.61–0.83)
NPV	0.89 (0.84–0.93)	0.63 (0.57–0.70)
PSI	0.35	0.35
LR+	3.59 (2.40–5.37) = small	3.18 (1.92–5.28) = small
LR−	0.54 (0.36–0.81) = unimportant	0.72 (0.43–1.20) = unimportant
DOR	6.61 (4.42–9.89)	4.41 (2.66–7.32)
Post-test odds (= pre-test odds × LR+)	2.91	2.58
CUI+	0.25 (very poor)	0.26 (very poor)
CUI−	0.75 (good)	0.59 (adequate)

Final diagnoses in the cognitive clinic were functional cognitive disorder (6) and MCI (2), the latter secondary to either alcohol misuse or mild traumatic brain injury; none had dementia. *La maladie du petit papier* had high specificity (0.94) but low sensitivity (0.03), and hence very low false positive rate (0.06), for a diagnosis of cognitive impairment (Randall and Larner 2018).

La maladie du petit papier is a low frequency sign in both cognitive disorders and general neurology clinics. In cognitive clinics it was associated with subjective memory complaint; like the "attended alone" sign, its presence may therefore support a diagnosis of cognitive normality. It may assist in a positive diagnosis of functional cognitive disorder (Randall and Larner 2018).

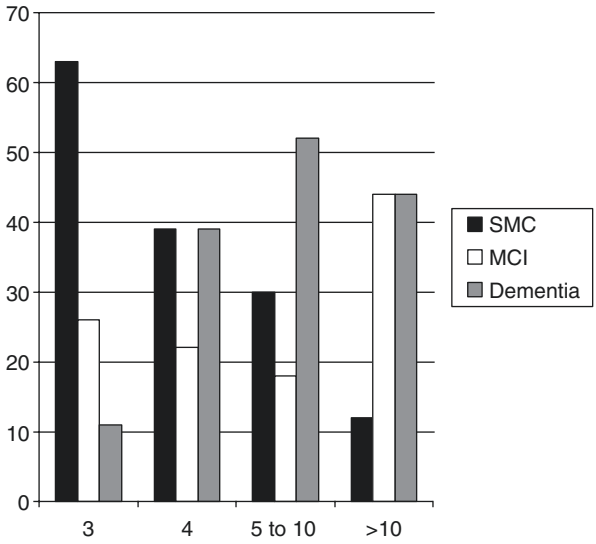

Fig. 3.3 Applause sign claps (abscissa) versus percentage of patients categorised by diagnosis (dementia/MCI/subjective memory complaint) (adapted from Bonello and Larner 2016) reprinted with permission

3.3 Summary and Recommendations

History taking is the cornerstone of any assessment for suspected dementia or cognitive impairment. It should encompass the history of the presenting complaint, past medical history, functional abilities, and family history. The importance of collateral history cannot be overemphasized. In certain circumstances, the history alone may be adequate for making a provisional diagnosis. If not diagnostic, it will guide the selection and contextualise the findings of subsequent neurological examination and investigations. Single item cognitive screening questions may have utility, but definitive evidence is awaited.

Although no signs are pathognomonic of dementia or cognitive impairment, nonetheless a number of neurological signs may be of use in assessment. In addition to signs elicited in the traditional, standard, textbook, canonical neurological examination, several other signs, which may be conveniently designated as "non-canonical" (Larner 2014a), may be of diagnostic value. In pragmatic diagnostic test accuracy studies the "attended alone" sign has been found to be very sensitive for absence of cognitive impairment; *la maladie du petit papier* may also support a diagnosis of cognitive normality. The head turning sign and the applause sign are both very specific (i.e. absent in the cognitively healthy). The head turning sign may be more useful in female patients. All these signs have the potential advantage of being easily observed and categorised, that is they all produce categorical data, which with the exception of the applause sign score, is dichotomous. The attended alone sign and the head turning sign have been noted to be of possible value in the differential diagnosis of functional cognitive disorders (Griem et al. 2016), and an independent study has claimed that "attended with" and head turning sign are simple, effective and sensitive (sic) methods of detecting cognitive impairment (Soysal et al. 2017; see also Williamson and Larner 2018).

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Assessment with Cognitive Screening Instruments

4

Contents

Abstract

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

Keywords

Dementia · Diagnosis · Cognitive screening instruments

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

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

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

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

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

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

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

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

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

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

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

4.1 Multidomain Cognitive Screening Instruments

4.1.1 Mini-Mental State Examination (MMSE)

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

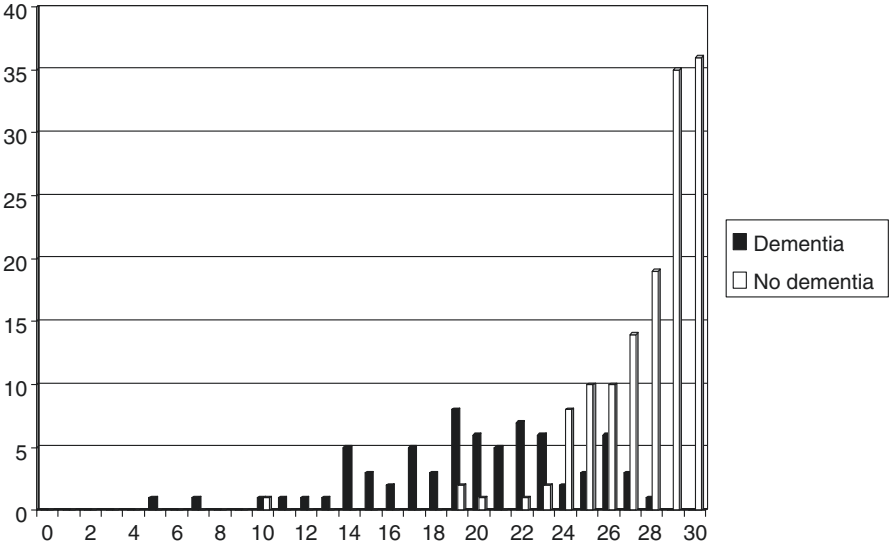

Fig. 4.1 MMSE scores vs. diagnosis (dementia/no dementia) in TYM study (adapted from Hancock and Larner 2011) reprinted with permission

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

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

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

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

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

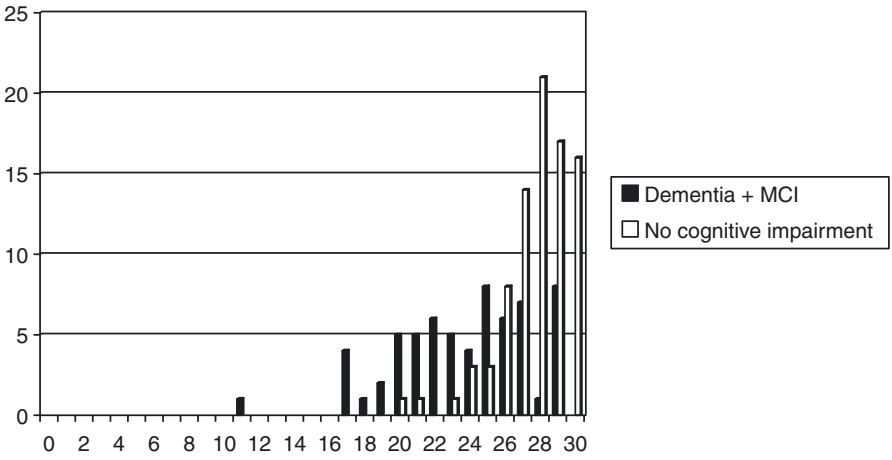

Fig. 4.2 MMSE scores vs. diagnosis (any cognitive impairment/no cognitive impairment) in MoCA study (adapted from Larner 2012a) reprinted with permission

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

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

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

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

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

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

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

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

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

4.1.1.1 MMSE Ala Subscore

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

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

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

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

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

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

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

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

4.1.2 Mini-Mental Parkinson (MMP)

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

4.1.3 Clock Drawing Test (CDT)

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

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

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

4.1.3.1 Backward Clock Test

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

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

4.1.4 Cognitive Disorders Examination (Codex)

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

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

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

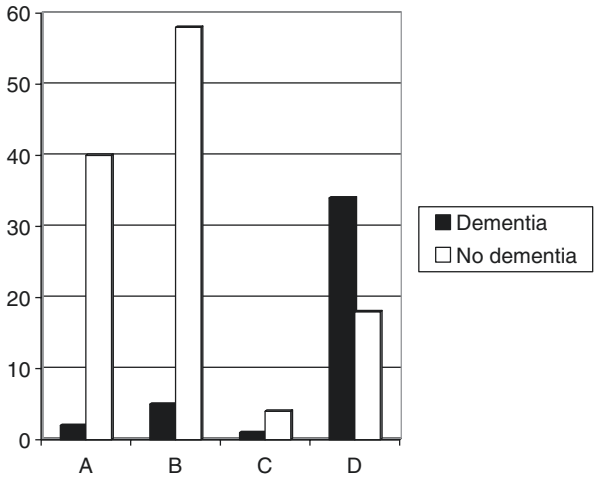

Fig. 4.3 Codex category vs. diagnosis (dementia/no dementia) (adapted from Ziso and Larner 2013) reprinted with permission

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

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

4.1.5 Addenbrooke's Cognitive Examinations

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

4.1.5.1 Addenbrooke's Cognitive Examination (ACE)

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

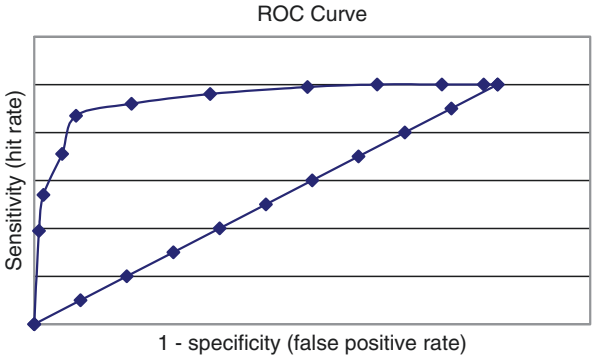

Fig. 4.4 ROC curve for ACE-R (adapted from Larner 2009a) reprinted with permission

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

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

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

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

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

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

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

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

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

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

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

4.1.5.4 ACE-III

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

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

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

4.1.5.5 Mini-Addenbrooke's Cognitive Examination (MACE)

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

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

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

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

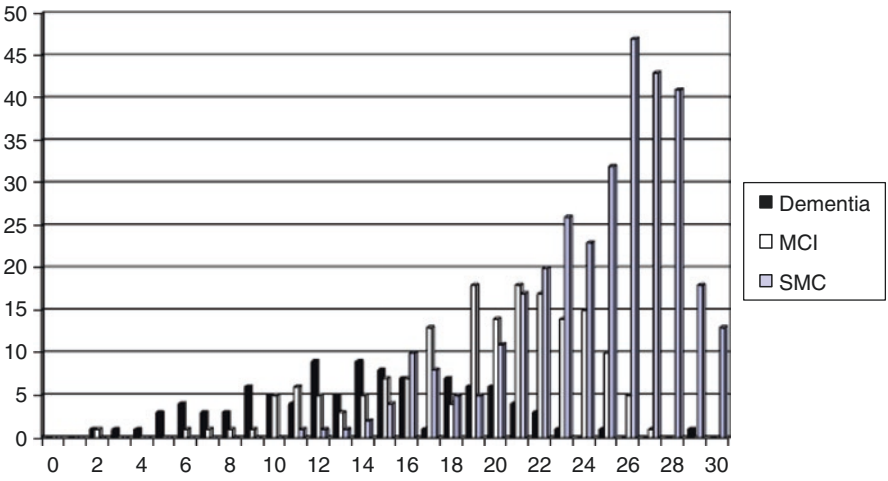

Fig. 4.5 MACE scores vs. patient diagnosis (Williamson and Larner 2018) reprinted with permission

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

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

4.1.6 Six-Item Cognitive Impairment Test (6CIT)

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

Case Study 4.2 (continued)

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

4.1.7 DemTect

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

Box 4.8 Item Content of DemTect

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

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

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

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

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

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

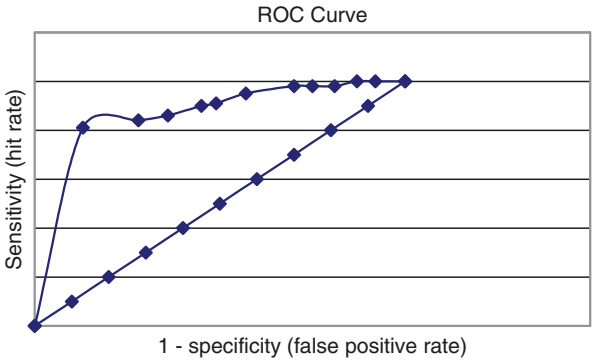

Fig. 4.6 ROC curve for DemTect (Larner 2007e) reprinted with permission

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

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

4.1.8 Montreal Cognitive Assessment (MoCA)

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

Box 4.9 Item Content of MoCA and s-MoCA

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

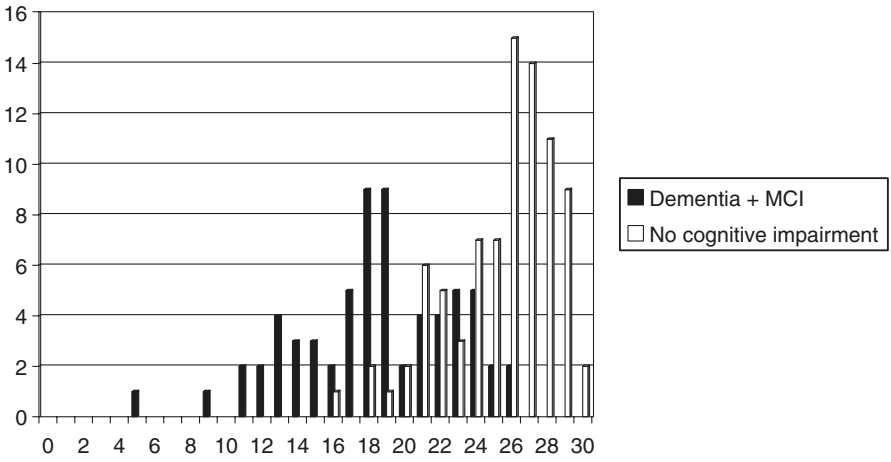

Fig. 4.7 MoCA scores vs diagnosis (cognitive impairment/no cognitive impairment) (Larner 2012a) reprinted with permission

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

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

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

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

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

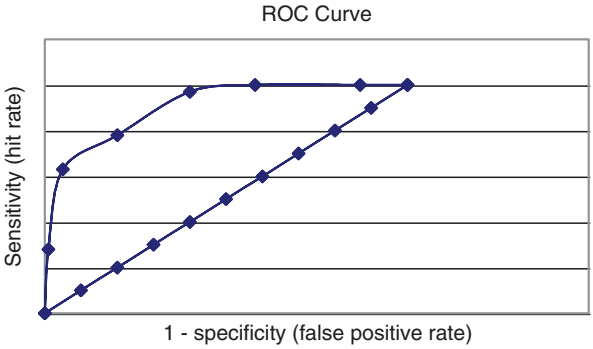

Fig. 4.8 ROC curve for MoCA (Larner 2012a) reprinted with permission

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

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

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

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

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

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

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

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

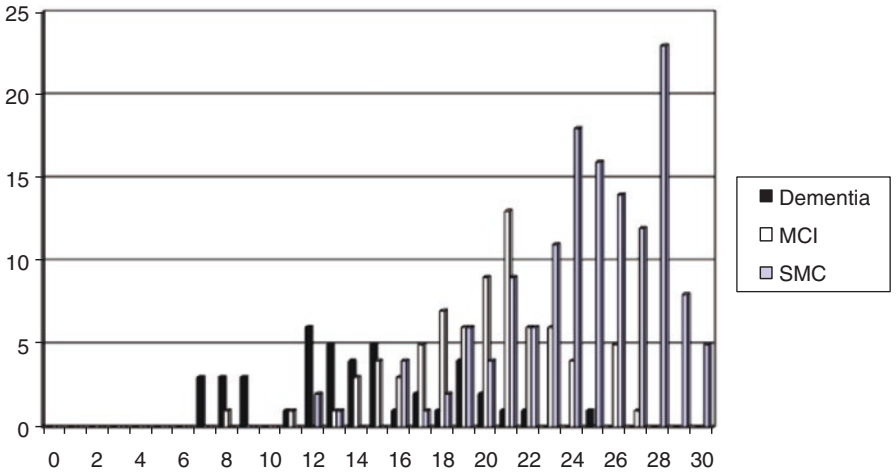

Fig. 4.9 MoCA scores vs diagnosis (dementia/MCI/SMC) (adapted from Larner 2017d) reprinted with permission

4.1.8.1 MoCA Subscores: MoCA Ala and MoCA VLOM Ratio

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

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

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

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

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

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

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

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

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

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

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

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

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

4.1.8.2 Short MoCA (s-MoCA)

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

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

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

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

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

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

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

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

4.1.9 Test Your Memory (TYM) Test

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

Box 4.10 Item Content of TYM

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

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

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

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

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

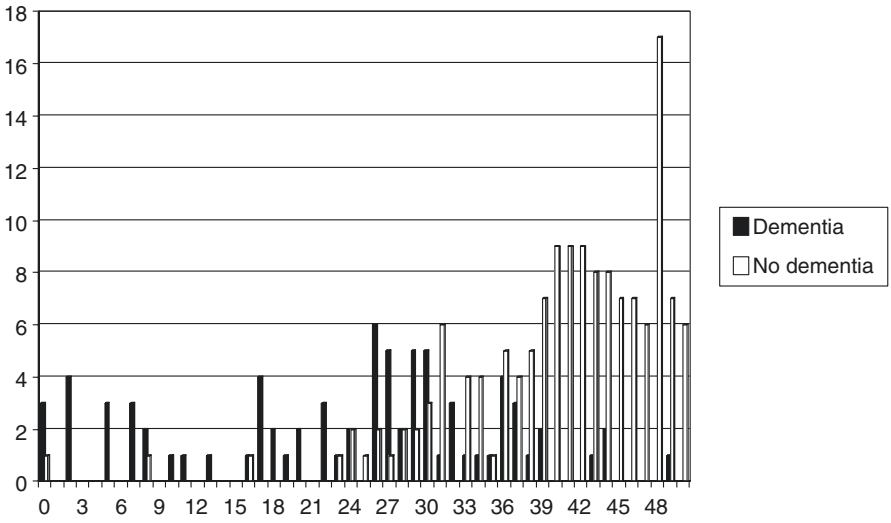

Fig. 4.10 TYM scores vs. diagnosis (dementia/no dementia) (Hancock and Larner 2011) reprinted with permission

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

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

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

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

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

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

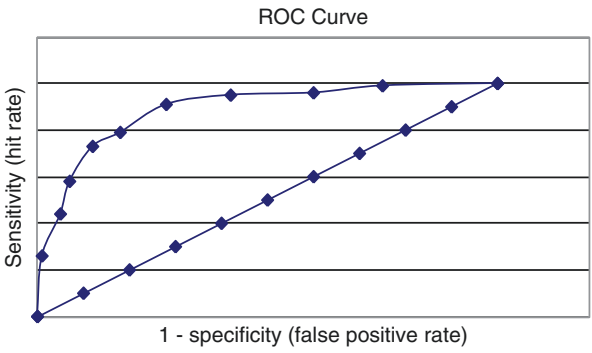

Fig. 4.11 TYM ROC curve (Hancock and Larner 2011) reprinted with permission

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

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

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

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

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

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

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

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

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

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

4.1.10 Free-Cog

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

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

4.1.11 Other Cognitive Screening Instruments: RBANS, MEAMS

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

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

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

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

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

4.2 Single Domain Cognitive Screening Instruments

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

4.2.1 Frontal Assessment Battery (FAB)

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

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

Box 4.11 Item Content of FAB

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

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

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

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

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

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

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

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

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

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

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

4.2.2 FRONTIER Executive Screen (FES)

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

Box 4.12 Item content of FRONTIER Executive Screen (FES)

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

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

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

4.2.3 Poppelreuter Figure

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

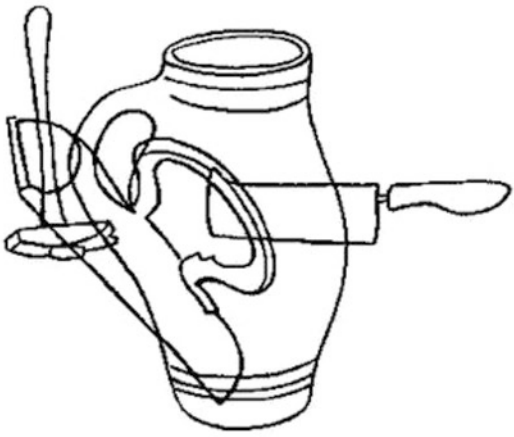

Fig. 4.12 Poppelreuter overlapping figure (Sells and Larner 2011) reprinted with permission

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

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

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

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

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

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

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

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

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

4.3 Summary and Recommendations

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

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

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Assessment with Non-Cognitive Screening Instruments

5

Contents

Abstract

This chapter examines the diagnostic utility of various screening instruments examining functional, behavioural and psychiatric, neurovegetative, and informant scales, collectively termed (for want of a better nomenclature) non-cognitive screening instruments, in the diagnosis of cognitive disorders. These supplement the cognitive screening instruments discussed in the previous chapter.

Keywords

Dementia · Diagnosis · Non-cognitive screening instruments

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The dementia syndrome may comprise more than simply cognitive decline (American Psychiatric Association 2000). Hence there may be a need to examine functional, behavioural, and neurovegetative domains as well as cognition in patients suspected to have a dementing disorder. This is consistent with a biopsychosocial model of disease (Engel 1977), and the willingness to explore these domains contradicts assertions that neurologists subscribe to a purely medical model of dementia. Furthermore, dementia has important differential diagnoses with affective disorders (especially anxiety and depression; see Sect. 5.2) and with delirium (Larner 2004). These differentials are not necessarily straightforward since the conditions may coexist, for example delirium is sometimes the presenting feature of an underlying neurodegenerative disorder (e.g. Rockwood et al. 1999), and depression is sometimes a precursor of dementia.

As mentioned previously (Chap. 4), it is the history and examination (Chap. 3) which set the context for the use of screening instruments examining both cognitive and non-cognitive domains and in light of which the results of the latter should be interpreted. The same methodology as used for assessment of the utility of neurological signs and cognitive screening instruments (see Chaps. 2, 3 and 4) may be applied to scales examining non-cognitive domains. All the studies reported here predate the publication of DSM-5 in 2013 and hence DSM-IV dementia diagnostic criteria are used where applicable throughout.

5.1 Functional Scales

The *Diagnostic and Statistical Manual of Mental Disorders* (DSM-IV) defined dementia as "the development of multiple cognitive deficits that include memory impairment (criterion A1) … sufficiently severe to cause impairment in occupational or social functioning (criterion B)" (American Psychiatric Association 2000:148, 149, 157). Hence, impairments in activities of daily living (ADLs) would appear, according to this definition, to be a *sine qua non* for the diagnosis of dementia. However, instruments used to assess social and occupational functions (the specific examples given in DSM-IV are going to school, working, shopping, dressing, bathing, handling finances) have seldom been used for diagnostic purposes, although they may often be used to plan appropriate care interventions for people with dementia.

Pfeffer et al. (1982) used the Functional Activities Questionnaire (FAQ) in the diagnosis of dementia in a "stable retirement community" in California, finding a sensitivity of 0.85 and specificity of 0.81 (hence, retrospectively calculated LR+ = 4.47; LR− = 0.19; Hancock and Larner 2007). They also administered Lawton and Brody's (1969) Instrumental Activities of Daily Living (IADL) Scale and reported a sensitivity of 0.57 and specificity of 0.92 (retrospectively calculated LR+ = 7.13; LR− = 0.46; no cut-off explicitly stated in the text; Hancock and Larner 2007). The paucity of studies examining ADL scales for diagnosis of dementia may be related to shortcomings in the extant scales (Sikkes et al. 2009); newer scales such as the Amsterdam IADL Questionnaire may obviate some of these problems (Sikkes et al. 2013).

5.1.1 Instrumental Activities of Daily Living (IADL) Scale

The Instrumental Activities of Daily Living (IADL) Scale assesses six basic ADLs (also known as the Physical Self-Maintenance Scale) and eight instrumental ADLs (Box 5.1) in a hierarchical manner according to degree of autonomy (Lawton and Brody 1969). It has been reported to have good reliability and validity (Hokoishi et al. 2001).

The diagnostic utility of the IADL Scale in the diagnosis of dementia in day-to-day clinical practice has been assessed prospectively in new referrals to the Cognitive Function Clinic (CFC) at the Walton Centre for Neurology and Neurosurgery (WCNN) in Liverpool and to the Brooker Centre, Runcorn (an old age psychiatry clinic), over a 2-year period (February 2004–February 2006) (Hancock and Larner 2007; Larner and Hancock 2008a). Scoring of each ADL domain was by forced choice, either 0 (dependent) or 1 (independent), giving a score range of 0–14 (higher better).

A total of 296 patients were assessed of whom 154 were judged to be demented. The most common cause of dementia was Alzheimer's disease (AD) or mixed AD/cerebrovascular disease (n = 122; 79%), with smaller numbers due to vascular dementia (13), frontotemporal lobar degeneration syndromes (FTLD; 11), and miscellaneous other causes (8). The IADL Scale proved easy to use, being completed in all cases, usually in under 5 min, often with the assistance of an informant

Box 5.1: Item Content of Instrumental Activities of Daily Living (IADL) Scale

Instrumental ADL:

Ability to use telephone
Shopping
Food preparation
Housekeeping
Laundry
Mode of transportation
Responsibility for own medications
Ability to handle finances

Basic ADL (Physical Self-Maintenance Scale):

Toileting
Feeding
Dressing
Grooming
Physical ambulation
Bathing

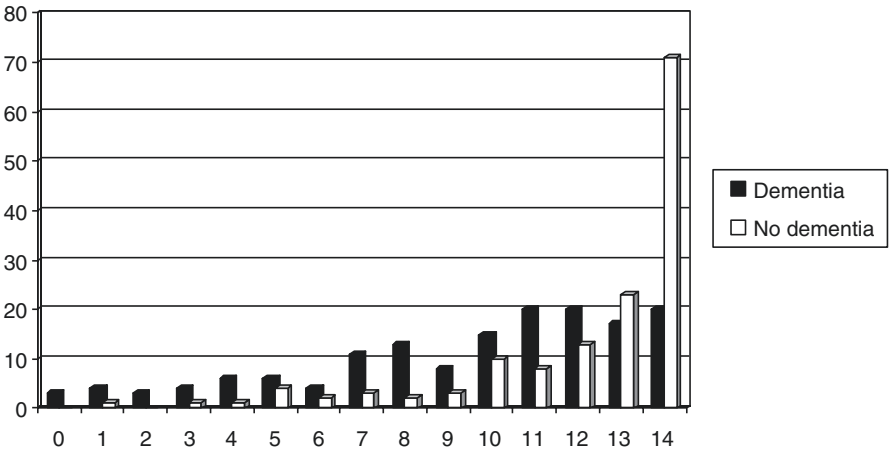

Fig. 5.1 Distribution of IADL Scale scores vs. diagnosis (Hancock and Larner 2007) reprinted with permission

($n = 233$), including spouse (130), other relative (84)—most often a child (60/84)—carer (10) or friend (9). The distribution of IADL scores is shown in Fig. 5.1.

Diagnostic utility of IADL proved suboptimal (Table 5.1) with only sensitivity achieving a value of >0.8. The relative risk or risk ratio for impaired ADL, defined by IADL scale cut-off score of ≤13/14, in non-demented compared to demented individuals was 0.57 (95% CI = 0.48–0.68).

Subscores of the IADL Scale were also examined, namely the instrumental activities part only (score range 0–8), and the 4-IADL scale as defined by Barberger-Gateau et al. (1992), namely ability to use telephone, use public/private transport, handle own medications, and handle finances (score range 0–4). Neither of these subscores produced better results in terms of diagnostic utility (see Fig. 5.2 for 4-IADL scale scores) (Hancock and Larner 2007).

The modest results for diagnostic utility of the IADL Scale might be accounted for in part by the fact that most patients in this population achieved high IADL Scale scores (Fig. 5.1) although this was no guarantee of the absence of dementia. It is well attested that such a ceiling effect is best avoided in diagnostic scales. Whether objective assessments accurately record changes in everyday life competence has been noted to relate mainly to the sensitivity of IADL instruments (Nygård 2003). Other investigators have also reported the absence of functional decline, as measured using the IADL Scale, in AD patients (Park et al. 2007). Combining IADL Scale scores with a cognitive measure (ACE-R) has also been examined (see Sect. 6.2.3; Larner and Hancock 2012).

It has been reported that use of the Disability Assessment for Dementia (DAD) scale (Gelinas et al. 1999) may be useful for differentiating FTLD from AD, since the former, especially behavioural variant frontotemporal dementia, has significant

Table 5.1 Demographic and diagnostic parameters for IADL Scale (adapted from Hancock and Larner 2007)

	IADL
N	296
F:M (% female)	151:145 (51)
Age range (years)	23–90 (median 64)
Prevalence of dementia (= pre-test probability)	0.52
Pre-test odds	1.08
Cut-off	**≤13/14**
Accuracy	0.69 (0.64–0.75)
Net reclassification improvement (NRI)	0.17
Sensitivity (Se)	0.87 (0.82–0.92)
Specificity (Sp)	0.50 (0.42–0.58)
Y	0.37
PPV (= post-test probability)	0.65 (0.59–0.72)
NPV	0.78 (0.70–0.87)
PSI	0.43
LR+	1.74 (1.46–2.07) = unimportant
LR−	0.26 (0.22–0.30) = small
DOR	6.70 (5.62–7.98)
Post-test odds (= pre-test odds × LR+)	1.77
CUI+	0.57 (adequate)
CUI−	0.39 (poor)
AUC ROC curve	0.75 (0.72–0.78)

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

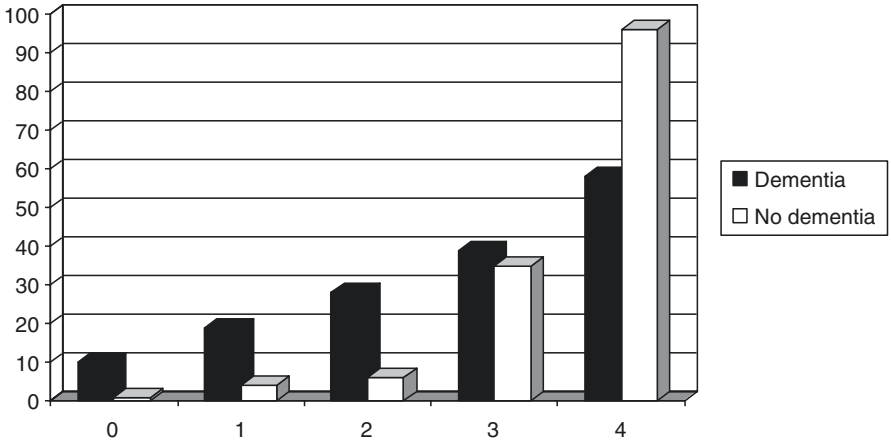

Fig. 5.2 Distribution of 4-IADL Scale scores vs. diagnosis (Hancock and Larner 2007) reprinted with permission

impact on activities of daily living (Mioshi et al. 2007). Analysing the data from the IADL study (Larner and Hancock 2008a), mean IADL Scale score for AD patients (n = 122) was 9.7 ± 3.4 and for FTLD patients (n = 11) was 10.5 ± 4.4. The null hypothesis that scores were not different between the two groups was not rejected ($t = 0.65$, $p > 0.5$). Likewise, using the 4-IADL score the mean scores (AD 2.8 ± 1.2; FTLD 3.0 ± 1.3) were not significantly different ($t = 0.47$, $p > 0.5$).

5.2 Behavioural and Psychiatric Scales

The International Psychiatric Association introduced the term "Behavioural and Psychological Symptoms of Dementia" (BPSD) in 1996 (Finkel et al. 1996) to encompass the wide range of such symptoms encountered in patients with dementia. BPSD, as well as cognitive deficits, form part of the definition of the dementia phenotype (American Psychiatric Association 2000; Ballard et al. 2001; Savva et al. 2009). Hence assessment of BPSD may be deemed desirable in the diagnosis and assessment of suspected dementia. Furthermore, the most common differential diagnosis of dementia in patients referred to memory clinics is affective disorder, particularly depression (Roose and Devanand 1999; Berrios and Hodges 2000).

Differentiating between dementia and depression as causes of memory impairment can be difficult on clinical grounds alone. Test instruments which might help with this differential diagnosis, and hence guide treatment options (e.g. cholinesterase inhibitor vs. antidepressant), would therefore be welcome.

Studies have been undertaken in CFC to examine whether use of questionnaires assessing depression, either specifically (Patient Health Questionnaire-9, Cornell Scale for Depression in Dementia) or along with other symptoms (Cambridge Behavioural Inventory) might be helpful in diagnosis and assessment of patients with cognitive complaints. A two question screener for depression (Arroll et al. 2003) is being used in an ongoing study of functional cognitive disorders (Bharambe and Larner, in preparation).

5.2.1 Cambridge Behavioural Inventory (CBI)

The Cambridge Behavioural Inventory (CBI) is a short, self-administered, informant questionnaire developed from an analysis of the behavioural and neuropsychiatric features which distinguish AD from FTLD (Bozeat et al. 2000). CBI is an 81 item, 13 subsection, questionnaire (Box 5.2) in which informants are asked to score various behavioural and psychiatric symptoms subjectively according to a frequency-based intensity scale (for most symptoms minimum = 0, not present; maximum = 4, constantly present; hence possible range of global CBI score = 0–324).

CBI has been shown to have adequate test-retest reliability and convergent validity with the Neuropsychiatric Inventory (NPI; Cummings et al. 1994) in an independent cohort (Nagahama et al. 2006). It has been used qualitatively in drug trials (Deakin et al. 2004). CBI may have clinical utility in differentiating different neurodegenerative disorders (Wedderburn et al. 2008). A revised version of the CBI,

Box 5.2: Item content of CBI

Memory	6 items
Orientation and attention	7 items
Everyday skills	8 items
Self care	7 items
Mood	9 items
Beliefs	7 items
Challenging behaviour	4 items
Disinhibition	5 items
Eating habits	5 items
Sleep	2 items
Stereotypic and motor behaviours	11 items
Motivation	8 items
Insight/awareness	2 items
Total score	**81 items**

CBI-R, has also been published (Wear et al. 2008; available at http://www.ftdrg.org/wp-content/uploads/cbi_caregiver.pdf).

The diagnostic utility of CBI has been assessed prospectively in new referrals to CFC and to the Brooker Centre, Runcorn, over an 18-month period (January 2006–June 2007) (Hancock and Larner 2008; Larner 2008a; Larner and Hancock 2008b). The data were originally presented as a validity study in CFC ($n = 75$), to determine a cut-off score for diagnostic accuracy, then as a reproducibility study in the Brooker Centre cohort ($n = 84$) using the same cut-off (Hancock and Larner 2008; for details of validity/reproducibility in diagnostic testing, see Sect. 2.3.1). Here, data are presented for the complete cohort ($n = 159$), as in the previous editions of this book (Larner 2012a:73–7; 2014a:160–4).

Dementia prevalence was higher in this cohort than in other cohort studies reported from these clinics (Table 5.2). This was because patients without dementia sometimes attend the clinic without an informant despite receiving written instructions to do so in their appointment letter ("attended alone" sign; see Sect. 3.2.1; Larner 2005a, b, 2009, 2014b); these individuals were by definition not represented in this cohort.

The results (Table 5.2) showed only modest diagnostic utility for the CBI, none of the parameters reaching satisfactory levels. For the differential diagnosis of AD and FTLD, the difference between the CBI global scores for patients with AD ($n = 79$, range 20–239, mean 93.6 ± 53.1) and FTD ($n = 11$, range 19–216, mean 101.2 ± 56.3) did not reach statistical significance ($t = 0.44$, $p > 0.5$) (Larner and Hancock 2008b).

Based on the CBI symptoms shown (by Bozeat et al. 2000) to be most suggestive of AD (memory, orientation and attention, everyday skills; item subtotal = 21, possible CBI subscore range = 0–84) and of FTLD (disinhibition, eating habits, stereotypic and motor behaviours; item subtotal = 21, possible CBI subscore

Table 5.2 Demographic and diagnostic parameters for CBI (adapted from Hancock and Larner 2008)

	CBI
N	159
F:M (% female)	73:86 (46)
Age range (years)	37–97
Prevalence of dementia (= pre-test probability)	0.63
Pre-test odds	1.70
Cut-off	**>80/324**
Accuracy	0.62 (0.54–0.69)
Net reclassification improvement (NRI)	−0.01
Sensitivity (Se)	0.54 (0.44–0.64)
Specificity (Sp)	0.75 (0.63–0.86)
Y	0.29
PPV (= post-test probability)	0.78 (0.69–0.88)
NPV	0.49 (0.39–0.59)
PSI	0.27
LR+	2.12 (1.32–3.41) = small
LR−	0.62 (0.38–0.99) = unimportant
DOR	3.44 (2.15–5.53)
Post-test odds (= pre-test odds × LR+)	3.61
CUI+	0.42 (poor)
CUI−	0.37 (poor)

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

range = 0–84), a CBI ratio subscore (AD:FTLD) was devised (Larner 2008a). The formulation of this ratio was based on the principles used to derive the VLOM ratio subscore from the Addenbrooke's Cognitive Examination (ACE), which is reported to differentiate AD and FTLD based on cognitive features (Mathuranath et al. 2000; see Sect. 4.1.5.2). A similar ratio may also be derived from the Montreal Cognitive Assessment (MoCA VLOM ratio; Rawle and Larner 2014; Sect. 4.1.8.1). The CBI ratio subscore in the patients recruited from CFC ($n = 75$) was found to have a maximal diagnostic accuracy (0.85) using a cut-off score of 1 (where <1 = FTLD, ≥1 = AD). Sensitivity and positive predictive value at this cut-off were high, but confidence intervals were large because patient numbers were small (Table 5.3).

CBI has also proved useful in documenting behavioural symptoms in individual cases (Larner 2008b, 2013; Case Study 5.1).

On the basis of these results, CBI global score cannot be recommended as a quantitative bedside test for the diagnosis of dementia in preference to cognitive tests, since its diagnostic utility proved to be only modest with cross-sectional use. However, CBI retains a place in the qualitative evaluation of patient symptoms which may guide appropriate patient management (e.g. as found in individual patients: Larner et al. 2007; Case Study 5.1). The overall benefit of CBI may be in providing a structured behavioural symptom profile rather than a summated behavioural score (Wedderburn et al. 2008).

Table 5.3 Demographic and diagnostic parameters for CBI ratio subscore for differential diagnosis of Alzheimer's disease and frontotemporal dementia (adapted from Larner 2008a)

	CBI ratio subscore
N	75
F:M (% female)	36:39 (48)
Age range (years)	39–85
Prevalence of dementia (= pre-test probability)	0.64
Pre-test odds	1.78
Cut-off	**<1**
Accuracy	0.85 (0.74–0.95)
Net reclassification improvement (NRI)	0.21
Sensitivity (Se)	0.95 (0.87–1.00)
Specificity (Sp)	0.44 (0.12–0.77)
Y	0.39
PPV (= post-test probability)	0.88 (0.77–0.98)
NPV	0.67 (0.29–1.00)
PSI	0.55
LR+	1.70 (0.94–3.07) = unimportant
LR−	0.12 (0.07–0.22) = moderate
DOR	14.0 (7.77–25.2)
Post-test odds (= pre-test odds × LR+)	3.02
CUI+	0.84 (excellent)
CUI−	0.29 (very poor)

Case Study 5.1: Clinical utility of behavioural screening instrument in diagnosis of dementia: CBI

Change in personality and decline in activities of daily living developed progressively in a professional woman in her early 40s. There was no past history of medical or psychiatric illness. An empirical trial of antidepressant medications produced no clinical response. The CBI, completed by the patient's husband, showed evidence for impaired self-care (difficulty self-grooming), mood change (rapid shifts in emotions), change in dietary habits (eating the same food repeatedly), disinhibition (acting impulsively) and stereotyped and motor behaviours (following routines, hoarding, echolalia). These features were suggestive of a diagnosis of behavioural variant frontotemporal dementia. Subsequent neuroimaging studies showed structural and functional changes consistent with this diagnosis (CT and MRI: marked bilateral frontal brain atrophy; SPECT: bilateral frontal hypoperfusion). Neurogenetic testing showed the hexanucleotide repeat expansion in the C9orf72 gene.

5.2.2 Patient Health Questionnaire-9 (PHQ-9)

The Patient Health Questionnaire-9 (PHQ-9) is a validated instrument for measurement of the severity of depression (Kroenke et al. 2001). It is a nine symptom depression checklist, with each symptom graded by frequency (score range 0–3)

Box 5.3: Item content of PHQ-9
Little interest or pleasure in doing things
Feeling down, depressed or hopeless
Trouble falling or staying asleep or else sleeping too much
Feeling tired or having little energy
Poor appetite or overeating
Feeling bad about self, a failure, have let self or family down
Trouble concentrating (reading, TV)
Moving or speaking so slowly that others have noticed; or fidgety, restless
Thought you would be better off dead, or of hurting yourself

over the preceding 2 weeks (Box 5.3). PHQ-9 scores range from 0 to 27, with 0–4 adjudged to indicate no depression, 5–9 mild depression, 10–14 moderate depression, and ≥15 severe depression (i.e. higher score = worse depression).

PHQ-9 has proved useful in the recognition of depression in the general population (Martin et al. 2006), in primary care (Gilbody et al. 2007a), and in medical settings (Gilbody et al. 2007b). PHQ-9 may also be sensitive to change over time and following treatment with antidepressants (Löwe et al. 2004, 2006). In the UK general practitioner (GP) Quality and Outcome Framework (British Medical Association 2006), PHQ-9 was one of the recommended measures of depression severity. Its reported use has been encountered in referrals to CFC from primary care (Menon and Larner 2011; Ghadiri-Sani and Larner 2014).

The diagnostic utility of PHQ-9 has been assessed prospectively in new referrals to CFC and to the Brooker Centre, Runcorn, over a 10-month period (June 2007–March 2008) (Hancock and Larner 2009a). PHQ-9 proved easy to use, being completed in all cases, although some patients required the assistance of a relative, friend, or other carer. PHQ-9 scores ranged from 0 to 25 (Fig. 5.3). For the demented group, the mode, median, and mean PHQ-9 scores were 0, 2, and 4.1 ± 5.4, respectively; for the non-demented group the mode, median, and mean scores were 0, 3.5, and 7.8 ± 7.9. The mean PHQ-9 scores differed significantly between the two groups ($t = 2.80$, df = 111, $p < 0.01$).

Diagnostic utility of PHQ-9 at the optimal accuracy (cut-off >9/27; Table 5.4) was modest. Performance compared unfavourably with a meta-analysis of PHQ-9 for a DSM-IV diagnosis of major depressive disorder (sensitivity 0.80, specificity 0.92, LR+ 10.12, LR− 0.22; Gilbody et al. 2007b).

The PHQ-9 cut-off of >9/27 coincided with the defined test threshold between mild and moderate depression (Kroenke et al. 2001). Dependent on clinical context, this cut-off might be taken as an indicator of the need or otherwise to prescribe antidepressant medication. Using this pragmatic threshold, the null hypothesis that the proportion of patients with at least moderate depression did not differ significantly between patients diagnosed with dementia (6/49 = 12%) and without dementia (26/64 = 41%) was examined, and rejected ($\chi^2 = 11.3$, df = 1, $p < 0.01$). Hence the relative risk or risk ratio for moderate depression, defined by a PHQ-9 cut-off score of >9/27, in non-demented compared to demented individuals was 3.32 (95% CI = 1.48–7.43).

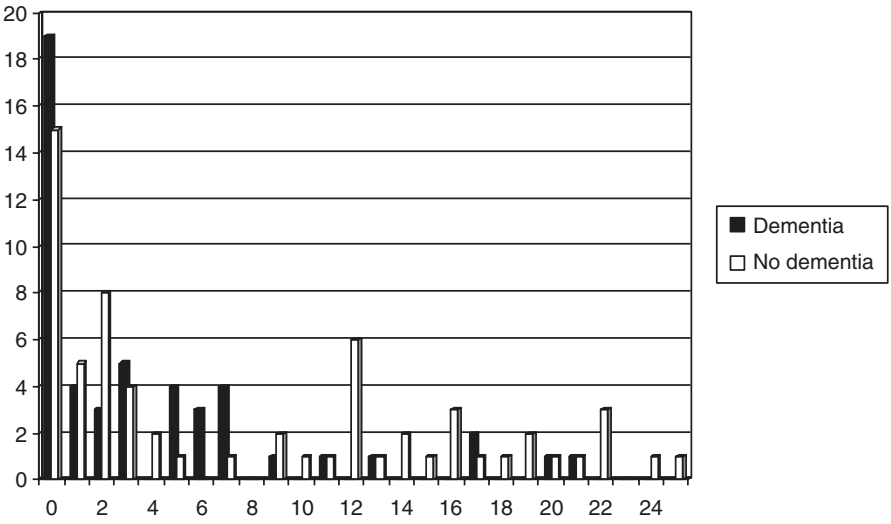

Fig. 5.3 Distribution of PHQ-9 scores vs. diagnosis (Hancock and Larner 2009a) reprinted with permission

Table 5.4 Demographic and diagnostic parameters for PHQ-9 (adapted from Hancock and Larner 2009a)

	PHQ-9
N	113
F:M (% female)	58:55 (51)
Age range (years)	29–94 (mean 68.3 ± 11.7)
Prevalence of dementia (= pre-test probability)	0.43
Pre-test odds	0.75
Cut-off	**>9/27**
Accuracy	0.62 (0.53–0.71)
Net reclassification improvement (NRI)	0.19
Sensitivity (Se)	0.86 (0.76–0.96)
Specificity (Sp)	0.44 (0.32–0.56)
Y	0.30
PPV (= post-test probability)	0.54 (0.43–0.65)
NPV	0.80 (0.67–0.93)
PSI	0.34
LR+	1.52 (1.19–1.95) = unimportant
LR−	0.32 (0.26–0.42) = small
DOR	4.67 (3.65–5.96)
Post-test odds (= pre-test odds × LR+)	1.14
CUI+	0.46 (poor)
CUI−	0.35 (very poor)
AUC ROC curve	0.63 (0.53–0.73)

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

The correlation coefficient for PHQ-9 scores and simultaneously recorded Mini-Mental State Examination (MMSE; Folstein et al. 1975; Sect. 4.1.1) scores ($n = 106$) was, as expected, very low ($r = 0.01$, $t = 0.08$, df = 104, $p > 0.5$), since these tests measure different constructs, and likewise for simultaneously recorded ACE-R scores ($n = 97$; $r = 0.12$, $t = 1.19$, df = 95, $p > 0.1$).

The correlation between PHQ-9 scores and CBI scores was examined in those patients undergoing both tests ($n = 50$). There was a low positive correlation ($r = 0.33$; $t = 2.40$, df = 48, $p \approx 0.02$). That the correlation was no better might be anticipated considering the wider coverage of behavioural features, not only depression, in the CBI. Overall performance of PHQ-9 was similar to that of the CBI (compare Tables 5.2 and 5.4).

5.2.3 Addenbrooke's Cognitive Examination (ACE) and Addenbrooke's Cognitive Examination-Revised (ACE-R)

Although the Addenbrooke's Cognitive Examination (ACE; Mathuranath et al. 2000; see Sect. 4.1.5.1) and its revision (ACE-R; Mioshi et al. 2006; see Sect. 4.1.5.3) are not behavioural and psychiatric scales (Hodges and Larner 2017), nonetheless they are included here because it has been reported that ACE scores may distinguish dementia and affective disorder (Dudas et al. 2005). Patients with dementia scored lower than individuals with "pure" affective disorder, with low scores on the memory domain tasks and letter fluency but with preserved category fluency indicating affective rather than "organic" pathology (Dudas et al. 2005). A later study of the Danish translation of ACE challenged this observation, finding great overlap in individual test scores for demented and depressed patients (Stokholm et al. 2009).

In a study undertaken at the Brooker Centre, Runcorn, over a 17-month period (December 2006–April 2008) ACE-R was administered to 119 patients of whom 54 had a final diagnosis of dementia and 19 of pure affective disorder, the remainder having either mixed or no pathology (using the diagnostic categories as per Dudas et al. 2005). Mean ACE-R (and MMSE) scores differed between these groups (Table 5.5) but statistical calculations of group differences were not undertaken (P Hancock, personal communication, 30 June 2008).

5.2.4 Cornell Scale for Depression in Dementia (CSDD)

The Cornell Scale for Depression in Dementia (CSDD) is a 19-item instrument based on both patient and informant interview (Alexopoulos et al. 1988a). Each item is rated for severity, ranging from 0 (absent) to 2 (severe), giving a possible total score range of 0–38 (higher worse). A total score >18 has been used to indicate a definite major depressive episode, >10 probable major depressive episode, and <6 absence of significant depressive symptoms. Initially designed to diagnose

Table 5.5 Demographic and diagnostic parameters for ACE-R and MMSE in dementia and pure affective disorder (P Hancock, personal communication, 30 June 2008)

			ACE-R/MMSE		
N			119		
F:M (% female)			63:56 (53)		
Mean age (years)			70.6 ± 9.9		
	n	F:M	Mean age (years)	Mean MMSE	Mean ACE-R
Dementia	54	27:27	74.2 ± 8.5	21.2 ± 3.9	60.3 ± 12.1
Pure affective disorder	19	11:8	60.0 ± 7.3	28.9 ± 1.1	87.9 ± 9.0
Mixed dementia + affective disorder	6	4:2	73.0 ± 5.2	26.3 ± 1.8	73.0 ± 7.1
No dementia	40	21:19	75.3 ± 11.6	27.4 ± 2.3	87.8 ± 10.8

depression in patients with dementia, CSDD has also been validated for depression diagnosis in non-demented populations (Alexopoulos et al. 1988b; Korner et al. 2006). Depressive symptoms as identified by CSDD have been reported as frequent amongst patients referred for dementia assessment in a specialist care setting (Knapskog et al. 2014).

In a study undertaken at the Brooker Centre, Runcorn, over a 44-month period a total of 242 patients with suitable informants were assessed with CSDD. Of these, 32 (13.2%) were judged to be depressed, 9 in the context of dementia (= 3.7% of whole cohort, 28.1% of those depressed). In all, 98 patients (40.5%) were judged to be demented by DSM-IV criteria and 144 (59.5%) not demented. CSDD scores ranged from 0 to 26, and showed a low negative correlation with patient age (−0.34; Hancock and Larner 2015).

For the group of patients diagnosed with depression (mean age 64.0 ± 13.4 years), the median and mean CSDD scores were 11 and 12.6 ± 6.4, respectively; for the non-depressed group (mean age 70.6 ± 11.9 years) the median and mean scores were 2 and 3.23 ± 4.0. The mean age of depressed and non-depressed patients differed significantly between the two groups (t = 2.91, df = 240, $p < 0.01$). CSDD scores also differed significantly between the two groups (t = 11.3, df = 240, $p < 0.001$).

For the group of patients diagnosed with dementia (mean age 75.7 ± 10.7 years), the median and mean CSDD scores were 2 and 3.2 ± 4.2, respectively; for the non-demented group (mean age 65.7 ± 11.7 years) the median and mean scores were 3 and 5.3 ± 5.9 (Fig. 5.4). The mean age of demented and non-demented patients differed significantly between the two groups (t = 6.71, df = 240, $p < 0.001$). The mean CSDD scores also differed significantly between the two groups (t = 3.11, df = 240, $p < 0.01$).

For the group of patients diagnosed with dementia, the median and mean MMSE scores ($n = 94$) were 20 and 19.1 ± 5.8, respectively; for the non-demented group ($n = 143$) the median and mean scores were 29 and 28.2 ± 3.0. The mean MMSE scores differed significantly between the two groups (t = 14.2, df = 235, $p < 0.001$).

The correlation between CSDD and MMSE scores was low ($r = 0.12$).

For the group of patients diagnosed with dementia, the median and mean ACE-R scores ($n = 50$) were 67.5 and 66.0 ± 12.4, respectively; for the non-demented group ($n = 133$) the median and mean scores were 90 and 87.1 ± 10.0. The mean ACE-R scores also differed significantly between the two groups (t = 11.9, df = 181, $p < 0.001$). The correlation between CSDD and ACE-R scores was low ($r = 0.26$). (The data from this study also permitted a weighted comparison between MMSE and ACE-R; Sect. 6.1.1, Table 6.10; Larner and Hancock 2014).

In light of the significant difference in CSDD scores between demented and non-demented patients, overall test accuracy for this differential diagnosis was calculated for all CSDD cut-offs, with an optimal test accuracy (0.59) being found at a cut point of ≤5/38. Various standard parameters of diagnostic performance were calculated for CSDD at this cut-off (Table 5.6), indicating the test at this cut-off had good sensitivity (0.80) but poor specificity (0.43) for a diagnosis of dementia. Diagnostic gain as measured by positive and negative likelihood ratios was unimportant (LR+ = 1.40) or small (LR− = 0.47). The area under the ROC curve was 0.60 (0.53–0.67).

The optimal overall accuracy cut point of ≤5/38 nearly coincides with the suggested CSDD cut point of <6 indicating absence of significant depressive symptoms, a threshold which might, dependent on clinical context, be taken as an indicator for the appropriateness (scores above) or otherwise (scores below) for prescribing antidepressant medication. Using this pragmatic threshold, the null hypothesis that the proportion of patients with CSDD ≤5/38 did not differ significantly between patients diagnosed with dementia (78/98 = 80%) and without dementia (62/144 = 43%) was examined, and rejected ($\chi^2 = 12.9$, df = 1, $p < 0.01$).

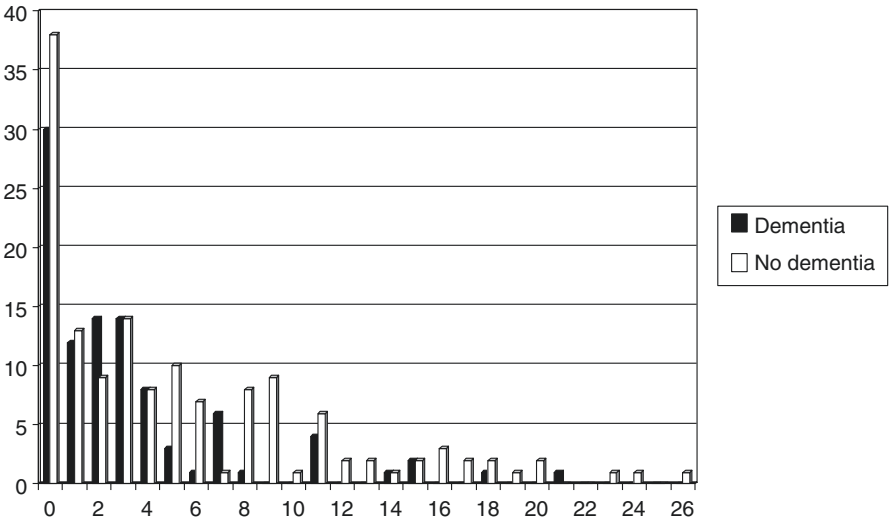

Fig. 5.4 Distribution of CSDD scores vs. diagnosis (Hancock and Larner 2015) reprinted with permission

Table 5.6 Demographic and diagnostic parameters for CSDD for dementia/no dementia differential diagnosis (adapted from Hancock and Larner 2015)

	CSDD
N	242
F:M (% female)	115:127 (47.5)
Age range (years)	37–97 years (median 69.5)
Prevalence of dementia (= pre-test probability)	0.405
Pre-test odds	0.68
Cut-off	**≤5/38**
Accuracy	0.59 (0.52–0.64)
Net reclassification improvement (NRI)	0.185
Sensitivity (Se)	0.80 (0.72–0.88)
Specificity (Sp)	0.43 (0.35–0.51)
Y	0.23
PPV (= post-test probability)	0.49 (0.41–0.56)
NPV	0.76 (0.66–0.85)
PSI	0.24
LR+	1.40 (1.17–1.66) = unimportant
LR−	0.47 (0.40–0.56) = small
DOR	2.95 (2.48–3.51)
Post-test odds (= pre-test odds × LR+)	0.95
CUI+	0.39 (poor)
CUI−	0.33 (very poor)
AUC ROC curve	0.60 (0.53–0.67)

Patient cohort seen at Memory Clinic, Brooker Centre, Runcorn

Hence, despite the limited differential diagnostic utility of CSDD in this clinic-based setting, CSDD may nonetheless be of pragmatic use in indicating those patients who might benefit from a trial of antidepressant therapy (significantly more in the non-dementia group).

The desirability of a study to compare PHQ-9 (Sect. 5.2.2) with CSDD in dementia clinics was previously mentioned (Larner 2012a:80). Although this study provided no direct comparison, the overall results of the two studies were comparable (see Tables 5.4 and 5.6; Figs. 5.3 and 5.4).

5.3 Neurovegetative Symptoms: Sleep Disorders

DSM-IV acknowledged that the "multiple cognitive impairments of dementia are often associated with anxiety, mood and sleep disturbances" (American Psychiatric Association 2000:150). Abnormal sleep is a feature not only of depression but also of a number of dementing disorders associated with impaired memory function. Sleep or lack of sleep may be a risk factor for Alzheimer's disease (Bubu et al. 2017) perhaps through changes in amyloid peptide metabolism (Macedo et al. 2017). Occasional examples of specific sleep signatures in neurodegenerative disease, such as REM sleep behaviour disorder (REMBD) in dementia with Lewy bodies (DLB)

and other synucleinopathies (Boeve et al. 2007), may be encountered in patients attending dedicated memory clinics (Larner et al. 2005). The Mayo Fluctuations Questionnaire, which may assist in the diagnosis of Parkinson's disease dementia (PDD) and DLB, specifically asks about sleep and sleepiness (Ferman et al. 2004; see Sect. 5.4.3).

It has become increasingly apparent in recent years that sleep is crucial for physiological memory function, perhaps most especially for memory consolidation (Payne 2011). Short sleep duration may be related to poor overall cognitive function (Lo et al. 2016). Sleep-related disorders may present de novo to memory clinics, such as restless legs syndrome (Davies and Larner 2009), shift-work sleep disorder (Davies and Larner 2009; Larner 2010a), and sleep apnoea syndromes (obstructive and central) (Larner and Ghadiali 2008; Lim and Larner 2008). Sleep breathing problems such as heavy snoring and sleep apnoea may accelerate clinical presentation of MCI and AD (Osorio et al. 2015), possibly through accelerating the rate of amyloid accumulation (Yun et al. 2017). Treating sleep breathing disorders may potentially delay onset of MCI and AD (Osorio et al. 2015).

Studies have been undertaken in CFC to examine whether use of sleep questionnaires (namely the Pittsburgh Sleep Quality Index, the Sleep Disorders Inventory, STOP-Bang, and the REM sleep behaviour screening questionnaire [RBDSQ]) might be helpful in diagnosis and assessment of patients with cognitive complaints. The Epworth Sleepiness Scale (ESS; Johns 1991) has also been used on occasion in the assessment of cognitive complaints (Larner 2003; Larner and Ghadiali 2008; Lim and Larner 2008; Case Study 8.5). The Jenkins Sleep Scale (Jenkins et al. 1988) or Questionnaire (JSS, JSQ) is being used in an ongoing study of functional cognitive disorders (Bharambe and Larner, in preparation).

5.3.1 Pittsburgh Sleep Quality Index (PSQI)

The Pittsburgh Sleep Quality Index (PSQI; Buysse et al. 1989) is a self-rated questionnaire which assesses sleep quality and disturbances over a 1-month period (Box 5.4) to generate seven component scores (range 0–3) and one global score (range 0–21). In the original study, a global PSQI score >5 distinguished good and poor sleepers (sensitivity 89.6%, specificity 86.5%).

Box 5.4: Item content (components) of PSQI
Q1. Subjective sleep quality
Q2. Sleep latency
Q3. Sleep duration
Q4. Habitual sleep efficiency
Q5. Sleep disturbances
Q6. Use of sleeping medication
Q7. Daytime dysfunction

The PSQI has been reported to be a stable measure of sleep quality (Knutson et al. 2006), with high test-retest reliability and construct validity (Gentili et al. 1995; Backhaus et al. 2002). PSQI has proved useful for characterizing sleep disturbances in conditions such as fibromyalgia and post-traumatic brain injury (Fictenberg et al. 2001; Osorio et al. 2006). Poor sleep quality has also been reported to have a possible role in the differential diagnosis of dementia syndromes, specifically of Parkinson's disease dementia and dementia with Lewy bodies from AD (Boddy et al. 2007). PSQI may be more sensitive than ESS for identifying sleep disorders in memory clinic attenders (LittleJohn et al. 2014). PSQI has been translated into a variety of languages.

The diagnostic utility of PSQI to facilitate clinical differential diagnosis of patients with and without dementia at the initial diagnostic interview has been assessed prospectively in new referrals to CFC and to the Brooker Centre, Runcorn, over a 2-year period (February 2006–February 2008) (Hancock and Larner 2009b). This was based on a clinical impression that non-demented patients attending CFC had poor sleep compared to those with dementia. Global PSQI scores ranged from 0 to 20 (dementia group 0–18, non-dementia group 0–20). The mean global PSQI score in the dementia and non-dementia subgroups was 5.1 (± 4.2) and 7.6 (± 5.1), respectively, a difference which proved statistically significant ($t = 4.64$, $p < 0.001$).

Using the PSQI categorisation of good (PSQI ≤5) or bad (PSQI >5) sleep quality, of the good sleepers ($n = 165$), 62% had dementia and 38% were not demented, whilst for the bad sleepers ($n = 145$) the corresponding figures were 36% and 64% respectively ($Z = 4.23$, $p < 0.01$). Hence, the relative risk or risk ratio for poor sleep quality, defined by a PSQI cut-off score of ≤5/21, in non-demented compared to demented individuals was 1.79 (95% CI = 1.38–2.31).

Diagnostic utility of PSQI was modest, with both sensitivity and specificity for the diagnosis of dementia <0.7 (Table 5.7). Area under the ROC curve was 0.64 (Fig. 5.5).

Analysis using a suggested 3-factor scoring model (Cole et al. 2006) encompassing sleep efficiency (Q3 + Q4; score range 0–6), perceived sleep quality (Q1 + Q2 + Q6; score range 0–9), and daily disturbance (Q5 + Q7; score range 0–6) did not result in better accuracy than the global PSQI score (best accuracy: sleep efficiency 0.62 at cut-off 2; perceived sleep quality 0.63 at cut-off 1; daily disturbance 0.57 at cut-off 1).

A subgroup of patients completed PHQ-9 (see Sect. 5.2.2) as well as PSQI ($n = 96$). PSQI scores and PHQ-9 scores showed a moderate positive correlation in both the dementia group ($n = 44$; $r = 0.53$, $t = 4.01$, $p < 0.001$) and the non-dementia group ($n = 52$; $r = 0.62$, $t = 5.64$, $p < 0.001$).

5.3.2 Sleep Disorders Inventory (SDI)

The importance of sleep disorders in established dementia syndromes has been increasingly recognised. Nocturnal sleep disturbance and abnormal daytime sleepiness may predict accelerated functional decline in dementia patients, as well as

Table 5.7 Demographic and diagnostic parameters for PSQI (adapted from Hancock and Larner 2009b)

	PSQI
N	310
F:M (% female)	152:158 (49)
Age range (years)	29–97 (mean 66.9 ± 13.0)
Prevalence of dementia (= pre-test probability)	0.50
Pre-test odds	1.00
Cut-off	**≤5/21**
Accuracy	0.63 (0.58–0.69)
Net reclassification improvement (NRI)	0.13
Sensitivity (Se)	0.66 (0.59–0.74)
Specificity (Sp)	0.60 (0.52–0.68)
Y	0.26
PPV (= post-test probability)	0.62 (0.55–0.70)
NPV	0.64 (0.56–0.72)
PSI	0.26
LR+	1.66 (1.32–2.08) = unimportant
LR−	0.56 (0.45–0.70) = unimportant
DOR	2.97 (2.38–3.71)
Post-test odds (= pre-test odds × LR+)	1.66
CUI+	0.41 (poor)
CUI−	0.38 (poor)
AUC ROC curve	0.64 (0.58–0.70)

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

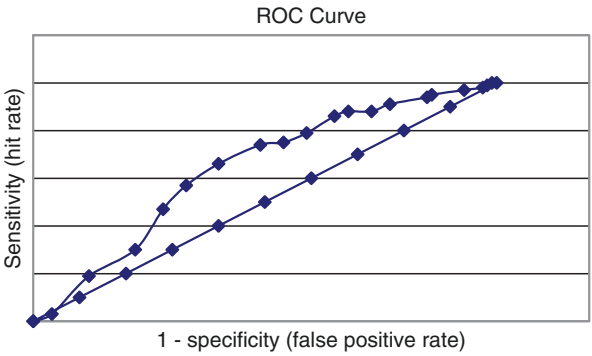

Fig. 5.5 PSQI ROC curve (Hancock and Larner 2009b) reprinted with permission

contributing to caregiver distress. Indeed, carers may find sleep disruption more challenging than memory problems. Sleep related problems are more common and severe in the advanced stages of dementia, although they may commence early in the disease course, and increase the likelihood of institutionalisation (Moe et al. 1995). Cholinesterase inhibitors may improve memory at least in part through beneficial effects on sleep (Schredl et al. 2001).

Box 5.5: Symptoms assessed in Sleep Disorders Inventory (SDI)
Difficulty falling asleep
Getting up during the night
Wandering, pacing, or inappropriate activities at night
Awakening caregiver during the night
Awakening at night, dressing, and planning to go out, thinking it is morning
Awakening too early in the morning (earlier than habitual)
Sleeping excessively during the day
Other night-time behaviours that are bothersome to caregiver

Methods to measure sleep parameters such as polysomnography and actigraphy are not widely available, and hence informant questionnaires may be the easiest way to assess sleep disturbance in dementia patients. The Sleep Disorders Inventory (SDI) was designed as a novel instrument for assessing and quantifying sleep disturbance in AD patients (Tractenberg et al. 2003). It was developed by the Alzheimer's Disease Cooperative Study through expansion of item 11 of the NPI (Cummings et al. 1994). In the SDI, eight different symptoms (Box 5.5) are assessed in terms of frequency, severity, and caregiver distress, the average for all eight symptoms giving the average frequency (0–4), average severity (0–3) and average caregiver distress (0–5). These are summed to give the global SDI score (0–12).

In the index study, in a cohort of pre-screened AD patients known to have disturbed sleep and candidates for a therapeutic trial of melatonin, SDI scores were significantly worse in patients with less than 6 h night-time total sleep time, and with worse cognitive, functional and behavioural status. SDI scores were not associated with gender, age, education, or duration of dementia (Tractenberg et al. 2003). No other studies of SDI appear to have been published.

SDI has been evaluated in a cohort of community-dwelling dementia patients who were not specifically sleep-disturbed, recruited jointly from CFC and through the auspices of the local Alzheimer's Society, a charitable patient support organisation (Larner and Culshaw 2008; Culshaw and Larner 2009). Fifty service users who were members of the Liverpool and South Sefton Alzheimer's Society branch were surveyed. The purposes of the study were explained to patients and carers. In addition to the SDI, a proforma was also supplied for patients and/or carers to indicate patient age, diagnosis, and date of diagnosis/duration of illness.

All 50 returned SDI questionnaires were completed appropriately. Stated dementia diagnoses were AD or combined AD and cerebrovascular disease (36), vascular dementia (8), FTD (5), and DLB (1). Although many of the patients were not diagnosed in CFC, nonetheless the diagnostic mix broadly reflected that encountered in the clinic, with the exception of an over-representation of vascular dementia cases.

The results (Table 5.8, left hand column) showed that this cohort was of similar distribution in age and gender, but had shorter disease duration and lower SDI scores, when compared with the index study (Table 5.8, right hand

Table 5.8 Demographic and diagnostic parameters for Sleep Disorders Inventory, compared with index (Tractenberg et al. 2003) study (adapted from Culshaw and Larner 2009)

	SDI	Index study (Tractenberg et al. 2003)
N	50	104
F:M (% female)	25:25 (50)	51:53 (49)
Age range (years)	52–98 (mean 74.3 ± 10.2)	47–92 (mean 75.5 ± 8.6)
Duration of disease	3.1 ± 3.1 years	4.6 ± 3.0 years
Prevalence dementia	1.00	1.00
SDI global score: range (0–12)	0–10.5 (mean 2.4 ± 2.8)	0.6–10.3 (mean 3.6 ± 2.2)
Average frequency rating (0–4)	1.5 ± 1.1	1.9 ± 0.8
Average severity rating (0–3)	1.0 ± 0.8	1.7 ± 0.5
Average caregiver distress rating (0–5)	1.4 ± 1.3	2.2 ± 1.1
SDI symptoms present (0–7)	3.7 ± 2.5	–

column). This latter finding was expected since there was no pre-selection of patients with sleep disturbance in this cohort, unlike the index study. SDI global score showed no correlation with either patient age ($r = 0.09$, $t = 0.66$, $p > 0.5$) or disease duration ($r = 0.13$, $t = 0.92$, $p > 0.1$), as reported in the Tractenberg et al. (2003) study.

These data confirmed the utility of SDI in assessing and quantifying sleep disturbance in dementia patients. As with all informant questionnaires, the validity of the data is open to question since it may be influenced by caregiver factors such as depression. Nonetheless, SDI was quick and easy to use and acceptable to caregivers. It may be a useful tool in the identification and quantification of sleep disturbances in community dwelling dementia patients. The study also illustrated the feasibility of using a patient support organisation, the Alzheimer's Society, to recruit patients for research purposes. This type of outreach initiative is important to ensure inclusivity in clinical studies and trials, since the population recruited may differ from that encountered in hospital-based dementia outpatient clinics.

5.3.3 STOP-Bang

Obstructive sleep apnoea (OSA) syndrome may cause cognitive impairment as a consequence of sleep disturbance and intermittent cerebral hypoxia (Shastri et al. 2016). One study suggested that 8.4% of young adults with suspected of dementia had OSA (Panegyres and Frencham 2007). Hence it may be of value to screen for OSA in patients attending a cognitive disorders clinic. STOP-Bang is an 8-item (Yes/No) screening questionnaire, high scores on which have been shown to indicate a high probability of OSA (Chung et al. 2008, 2012).

The diagnostic utility of STOP-Bang has been examined in CFC (Stagg and Larner 2015a; Ziso and Larner 2016a; Larner and Ziso 2018). Over a 3-month study period (October–December 2014), 92 new patient referrals were seen, 25 of whom were exclusions from STOP-Bang screening for the following reasons: pre-existing

diagnosis of OSA (6); pre-existing diagnosis of dementia or amnesia with established aetiology (10); no cognitive complaint (1); patient not an English speaker or requiring a translator (3); patient declined or unable to complete STOP-Bang (5).

The demographics of the remaining 67 patients showed a male preponderance (F:M = 26:41, 39% female), with a patient age range of 25–88 years (median 60). Final clinical diagnoses were dementia (10), MCI (13), and subjective memory complaint (44). This prevalence of cognitive impairment (dementia and MCI; 0.34) was typical of non-overlapping cohorts from CFC. STOP-Bang scores did not correlate with patient age ($r = 0.06$), nor with scores on the MMSE ($r = -0.17$) or the mini-Addenbrooke's Cognitive Examination (MACE; see Sect. 4.1.5.5: $r = -0.13$).

STOP-Bang score ≥3/8, the criterion for "suspected high risk of OSA", was observed in 33/67 patients. However, in only one case did the diagnostician think it very likely on clinical grounds that OSA contributed to the presenting cognitive problems, and possibly so in another five cases. Of the 33 with STOP-Bang score ≥3/8, 14 had clear alternative explanations for cognitive complaint, such as clinical (with or without or radiological) evidence for an underlying neurodegenerative disorder and/or depression.

Hence, STOP-Bang is a very sensitive screening test, which may generate significant numbers of false positive results, e.g. any tired male over 50 years will score 3/8 on STOP-Bang.

5.3.4 REM Sleep Behaviour Screening Questionnaire (RBDSQ)

REM sleep behaviour disorder (RBD) may be a feature of Parkinson's disease and other synucleinopathies (Boeve et al. 2007), and may be encountered in patients with these disorders who attend cognitive disorders clinics (Larner et al. 2005). A REM Sleep Behavior Disorder Screening Questionnaire (RBDSQ) was described by Stiasny-Kolster et al. (2007) but there appear to have been no independent studies of its diagnostic accuracy.

The diagnostic accuracy of RBDSQ was examined in CFC. Over a 3-month period (October–December 2015), 94 consecutive patients were assessed (F:M = 44:50, 47% female; age range 23–88 years, median 64; new:follow-up = 83:11); 25 were diagnosed with dementia (DSM-IV-TR criteria), 24 with MCI (Petersen criteria), the remainder with subjective memory complaint. Of the 15 patients who either volunteered or admitted on questioning to sleep problems and attended with a regular bed partner, 11 completed RBDSQ (2 patients with known obstructive sleep apnoea were excluded). Comparing RBDSQ cut-off score ≥5/13 as defined in the index study versus the reference standard of expert clinical diagnosis blind to RBDSQ score, the test was sensitive (1.00) but not specific (0.5) for diagnosis of RBD. False positives included single cases of mixed dementia, subjective memory complaint, and periodic leg movements of sleep. Hence in this pragmatic study, RBDSQ was acceptable to patients and their bed partners and was sensitive but not specific for the diagnosis of RBD (Ziso and Larner 2016b). RBDSQ has also proved of use in individual cases (Case Study 5.2).

Case Study 5.2: Clinical utility of neurovegetative screening instrument in diagnosis of dementia: RBDSQ
A 73 year-old man attended CFC with his wife, and she reported that over the past 5 years her husband's sleep had been disturbed on most nights with falls out of bed and by what she spontaneously described as "acting out his dreams". On the REM Sleep Behavior Disorder Screening Questionnaire he scored 11/13, where a cut-off of 5 or above suggests the presence of REMBD. Cognition appeared intact, and he scored 4/28 on the Six-Item Cognitive Impairment Test (normal).

The Fluctuations Composite Scale (FCS; Sect. 5.4.3) also explores sleep disturbance in parkinsonian syndromes.

5.4 Collateral Information and Informant Scales

The importance of collateral history from a knowledgeable informant when assessing individuals complaining of memory problems and in the diagnosis of dementia syndromes, particularly AD, has been emphasized in diagnostic guidelines (Knopman et al. 2001; Waldemar et al. 2007). It has been said that it takes at least two to diagnose dementia (Lipton and Marshall 2013:21). Formalised input to the diagnostic process from a caregiver may be achieved through the use of structured interviews of informants, or informant scales. Informant scales have the advantage of effectively making intraindividual comparisons over time (i.e. longitudinal assessment), whereas patient performance-based scales make interindividual comparisons (against specified norms or cut-offs) at a single time point (i.e. cross-sectional assessment).

Informant scales which have gained widespread usage include the Neuropsychiatric Inventory (NPI; Cummings et al. 1994) and the Informant Questionnaire on Cognitive Decline in the Elderly (IQCODE; Jorm and Jacomb 1989; Cherbuin and Jorm 2017). The utility of other informant scales (total or partial), such as the Cambridge Behavioural Inventory (CBI), the Cornell Scale for Depression in Dementia (CSDD), and the Sleep Disorders Inventory (SDI), has already been discussed (see Sects. 5.2.1, 5.2.4 and 5.3.2 respectively).

Because of the importance of collateral history in the assessment of cognitive problems, all patients referred to CFC are sent written instructions, printed in bold type, requesting them to attend the clinic with someone who knows them well and can give information about them. This is included with the letter giving the details of the clinic appointment. Failure to attend consultation with an informant, despite the prior provision of written instructions to do so, the "attended alone" sign, may be a robust indicator of absence of dementia (Larner 2005a, b, 2009) and is highly sensitive for identification of cognitively healthy individuals (Larner 2014b; see Sect. 3.2.1).

5.4.1 Informant Questionnaire on Cognitive Decline in the Elderly (IQCODE)

The Informant Questionnaire on Cognitive Decline in the Elderly (IQCODE) asks an informant about change in a person's everyday cognitive function over a 10-year period (Jorm and Jacomb 1989). Each of a series of 26 statements is graded by the informant on a five point scale ranging from 1 to 5 (viz. much improved, a bit improved, not much change, a bit worse, much worse), the overall score being given by the sum of these responses divided by the total number of responses given (hence overall IQCODE score range = 1–5, higher scores suggest greater impairment). Hence IQCODE correlates negatively with cognitive screening instruments such as MMSE and ACE-R (see Sect. 6.1.6, Table 6.18). Up to three missing items are generally permitted with the original, long, form of IQCODE (Jorm and Jacomb 1989). A shorter, 16 item, form has also been developed (Jorm 2004).

Studies have suggested that the IQCODE may be as good as the MMSE (see Sect. 4.1.1) in the diagnosis of dementia (Jorm et al. 1991). However, unlike the MMSE and other cognitive screening instruments, the IQCODE is relatively unaffected by patient education and pre-morbid ability. In light of its performance, IQCODE has been widely adopted in clinical practice (Jorm 2004; Cherbuin and Jorm 2017). The evidence for its diagnostic properties in community settings, primary and secondary care, is favourable (Quinn et al. 2012; Harrison et al. 2014, 2015). However, a review of cognitive screening instruments found few studies of IQCODE had been performed in a memory clinic setting (Cullen et al. 2007). Flicker et al. (1997) reported test sensitivity of 0.74 and specificity of 0.71 using an IQCODE cut-off of 3.9, and Stratford et al. (2003) reported area under the ROC curve of 0.82.

The diagnostic utility of IQCODE has been assessed prospectively in consecutive new patient referrals who attended with an informant at CFC and at the Brooker Centre, Runcorn, over a 12-month period (July 2007–July 2008) (Hancock and Larner 2009c).

The long form of IQCODE was used, rather than the short form, in order to obtain results easily comparable with the aforementioned study of Flicker et al. (1997). The dementia prevalence in this cohort (59%) was higher than in other patient cohorts from these clinics but similar to that recorded in a previous study which examined an informant questionnaire, the CBI (see Sect. 5.2.1).

IQCODE proved easy to use, being completed in all cases (up to three missing items were permitted). In the demented group the mean (±SD) IQCODE score was 4.10 ± 0.43, and in the non-demented group 3.76 ± 0.44. The mean IQCODE scores differed significantly between the two groups ($t = 4.52$, df = 142, $p < 0.001$).

Diagnostic utility of IQCODE was modest (Table 5.9) with only sensitivity reaching the desired level using the most accurate cut-off score (≥3.6). Area under the ROC curve was 0.71 (Fig. 5.6), comparing unfavourably with the finding of Stratford et al. (2003).

Patients administered the PHQ-9 (see Sect. 5.2.2) at the same time that an informant completed the IQCODE ($n = 58$) allowed correlation between these scales to

Table 5.9 Demographic and diagnostic parameters for IQCODE (adapted from Hancock and Larner 2009c)

	IQCODE
N	144
F:M (% female)	73:71 (51)
Age range (years)	29–94 (mean 67.7 ± 11.4)
Prevalence of dementia (= pre-test probability)	0.59
Pre-test odds	1.44
Cut-off	**≥3.6**
Accuracy	0.67 (0.59–0.74)
Net reclassification improvement (NRI)	0.08
Sensitivity (Se)	0.86 (0.78–0.93)
Specificity (Sp)	0.39 (0.27–0.51)
Y	0.25
PPV (= post-test probability)	0.67 (0.58–0.76)
NPV	0.66 (0.50–0.81)
PSI	0.33
LR+	1.41 (1.12–1.76) = unimportant
LR−	0.36 (0.29–0.45) = small
DOR	3.89 (3.11–4.85)
Post-test odds (= pre-test odds × LR+)	2.03
CUI+	0.58 (adequate)
CUI−	0.26 (very poor)
AUC ROC curve	0.71 (0.62–0.79)

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

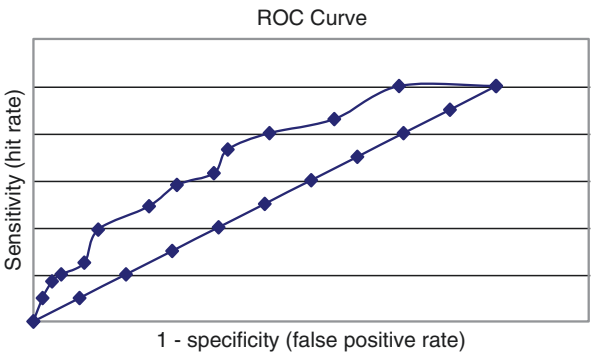

Fig. 5.6 IQCODE ROC curve (Hancock and Larner 2009c) reprinted with permission

be calculated ($r = 0.31$, $t = 2.4$, df = 56, $p \approx 0.02$). Previous studies have shown a small positive association between IQCODE and measures of anxiety, depression and general psychological distress (Jorm 2004).

Although diagnostic utility was modest, nonetheless IQCODE may have a role in patient assessment, as a complement to other, cognitive, scales (see Sect. 6.2.2.1). Using shorter forms (16- or 7-item) of the IQCODE and a shorter time frame (2 years as opposed to 10 years) might improve the diagnostic utility (Ehrensperger et al. 2010).

A potential role for IQCODE in the differential diagnosis of AD and FTLD has also been explored, based on a clinical impression of differential IQCODE impairments in these conditions (Larner 2010b). Mean IQCODE score for patients with the behavioural variant of frontotemporal dementia (bvFTD; $n = 13$; age range 47–76 years, mean 60.2 ± 7.3 years) was 4.34 ± 0.31, and for AD patients ($n = 41$; age range 52–92 years, mean 70.6 ± 9.0 years) was 3.94 ± 0.39, a difference which proved statistically significant ($t = 3.25$, df = 52, $p < 0.01$). The null hypothesis that the proportion of patients with an IQCODE score ≥4.0 did not differ significantly between the bvFTD (11/13 = 84.6%) and AD (17/41 = 41.4%) groups was examined. The result of the χ^2 test permitted rejection of the null hypothesis ($\chi^2 = 6.51$, df = 1, $p < 0.02$), a finding corroborated by the Z test (Z = 2.67, $p < 0.01$). These preliminary data suggested that a high IQCODE score (≥4.0) is more likely to occur in bvFTD than in AD, and hence that use of IQCODE scores to assist in the differential diagnosis of AD and bvFTD might be worthy of further examination.

Combining IQCODE scores with cognitive measures (MMSE, ACE-R) has also been examined (see Sect. 6.2.2.1; Hancock and Larner 2009c).

5.4.2 AD8

AD8 is a brief, 8-item, informant screening questionnaire for dementia which is sensitive and reliable for the differentiation of demented and non-demented individuals (Galvin et al. 2005, 2006; Galvin and Goodyear 2017). Each of a series of 8 statements is graded by the informant as yes, no, or don't know, the overall score being given by the sum of "yes" responses (range 0–8). Using the specified cut-offs (0–1: normal cognition; 2 or greater: cognitive impairment is likely to be present), from the index study of 995 individuals included in development and validation samples the sensitivity and specificity of AD8 were 0.84 and 0.80 respectively (www.alzheimer.wustl.edu/about_us/pdfs/ad8form2005.pdf, accessed 31/12/17). AD8 has been used in various settings to identify cognitive impairment (e.g. Carpenter et al. 2011) and has also been used as a self-rating scale (Galvin et al. 2007).

The diagnostic utility of AD8 has been assessed prospectively in CFC (Ziso et al. 2014, 2015; Larner 2015, 2016). Over the 12-month study period (July 2013–July 2014), 334 new patient referrals were seen. Of these, 107 attended the clinic alone despite being instructed in their appointment letter to attend with a relative, friend or carer who might provide collateral history. Of the 227 patients (= 68%) attending with another person (comparable with a previous 3-year study of consecutive CFC patients (480/726 = 66%; Larner 2014b), in 15 cases the accompanying person was deemed inadequate as a reliable informant for the following reasons: carer with little knowledge of patient (8); dementia diagnosis already made (5); not fluent in English language (1); minor, <10 years old (1). Hence 212 patient-reliable informant dyads (= 63.5% of whole cohort; 93.4% of those attending with another) were assessed. AD8 scores showed no correlation with patient age ($r = 0.019$; $t = 0.28$, df = 210, $p > 0.5$).

Diagnostic accuracy of AD8 was calculated at the specified cut-off of ≥2/8 ("cognitive impairment is likely to be present") for the criterion diagnosis of any cognitive impairment (either dementia or MCI; see Table 5.10). At this cut-off, AD8 had good sensitivity for the diagnosis of cognitive impairment but poor specificity (0.97 and 0.17 respectively). Examining all possible AD8 cut-offs, ≥2/8 was the most accurate (0.67).

Looking at the diagnostic performance of AD8 at this cut-off for diagnosis of dementia (n = 69) versus no dementia, and for diagnosis of MCI (n = 62) versus no cognitive impairment, outcomes were very similar (sensitivity 0.97 for both; specificity 0.11 and 0.17 respectively). Testing the null hypothesis, mean AD8 scores differed significantly between dementia (6.5 ± 1.7) and MCI (5.2 ± 1.9) patients ($t = 4.10$, $df = 129$, $p < 0.001$) (Fig. 5.7).

These data indicate that AD8 is highly sensitive for detection of cognitive impairment but with a much lower specificity. It is simpler to administer and score than IQCODE.

AD8 is being examined in an ongoing study of cognitive complaints in an epilepsy clinic population (Aji and Larner, in preparation).

Table 5.10 Demographic and diagnostic parameters for AD8 for diagnosis of any cognitive impairment (adapted from Larner 2015)

	AD8
N	212
F:M (% female)	106:106 (50)
Age range (years)	16–92 (median 64.5)
Prevalence of cognitive impairment (dementia + MCI) (= pre-test probability)	0.618 (0.325 and 0.292)
Pre-test odds	1.62
Cut-off	**≥2/8**
Accuracy	0.67 (0.60–0.73)
Net reclassification improvement (NRI)	0.052
Sensitivity (Se)	0.97 (0.94–0.99)
Specificity (Sp)	0.17 (0.09–0.26)
Y	0.14
PPV (= post-test probability)	0.65 (0.59–0.72)
NPV	0.78 (0.59–0.97)
PSI	0.43
LR+	1.17 (1.06–1.30) = unimportant
LR−	0.17 (0.16–0.20) = moderate
DOR	6.63 (5.98–7.36)
Post-test odds (= pre-test odds × LR+)	1.89
CUI+	0.63 (adequate)
CUI−	0.13 (very poor)
AUC ROC curve	0.67 (0.63–0.70)
Effect size (Cohen's d)	0.62 (medium)

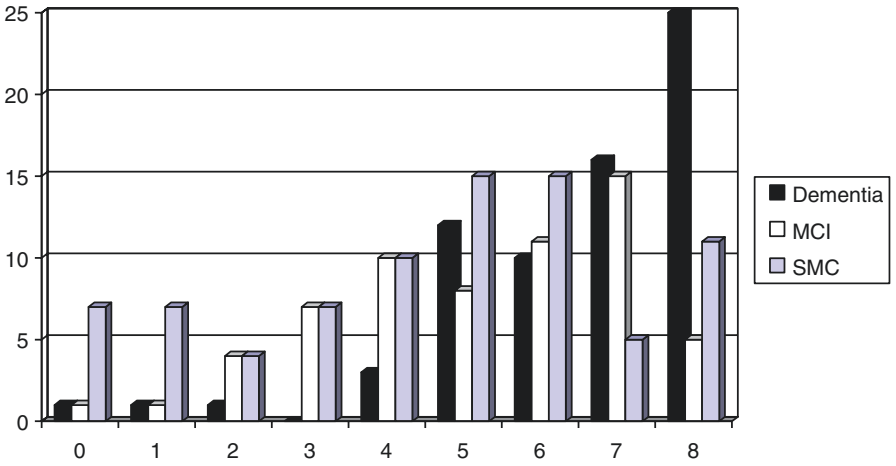

Fig. 5.7 Distribution of AD8 scores vs. diagnosis (adapted from Larner 2015) reprinted with permission

Box 5.6: Fluctuations Composite Scale (after Ferman et al. 2004)

	Score 1	Score 0
1. Are there times when the patient's flow of ideas seems disorganised, unclear or not logical?	YES	NO
2. Does the patient stare into space for long periods of time?	YES	NO
3. How much time does the patient spend sleeping during the day (before 7 pm)?	2 h or more	Less than 2 h
4. How often is the patient drowsy and lethargic during the day, despite getting enough sleep the night before?	All the time or several times a day?	Once a day or less?

5.4.3 Fluctuations Composite Scale (FCS)

The Fluctuations Composite Scale (FCS) is an informant questionnaire, derived from the Mayo Fluctuations Questionnaire (Ferman et al. 2004), comprising four yes-no questions about disorganised speech and disturbed arousal, with score range 0–4 (Box 5.6). FCS score ≥ 3/4 was reported to distinguish reliably between AD and DLB in a study examining pre-defined diagnostic groups (DLB, AD) and a normal control group (Ferman et al. 2004).

In a pragmatic study of 25 patients who at initial clinical assessment in CFC were suspected to have a synucleinopathy, at the FCS cut-off score of ≥4/4 the test was very specific (1.00) but not very sensitive (0.29) for the diagnosis of synucleinopathy, with maximal positive predictive value (PPV = 1.00). At the FCS cut-off score of <1/4, the test was very sensitive (1.00) but not specific (0.09) with only modest

PPV (0.58). Using the cut-off of ≥3/4 used by Ferman et al. (2004), sensitivity (0.57), specificity (0.55) and PPV (0.62) were suboptimal. For the whole group, there was a very weak negative correlation between patient age and FCS score ($r = -0.02$), a weak negative correlation between FCS score and MMSE score ($r = -0.10$), but a strongly negative correlation between patient age and MMSE score ($r = -0.50$) (Larner 2012b).

5.4.4 Zarit Burden Interview (ZBI)

A large number of instruments designed to assess and quantify caregiver burden in dementia is available. The Zarit Burden Interview (ZBI) was originally described in 1980 as a 29-item instrument (Zarit et al. 1980), but a number of other ZBI versions have subsequently been published, including full (22 items, score range 0–88), short (12 items, score range 0–48), and screening (4 items, score range 0–16) versions (Zarit et al. 1985; Hebert et al. 2000; Bédard et al. 2001).

Caregiver burden was measured using different ZBI versions at the initial assessment of patients referred to CFC (Stagg and Larner 2015b; Larner 2016). Consecutive new patient referrals who attended with cohabiting spouses/partners were recruited prospectively over a 6-month period (July 2014–January 2015). In all, 45 patient:spouse dyads were seen (patients: F:M = 14:31, 31% female; age range 30–85 years, median 65). Informants were thus predominantly female (69%), as in a previous non-overlapping cohort (AD8 study, 74%; Larner 2015, see Sect. 5.4.2). Final patient diagnoses were dementia (16), MCI (15), and subjective memory complaint (SMC; 14).

Caregiver burden was assessed as high or low according to the pre-specified cut-offs for each ZBI version. Cohen's kappa statistic for full, short and screening ZBI versions showed "almost perfect agreement" or "excellent agreement" (>0.8) for these categorisations. ZBI scores from the full, short, and screening versions showed no correlation with patient age, or with MMSE or MACE scores. (MMSE has been reported to show an inverse correlation with ZBI in a sample with low average schooling; Oliveira et al. 2011.)

ZBI scores showed a large and overlapping range for each diagnostic group. Mean ZBI scores did not differ significantly between patient groups with dementia versus SMC; any cognitive impairment (= dementia + MCI) versus SMC; dementia versus MCI; and MCI versus SMC. This contrasted with the findings for MMSE and for MACE.

Hence ZBI lacks utility as an informant based cognitive screening instrument, unlike the IQCODE and AD8. However, ZBI has pragmatic use as an instrument for the identification and quantification of caregiver burden at initial diagnostic assessment of patients with cognitive complaints and may therefore be used to plan appropriate caregiver interventions independent of patient diagnosis.

5.5 Summary and Recommendations

The diagnostic utility of a variety of non-cognitive screening instruments, examining function, behaviour, and neurovegetative features, has been examined in CFC in pragmatic diagnostic test accuracy studies. The various diagnostic metrics examined are generally less impressive than for CSIs (Chap. 4), as might be anticipated, but place AD8 at or near the top in most categories, so this may be the most suitable informant screening test in a dedicated Cognitive Function Clinic (i.e. high prevalence setting).

Diagnostic inutility notwithstanding, many of these non-cognitive screening instruments have pragmatic value. For example, PHQ-9 or CSDD scores may help the clinician to decide which patients presenting to the clinic merit a trial of antidepressant medication (Hancock and Larner 2009a, 2015); PSQI scores may indicate which patients have significant sleep disturbance which may be amenable to treatment in its own right (Hancock and Larner 2009b); and IADL scores are of pragmatic value in planning patient management (Hancock and Larner 2007).

These considerations prompt the recommendation that, although none of the non-cognitive screening instruments need necessarily be used in the diagnosis of dementia or MCI, dependent on individual clinical circumstances emerging from the history (patient and collateral), it may be appropriate to pursue other non-cognitive tests for pragmatic purposes. If depression is suspected then PHQ-9 or CSDD may be appropriate; if behavioural disturbance then CBI; if functional ability is in question then IADL; if sleep disturbance then PSQI or SDI.

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Comparing, Combining and Converting Screening Instruments

6

Contents

A. J. Larner, *Dementia in Clinical Practice: A Neurological Perspective*,
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Abstract

This chapter examines various methods of comparing, combining and converting various screening instruments. Methods of comparing cognitive scales include not only the standard measures of discrimination considered in previous chapters but also weighted comparison and effect size, as well as meta-analysis. The diagnostic utility of combinations of scales, both cognitive and non-cognitive, is also considered, as well as ways to make approximate conversions between the scores of different screening tests.

Keywords

Dementia · Diagnosis · Combinations · Cohen's d · Effect size · Equivalent increase · Limits of agreement · Linear regression equation · Meta-analysis · Weighted comparison

6.1 Comparing Cognitive Screening Instruments

As is evident from the previous two chapters, there are many screening instruments, focusing on either cognitive or non-cognitive domains of function, which may be used in the assessment of patients presenting with cognitive complaints (interpreted in the context of the patient history and examination; Chap. 3). How does one decide which of these instruments should be used, which is optimal? The role of clinician preference should not be underestimated in this choice, but ideally it should be based on some rigorous method of comparison between tests.

One strategy, adopted in previous editions of this book (Larner 2012a:50–2, 97–8; 2014a:131–3, 189–91), is to construct "leagues tables" for various diagnostic metrics e.g. likelihood ratios, diagnostic odds ratios, clinical utility indexes, and area under the receiver operating characteristic curve (AUC ROC) (see also Larner 2015a, Chap. 4). As was then pointed out, such "league table" comparisons relate to historical and usually non-overlapping patient cohorts, so direct comparisons between instruments cannot be made. Nonetheless, such "league tables" may give some clues as to the relative merits of the tests used in pragmatic studies.

Ideally however, comparison requires head-to-head studies where two (or more) instruments are administered (in random order), and blinded to the result of the other(s), to the cohort of patients undergoing assessment. This is potentially a time-consuming strategy, and fatiguing for patients, although it has been used in some studies performed in the Cognitive Function Clinic (CFC) at the Walton Centre for Neurology and Neurosurgery (WCNN) in Liverpool to compare cognitive screening instruments (CSIs), e.g. MMSE vs. ACE (Larner 2005), MMSE vs. ACE-R (Larner 2009, 2013a), MMSE vs. MoCA (Larner 2012b), MMSE vs. MMP (Larner 2012c), MACE vs. MMSE (Larner 2015a, b), and MACE vs. MoCA (Larner 2017a). Ideally tests should be administered sequentially in counter-balanced order to avoid bias, although this is not possible in some circumstances (e.g. because MMSE is incorporated into both ACE and ACE-R; Sects. 4.1.5.1 and 4.1.5.3).

Other methods of comparison may be based on:

- measures of discrimination (Sect. 2.3.2), as documented for individual screening instruments (Chaps. 4 and 5), such as weighted comparison or Q* index;
- measures based on the reference standard diagnosis, such as effect size (Cohen's d);
- or measures of association (non-diagnostic), such as correlation, test of agreement (Cohen's kappa statistic), or Bland-Altman limits of agreement (Sect. 2.3.3).

6.1.1 Weighted Comparison (WC) and Equivalent Increase (EI)

The shortcomings of AUC ROC as an overall measure of diagnostic test accuracy have been emphasized (Mallett et al. 2012), specifically the fact that this unitary metric combines test accuracy over a range of thresholds which may be both clinically relevant and clinically nonsensical. It has been argued that the most relevant and applicable presentation of diagnostic accuracy test results should include interpretation in terms of patients, clinically relevant values for test thresholds, disease prevalence, and clinically relevant relative gains and losses (Mallett et al. 2012).

One such index is the weighted comparison (WC) measure described by Moons et al. (1997) which gives weighting to the difference in sensitivity and specificity of two tests and takes into account the relative clinical misclassification costs of false positive diagnosis and also disease prevalence. This may be expressed by the equation:

$$\mathrm{WC} = \Delta\text{sensitivity} + \left[\left(1-\pi/\pi\right)\times \text{relative cost}\left(\mathrm{FP}/\mathrm{TP}\right)\times \Delta\text{specificity}\right]$$

where π = prevalence; FP = false positives; and TP = true positives.

The relative misclassification cost (FP/TP) is a parameter which seeks to define how many false positives a true positive is worth. Clearly, such a "cost" is very difficult to estimate. In the context of diagnostic accuracy studies for CSIs, it may be argued that high test sensitivity to identify all true positives, with the accompanying risk of false positives (e.g. emotional consequences for a patient of an incorrect diagnosis, and/or inappropriate treatment), is more acceptable than tests with low sensitivity but high specificity which risk false negative diagnoses (i.e. missing true positives, and possibly the opportunity to initiate symptomatic or disease-modifying treatment). This argument is of course moot in the current absence of disease modifying therapies for most causes of dementia or MCI. For studies in CFC, FP/TP was arbitrarily set at 0.1, following previous authors (Mallett et al. 2012), reflecting the desire for high test sensitivity.

Of note, the WC equation used here (Moons et al. 1997) does not take into account false negative diagnoses, which of course have their own potential cost. However, another index, addressing whether screening tests are "costworthy", also incorporates the benefit (advantage) of TP test for an identified individual and the cost (harm) of FP test for a wrongly identified individual but without reference to false negatives (Ashford 2008).

To aid interpretation, another parameter may be calculated using WC, namely the equivalent increase (EI) in TP patients per 1000, using the equation:

$$\text{EI} = \text{WC} \times \text{prevalence} \times 1000$$

As this is a measure of patient numbers, results are rounded to integer values.

Weighted comparison and calculation of equivalent increase has been undertaken for a number of the CSIs examined in CFC. These have compared patient performance-related CSIs: MMSE with ACE-R, MoCA, TYM, MMP (Larner 2013b), 6CIT (Abdel-Aziz and Larner 2015) and MACE (Larner 2015a), as well as TYM against ACE-R, and MoCA against MACE (Larner 2016a, 2017a). Comparison of performance-related CSIs and informant scales has also been examined: AD8 with MMSE and 6CIT (Larner 2015c). Most comparisons have been for the diagnosis of dementia, but some also for the diagnosis of MCI. The figures for sensitivity, specificity, AUC ROC, prevalence of dementia/MCI/cognitive impairment were extracted from each study, and Δsensitivity, Δspecificity, and WC and EI were then calculated (Tables 6.1, 6.2, 6.3, 6.4, 6.5, 6.6, 6.7, 6.8 and 6.9).

The dataset from a patient cohort seen in an old age psychiatry memory clinic (Hancock and Larner 2015; Sect. 5.2.4) permitted a further weighted comparison of MMSE and ACE-R in an independent cohort (n = 181) to be undertaken, with results akin to that from the CFC study (Larner and Hancock 2014; compare Tables 6.1 and 6.10).

Table 6.1 Weighted comparison ACE-R vs. MMSE for diagnosis of dementia (adapted from Larner 2013b; data from Larner 2009, 2013a)

	ACE-R	MMSE
Sensitivity (Se)	0.87	0.70
Specificity (Sp)	0.91	0.89
AUC ROC	0.94	0.91
Prevalence of dementia (π)	0.35	
ΔSensitivity	0.17	
ΔSpecificity	0.02	
Weighted comparison (WC)	0.17 = net benefit	
Equivalent increase (EI)	+61	

Table 6.2 Weighted comparison MoCA vs. MMSE for diagnosis of any cognitive impairment (adapted from Larner 2013b; data from Larner 2012b)

	MoCA	MMSE
Sensitivity (Se)	0.97	0.65
Specificity (Sp)	0.60	0.89
AUC ROC	0.91	0.83
Prevalence of cognitive impairment (π)	0.43	
ΔSensitivity	0.32	
ΔSpecificity	−0.29	
Weighted comparison (WC)	0.28 = net benefit	
Equivalent increase (EI)	+121	

Table 6.3 Weighted comparison TYM vs. MMSE for diagnosis of dementia (adapted from Larner 2013b; data from Hancock and Larner 2011)

	TYM	MMSE
Sensitivity (Se)	0.73	0.79
Specificity (Sp)	0.88	0.95
AUC ROC	0.89	0.94
Prevalence of dementia (π)	0.35	
ΔSensitivity	−0.06	
ΔSpecificity	−0.07	
Weighted comparison (WC)	−0.07 = net loss	
Equivalent increase (EI)	−26	

Table 6.4 Weighted comparison MMP vs. MMSE for diagnosis of dementia (adapted from Larner 2013b; data from Larner 2012c)

	MMP	MMSE
Sensitivity (Se)	0.51	0.45
Specificity (Sp)	0.97	0.98
AUC ROC	0.89	0.87
Prevalence of dementia (π)	0.23	
ΔSensitivity	0.06	
ΔSpecificity	−0.01	
Weighted comparison (WC)	0.06 = net benefit	
Equivalent increase (EI)	+13	

Table 6.5 Weighted comparison 6CIT vs. MMSE: (a) for diagnosis of dementia vs. no dementia (n = 150); (b) for diagnosis of dementia vs. MCI (n = 65); (c) for diagnosis of MCI vs. subjective memory complaint (n = 128) (adapted from Abdel-Aziz and Larner 2015)

	6CIT	MMSE
(a)		
Sensitivity (Se)	0.77	0.59
Specificity (Sp)	0.80	0.85
Prevalence of dementia (π)	0.147	
ΔSensitivity	0.18	
ΔSpecificity	−0.05	
Weighted comparison (WC)	0.15 = net benefit	
Equivalent increase (EI)	+22	
(b)		
Sensitivity	0.77	0.59
Specificity	0.65	0.74
Prevalence of dementia (π)	0.338	
ΔSensitivity	0.18	
ΔSpecificity	−0.09	
WC	0.16 = net benefit	
EI	+55	
(c)		
Sensitivity	0.56	0.51
Specificity	0.71	0.75
Prevalence of MCI (π)	0.336	
ΔSensitivity	0.05	
ΔSpecificity	−0.04	
WC	0.04 = net benefit	
EI	+14	

Table 6.6 Weighted comparison MACE (cut-off ≤25/30) vs. MMSE (cut-off ≤24/30): (a) for diagnosis of dementia vs. no dementia (n = 135); (b) for diagnosis of MCI vs. subjective memory complaint (n = 111) (adapted from Larner 2015a)

	MACE	MMSE
(a)		
Sensitivity (Se)	1.00	0.92
Specificity (Sp)	0.28	0.72
Prevalence of dementia (π)	0.177	
ΔSensitivity	0.08	
ΔSpecificity	−0.45	
Weighted comparison (WC)	−0.13 = net loss	
Equivalent increase (EI)	−22	
(b)		
Sensitivity	1.00	0.54
Specificity	0.43	0.86
Prevalence of MCI (π)	0.35	
ΔSensitivity	0.46	
ΔSpecificity	−0.43	
WC	0.38 = net benefit	
EI	+133	

Table 6.7 Weighted comparison TYM vs. ACE-R (adapted from Hancock and Larner 2011, corrected from Larner 2014a:137)

	TYM	ACE-R
Sensitivity (Se)	0.73	0.90
Specificity (Sp)	0.88	0.93
AUC ROC	0.89	0.98
Prevalence of dementia (π)	0.35	
ΔSensitivity	−0.17	
ΔSpecificity	−0.05	
Weighted comparison (WC)	−0.18 = net loss	
Equivalent increase (EI)	−63	

Table 6.8 Weighted comparison MACE (cut-off ≤25/30) vs. MoCA (cut-off ≥26/30): (a) for diagnosis of dementia vs. no dementia (n = 260); (b) for diagnosis of MCI vs. subjective memory complaint (n = 217) (adapted from Larner 2017a)

	MACE	MoCA
(a)		
Sensitivity (Se)	0.98	1.00
Specificity (Sp)	0.35	0.31
Prevalence of dementia (π)	0.17	
ΔSensitivity	−0.02	
ΔSpecificity	0.04	
Weighted comparison (WC)	−0.00047 = net loss	
Equivalent increase (EI)	< −1 (= −0.08)	
(b)		
Sensitivity	0.95	0.92
Specificity	0.51	0.44
Prevalence of MCI (π)	0.29	
ΔSensitivity	0.03	
ΔSpecificity	0.07	
WC	0.047 = net benefit	
EI	+14	

Table 6.9 Weighted comparison AD8 vs. (a) MMSE (n = 125), and (b) 6CIT (n = 169) for diagnosis of cognitive impairment vs. no cognitive impairment (adapted from Larner 2015c)

(a)

	AD8	MMSE
Sensitivity (Se)	0.97	0.53
Specificity (Sp)	0.15	0.75
Prevalence of cognitive impairment (π)	0.576	
ΔSensitivity	0.44	
ΔSpecificity	−0.60	
Weighted comparison (WC)	0.40 = net benefit	
Equivalent increase (EI)	+230	

(b)

	AD8	6CIT
Sensitivity	0.96	0.72
Specificity	0.17	0.55
Prevalence of cognitive impairment (π)	0.621	
ΔSensitivity	0.24	
ΔSpecificity	−0.38	
WC	0.22 = net benefit	
EI	+137	

Table 6.10 Weighted comparison ACE-R vs. MMSE for diagnosis of dementia (data adapted from Larner and Hancock 2014)

	ACE-R	MMSE
Sensitivity (Se)	0.82	0.62
Specificity (Sp)	0.89	0.95
Prevalence of dementia (π)	0.276	
ΔSensitivity	0.20	
ΔSpecificity	−0.06	
Weighted comparison (WC)	0.18 = net benefit	
Equivalent increase (EI)	+50	

The various WC and EI findings are summarised in Table 6.11 (Larner 2015d:105). The data suggest that for the diagnosis of dementia ACE-R is superior to MMSE and TYM; for diagnosis of any cognitive impairment MoCA and AD8 are superior to MMSE, and AD8 is superior to 6CIT; and for diagnosis of MCI MACE is superior to MMSE. All WC evaluations were in the same direction as the available values for AUC ROC, i.e. favoured ACE-R, MoCA, MMP, and 6CIT vs. MMSE, favoured MMSE vs. TYM, and favoured ACE-R vs. TYM (Larner 2013b).

The calculation of WC and EI is largely dependent on differences in test sensitivity, which are ultimately dependent on the test cut-off used, like many other measures of discrimination derived from the 2 × 2 table (Sect. 2.3.2). Choice of a different method for determining test cut-off may potentially change the outcome of weighted comparisons, from net benefit to net loss (Larner 2015e).

Table 6.11 Summary of weighted comparison and equivalent increase between CSIs for identification of (a) dementia vs. no dementia, (b) any cognitive impairment (= dementia + MCI) vs. no cognitive impairment, and (c) MCI vs. subjective memory complaint (adapted from Larner 2015d:105)

	Weighted comparison (WC)	Classification	Equivalent increase (EI)
(a)			
ACE-R vs. MMSE	0.17; 0.18	Net benefit	+61; +50
TYM vs. MMSE	−0.07	Net loss	−26
MMP vs. MMSE	0.06	Net benefit	+13
6CIT vs. MMSE	0.15	Net benefit	+22
TYM vs. ACE-R	−0.18	Net loss	−63
MACE vs. MMSE	−0.13	Net loss	−22
MACE vs. MoCA	−0.00047	Net loss	< −1
(b)			
MoCA vs. MMSE	0.28	Net benefit	+121
AD8 vs. MMSE	0.40	Net benefit	+228
AD8 vs. 6CIT	0.22	Net benefit	+137
(c)			
6CIT vs. MMSE	0.04	Net benefit	+14
MACE vs. MMSE	0.38	Net benefit	+133
MACE vs. MoCA	0.047	Net benefit	+14

6.1.2 Q* Index

Another potentially useful summary measure denoting the diagnostic value of a screening instrument is the Q* index derived from the ROC curve (Walter 2002). Q* index is defined as the "point of indifference on the ROC curve", where the sensitivity and specificity are equal, or, in other words, where the probabilities of incorrect test results are equal for disease cases and non-cases (i.e. indifference between false positive and false negative diagnostic errors, with both assumed to be of equal value/cost). The Q* index is that point in ROC space which is closest to the ideal top left-hand ("northwest") corner of the ROC curve, where the anti-diagonal through ROC space intersects the ROC curve (Fig. 6.1).

Q* index was derived for a number of CSIs examined in pragmatic diagnostic test accuracy studies undertaken in CFC (Larner 2015f; Table 6.12). Q* index ranged from 0.88 for ACE-R to 0.76 for MACE. The ranking of Q* index for the various CSIs examined paralleled that for AUC ROC, with ACE-R ranked highest and MACE lowest using either parameter.

Comparing the Q* index cut-off point with cut-offs defined in CSI index studies, the former was always lower (and hence less sensitive but more specific) than the latter. Comparing test sensitivity and specificity at the Q* index cut-off point showed that for all CSIs with the exception of ACE-R, Q* index-derived test cut-offs lay between those derived from maximal correct classification accuracy and maximal Youden index. Hence, if Q* index point were used as the test cut-off, it was more

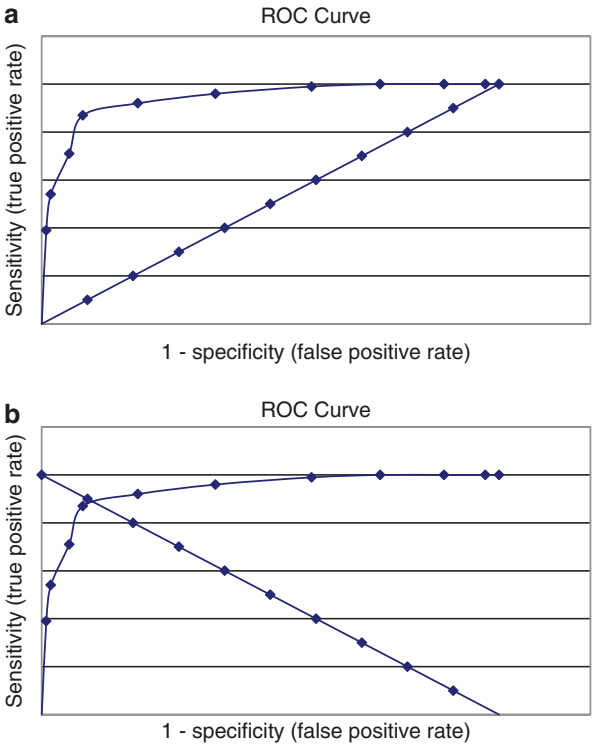

Fig. 6.1 (**a**) Typical receiver operating characteristic (ROC) curve or plot with diagonal or chance line (data for ACE-R adapted from Larner 2009, 2013b, see Fig. 4.4) reprinted with permission; (**b**) typical ROC curve (same data points as a) with anti-diagonal line: where the lines cross in ROC space indicates equal test sensitivity and specificity, by definition the Q* index (the point closest to the ideal top left-hand corner of the ROC curve) (Larner 2015f) reprinted with permission

Table 6.12 Summary of Q* index for various CSIs compared with area under the receiver operating characteristic curve (AUC ROC) (adapted from Larner 2015f)

CSI	Q* index (ranking)	AUC ROC (95% CI) (ranking)	Reference
MMSE	0.82 (2)	0.91 (0.88–0.95) (2=)	Larner (2013b)
ACE-R	0.88 (1)	0.94 (0.91–0.97) (1)	Larner (2013b)
MoCA	0.79 (4)	0.91 (0.86–0.95) (2=)	Larner (2012b)
TYM	0.80 (3)	0.89 (0.84–0.93) (4)	Hancock and Larner (2011)
MACE	0.76 (5)	0.86 (0.83–0.90) (5)	Larner (2015a)

sensitive (and less specific) than if using the maximal correct classification accuracy cut-off, and less sensitive (and more specific) than if using the maximal Youden index cut-off. Q* index cut-offs reduced the sensitivity of very sensitive tests such as the ACE-R, MoCA, TYM and MACE ≤25/30, but improved sensitivity for very specific tests such as MACE ≤21/30 (Larner 2015f).

If a metric to compare diagnostic tests is required, Q* index has merit and, since it is based on sensitivity and specificity, may perhaps be preferred to AUC ROC results as a more intuitive measure.

6.1.3 Comparing Test Speed Versus Test Accuracy

The trade-off between speed and accuracy in the performance of voluntary movements, such that more accurate movements are performed more slowly, has long been recognised (Woodworth 1899). This speed-accuracy trade-off may perhaps apply to any task, and since speed is inversely proportional to time it may also be formulated as a time-accuracy trade-off, longer times being required for greater accuracy.

Is there is a trade-off between CSI diagnostic accuracy and administration time, or in other words are shorter CSIs less accurate than longer ones which may sample more cognitive domains and/or in greater depth? This was examined for a number of CSIs used in CFC by comparing parameters of test diagnostic accuracy against duration of test administration. The latter is not routinely measured in the clinical setting (there are exceptions when a stopwatch has been used, but this is usually for research purposes; Lees et al. 2017), although approximate timings can be given (see Sect. 2.1.3, Box 2.1). Hence, more easily accessible surrogate measures of test duration were used, namely either the overall test score or the total number of items/questions in the test (Larner 2015g, h).

Two measures of diagnostic accuracy, the correct classification accuracy or overall test accuracy (defined as the sum of true positives and true negatives divided by the total number of patients tested; Sect. 2.3.2, Box 2.3) and the area under the receiver operating characteristic curve (AUC ROC) were plotted (= output or effect, hence the dependent variable, y axis) against overall test score and against the total number of items/questions in the test (= inputs or causes, hence independent variables, x axis). Correlations between correct classification accuracy and AUC ROC and the surrogate time measures were also calculated.

Data (Table 6.13) were extracted from several pragmatic prospective diagnostic test accuracy studies examining nine performance-based CSIs: Addenbrooke's Cognitive Examination (ACE), Addenbrooke's Cognitive Examination-Revised (ACE-R), DemTect, Mini-Addenbrooke's Cognitive Examination (MACE), Mini-Mental Parkinson (MMP), Mini-Mental State Examination (MMSE), Montreal Cognitive Assessment (MoCA), Six-item Cognitive Impairment Test (6CIT), and the Test Your Memory (TYM) test (see Chap. 4 for index studies).

Correct classification accuracy was positively correlated with both total test score ($r = 0.58$) and with total number of test items/questions ($r = 0.66$). Both correlations were classified as moderate, and respectively either did not reach statistical significance ($t = 1.89$, df = 7, $p > 0.1$) or showed a trend towards significance ($t = 2.33$, df = 7, $0.1 > p > 0.05$).

AUC ROC curve was positively correlated with total test score ($r = 0.83$; Fig. 6.2) and with total number of test items/questions ($r = 0.79$; Fig. 6.3). Both correlations were classified as high and both reached statistical significance ($t = 3.86$, df = 7, $p < 0.01$; and $t = 3.46$, df = 7, $p < 0.02$, respectively).

These analyses suggested that there is a trade-off for CSIs between two surrogate measures of duration of test administration and two measures of test diagnostic accuracy. Investing more time during the clinical encounter in administering longer CSIs might therefore pay dividends in terms of improved accuracy of dementia

Table 6.13 Approximate administration time for cognitive screening instruments (CSIs) and surrogate measures thereof (total test score, total number of test items/questions) with diagnostic accuracy (overall correct classification and area under ROC curve) for diagnosis of dementia (adapted from Larner 2015h)

CSI	Approximate, estimated, administration time (min)	Total test score	Number of test items or questions	Accuracy (95% CI)	AUC ROC (95% CI)	Data source
ACE	15–20	100	52	0.84 (0.80–0.88)	0.93 (0.90–0.96)	Larner (2007a)
ACE-R	15–20	100	66	0.89 (0.85–0.93)	0.94 (0.91–0.97)	Larner (2013a)
DemTect	8–10	18	13	0.78 (0.71–0.86)	0.87 (0.80–0.93)	Larner (2007b)
MACE	5–10	30	10	0.84 (0.78–0.91)	0.86 (0.83–0.90)	Larner (2015a)
MMP	5–10	32	23	0.86 (0.81–0.91)	0.89 (0.84–0.94)	Larner (2012c)
MMSE	5–10	30	21	0.86 (0.81–0.90)	0.87 (0.81–0.92)	Larner (2012c)
MoCA	10–15	30	22	0.81 (0.75–0.88)	0.91 (0.86–0.95)	Larner (2012b)
6CIT	2–3	28	7	0.80 (0.75–0.85)	0.90 (0.85–0.95)	Abdel-Aziz and Larner (2015)
TYM	5–10 (self-administered under medical supervision)	50	25	0.83 (0.78–0.88)	0.89 (0.84–0.93)	Hancock and Larner (2011)

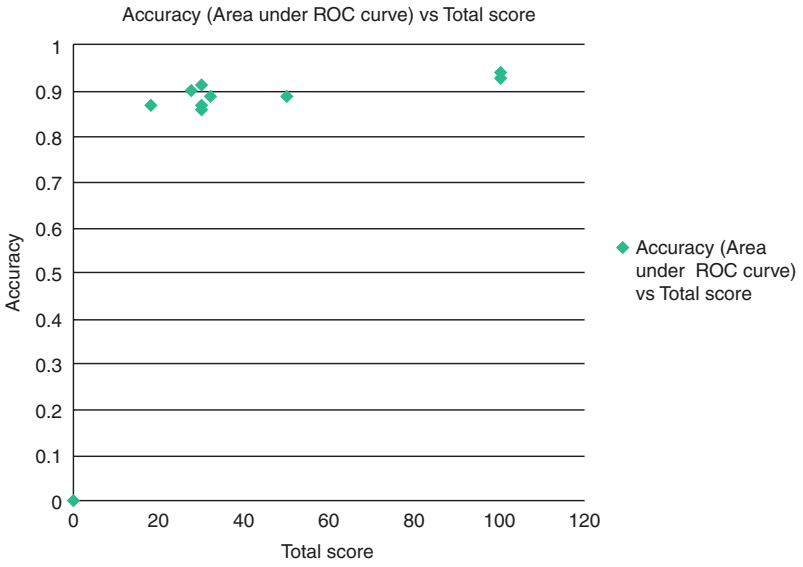

Fig. 6.2 Scatter plot of area under ROC curve (= measure of accuracy) versus total test score (= surrogate measure of test administration time) (adapted from Larner 2015h) reprinted with permission

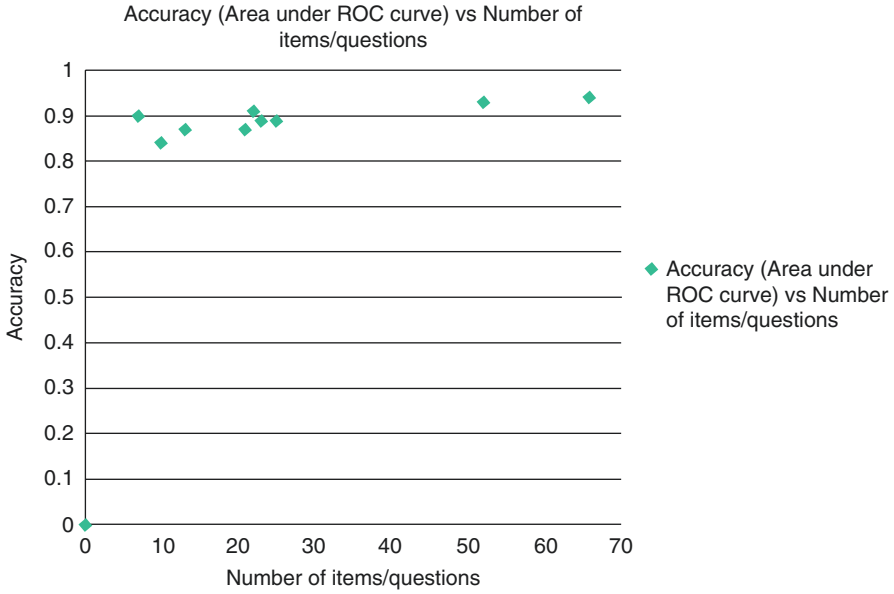

Fig. 6.3 Scatter plot of area under ROC curve (= measure of accuracy) versus total number of test items/questions (= surrogate measure of test administration time) (adapted from Larner 2015h) reprinted with permission

diagnosis. In light of these findings it might be argued on pragmatic grounds that a policy of longer outpatient clinic appointments in clinic templates (Sect. 2.1.3) for patients with cognitive complaints (e.g. 45–60 min), as compared to general neurology outpatient appointments (e.g. 15–30 min), is justified in order to permit adequate time for the administration of longer CSIs to facilitate the desired outcome of more accurate diagnosis. To borrow informally an analogy from science and engineering, there may be a lower "signal to noise ratio" when using longer CSIs (where the delivered strength of "signal" is related to statistical significance, and "noise" to standard deviation) due to their increased "bandwidth" (i.e. broader range of test scores or items) (Larner 2015h). The greater neuropsychological coverage of longer CSIs, one of the desiderata suggested by expert consensus (Malloy et al. 1997), may reduce test ceiling and floor effects.

6.1.4 Meta-Analysis: ACE and ACE-R

Meta-analysis is now a standard statistical approach to combine the results of multiple studies to improve estimates of effect size or resolve uncertainties when individual results disagree.

A meta-analysis of studies was undertaken to better understand ACE (Mathuranath et al. 2000; Sect. 4.1.5.1) and ACE-R (Mioshi et al. 2006; Sect. 4.1.5.3) utility (Larner and Mitchell 2014), using methods similar to those applied in previous meta-analyses of MMSE diagnostic accuracy (Mitchell 2009, 2013, 2017).

Literature search to end May 2013 identified 29 reports of studies of the ACE, 13 using the English version and 16 using non-English versions. All the studies identified were from high prevalence specialist secondary care settings. After application of exclusion criteria, 5 ACE studies were deemed suitable for meta-analysis (Mathuranath et al. 2000; Garcia-Caballero et al. 2006; Larner 2007a; Stokholm et al. 2009; Yoshida et al. 2011). Across the 5 included studies there were 529 cases of dementia out of a population of 1090, a prevalence of 49%. There was no evidence of publication bias (Harbord bias = −8.23, 95% CI = −29.1 to 12.6, $p = 0.37$; Harbord et al. 2006).

Pooling the raw data from these studies demonstrated that 512 out of 529 cases were correctly identified using the ACE, giving a pooled sensitivity of 0.968. On meta-analytic weighting this was corrected to 0.969 (95% CI = 0.927 to 0.994). Non-cases (377) were correctly ruled-out from a sample of 561 comparison subjects to give a pooled specificity of 0.672. On meta-analysis this was corrected to 0.774 (95% CI = 0.583 to 0.918). Unadjusted the PPV was therefore 0.747 and the NPV 0.955 (Larner and Mitchell 2014).

Literature search to end May 2013 identified 31 reports of studies of the ACE-R, 16 using the English version and 15 using non-English versions. All the studies identified were from high prevalence specialist secondary care settings. After application of exclusion criteria, 5 studies were deemed suitable for meta-analysis (Mioshi et al. 2006; Larner 2009, 2013a; Alexopoulos et al. 2010; Yoshida et al. 2012; Dos Santos Kawata et al. 2012). Across the 5 included studies there were 560 cases of dementia out of a population of 1156, a dementia prevalence of 48%. Harbord bias was not significant (0.097, 95% CI = −18.95 to 19.14, $p = 0.99$; Harbord et al. 2006).

Pooling the raw data from these studies demonstrated that 514 out of 560 cases were correctly identified using the ACE-R, giving a pooled sensitivity of 0.918. This was adjusted on meta-analysis to 0.957 (95% CI = 0.922 to 0.982). Non-cases (383) were correctly ruled-out from a sample of 596 comparison subjects to give a pooled specificity of 0.643. This was corrected on meta-analysis to 0.875 (95% CI = 0.638 to 0.994). Unadjusted the PPV was therefore 0.707 and the NPV 0.893 (Larner and Mitchell 2014).

Combining the studies (n = 9) which used the MMSE against either the ACE (n = 5) or ACE-R (n = 4) generated a pooled MMSE sensitivity of 0.920 (95% CI = 0.849 to 0.968) and specificity of 0.869 (95% CI = 0.805 to 0.921) (Larner and Mitchell 2014), inverting the pattern of low sensitivity and high specificity typically seen in diagnostic test accuracy studies of MMSE (see Sect. 4.1.1; Tables 4.1–4.7).

6.1.5 Effect Size (Cohen's d)

Effect size may be denoted by a variety of summary indices, of which Cohen's d is probably the most commonly used in the medical literature (Cohen 1988). This parameter is calculated as the difference of the means of two groups divided by the weighted pooled standard deviations of the groups (see Sect. 2.3.2, Fig. 2.2). Cohen

(1988, 1992) suggested that effect sizes of 0.2 to 0.3 were small, 0.5 medium, and ≥0.8 large.

Effect size (Cohen's d) for a number of the CSIs examined in CFC has been calculated (Larner 2014b, 2016b) based on data from previous pragmatic diagnostic accuracy studies which examined the MMSE, MMP, 6CIT, MoCA, TYM, ACE-R, AD8, and MACE. Mean test scores for demented and non-demented groups, and for mild cognitive impairment and subjective memory complaint groups, along with their standard deviations, were applied to the Cohen's d formula to calculate effect sizes.

Comparing patients with dementia and no dementia suggested large but similar effect sizes for all of the CSIs examined (Table 6.14). These values suggested a consistent difference in test scores between demented and non-demented individuals.

Comparing patients with mild cognitive impairment and no dementia (subjective memory complaint) suggested smaller effect sizes for all of the CSIs examined than in the dementia versus no dementia distinction (Table 6.15). However, effect sizes for the MoCA and MACE were larger than for other tests. These values suggested a

Table 6.14 Effect size (Cohen's d) for diagnosis of dementia versus no dementia (MCI + SMC) (adapted from Larner 2014b, 2015d:99)

CSI	Cohen's d	Study
ACE-R	1.87 (large)	Larner and Hancock (2014)
AD8	0.84 (large)	Larner (2015c)
MACE	1.52, 1.71 (large)	Larner (2015a) and Williamson and Larner (2018)
MMP	1.78 (large)	Larner (2012c)
MMSE	1.48, 1.59, 1.56 (large)	Larner (2012b, c, 2015a)
MoCA	1.80, 2.01 (large)	Larner (2012b, 2017a)
6CIT	1.89 (large)	Abdel-Aziz and Larner (2015)
TYM	1.62 (large)	Hancock and Larner (2011)

Table 6.15 Effect size (Cohen's d) for diagnosis of mild cognitive impairment versus subjective memory complaint (adapted from Larner 2014b, 2015d:99, 2016b)

CSI	Cohen's d	Study
ACE-R	0.73 (medium)	Larner and Hancock (2014)
AD8	0.31 (medium)	Larner (2015c)
MACE	1.59, 1.23 (large)	Larner (2015a) and Williamson and Larner (2018)
MMP	0.81 (large)	Larner (2012c)
MMSE	0.92 (large), 0.69 (medium), 1.26 (large)	Larner (2012b, c, 2015a)
MoCA	1.45, 1.25 (large)	Larner (2012b, 2017a)
s-MoCA	1.19, 1.37	Larner (2017b)
6CIT	0.65 (medium)	Abdel-Aziz and Larner (2015)
TYM	0.48 (medium)	Hancock and Larner (2011)

consistent difference in test scores between MCI and non-demented individuals, but with MoCA and MACE performing best. Since MoCA was designed to identify MCI cases (Nasreddine et al. 2005) this observation might be anticipated.

Looking at subgroups of older people (age ≥ 65 years) suggested larger effect sizes in this at-risk group in these cohorts (Table 6.16, Fig. 6.4; Wojtowicz and Larner 2017).

Table 6.16 Effect size (Cohen's d) for whole cohorts and for older (≥65 years) subgroups for diagnoses of dementia versus MCI and MCI versus SMC (adapted from Wojtowicz and Larner 2017)

	Cohen's d (Effect size)		
	Dementia vs. MCI	MCI vs. SMC	Study
MMSE-all MMSE-old	0.79 (medium) 0.88 (large)	1.03 (large) 1.41 (large)	Larner (2015a, b)
MACE-all MACE-old	1.08 (large) 1.37 (large)	1.11 (large) 1.82 (large)	Larner (2015a, b, 2017a)
MoCA-all MoCA-old	1.42 (large) 1.76 (large)	1.25 (large) 1.72 (large)	Larner (2017a)
6CIT-all 6CIT-old	1.49 (large) 1.79 (large)	0.65 (medium) 0.83 (large)	Abdel-Aziz and Larner (2015)
AD8-all AD8-old	0.71 (medium) 0.90 (large)	0.31 (medium) 0.77 (medium)	Larner (2015c)
s-MoCA-all s-MoCA-old	1.33 (large) 1.46 (large)	1.37 (large) 1.70 (large)	Larner (2017b)

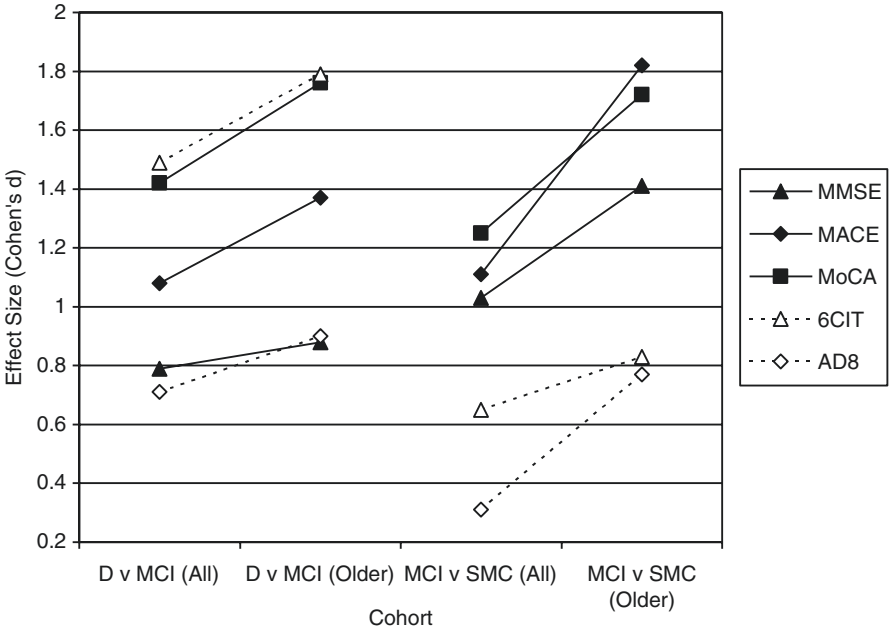

Fig. 6.4 Effect sizes (Cohen's d) for whole cohorts and for older (≥65 years) subgroups for diagnoses of dementia versus MCI and MCI versus SMC (Wojtowicz and Larner 2017) reprinted with permission

6.1.6 Correlation

Calculation of a correlation coefficient (e.g. Pearson product moment correlation coefficient) between the scores of different screening instruments applied to the same population is often performed. In diagnostic test accuracy studies correlation is not necessarily taken to imply causation (unlike research into disease aetiology, although correlation is never equivalent to causality), and hence any correlates of the target disorder may be potentially diagnostically useful, independent of any causal interpretation. Correlation is a measure of the strength of association between datasets, but it is also sometimes incorrectly assumed that high correlations give a measure of how well tests agree. Whilst the potential of a new test may be suggested if it correlates with an existing test, indicating concurrent validity, correlation is not agreement. Indeed, high correlation may in fact mask lack of agreement (Bland and Altman 1986; see Sect. 6.1.8).

Examples of correlations between different CSI scores and between CSI scores and informant and/or non-cognitive screening instruments from studies undertaken in CFC are shown in Tables 6.17 and 6.18. Unsurprisingly CSI scores are generally highly

Table 6.17 Summary of correlation coefficients for different cognitive screening instruments examined in pragmatic diagnostic test accuracy studies in CFC (adapted from Larner 2015d:100)

	r	Performance	*t*	*p*
MMSE - MMP	0.93	High	35.7	<0.001
MMSE - Codex	−0.68	Moderate	6.83	<0.001
MMSE - ACE	0.92	High	28.9	<0.001
MMSE - ACE-R	0.90	High	32.8	<0.001
MMSE - MACE	0.80	High	15.5	<0.001
MMSE - 6CIT	−0.73	High	13.0	<0.001
MMSE - DemTect	0.76	High	12.0	<0.001
MMSE - MoCA	0.85	High	19.2	<0.001
MMSE - TYM	0.81	High	19.9	<0.001
MMSE - H-TYM	0.22	Low	1.37	$0.1 > p > 0.05$
MMSE - s-MoCA	0.80	High	16.2	<0.001
6CIT - MACE	−0.81	High	6.56	<0.001
6CIT - H-TYM	−0.45	Low	2.55	<0.02
DemTect - ACE	0.79	High	12.5	<0.001
ACE-R - TYM	0.86	High	20.0	<0.001
MACE - MoCA	0.83	High	24.2	<0.001
MACE - s-MoCA	0.79	High	20.4	<0.001
MACE - Free-Cog[a]	0.91	High	9.25	<0.001
MoCA - s-MoCA	0.95	High	48.0	<0.001

MMSE Mini-Mental State Examination; *MMP* Mini-Mental Parkinson; *ACE* Addenbrooke's Cognitive Examination; *ACE-R* Addenbrooke's Cognitive Examination-Revised; *MACE* Mini-Addenbrooke's Cognitive Examination; *6CIT* Six-Item Cognitive Impairment Test; *MoCA* Montreal Cognitive Assessment; *TYM* Test Your Memory (TYM) test; *H-TYM* Hard Test Your Memory (TYM) test; *s-MoCA* short Montreal Cognitive Assessment

[a]Preliminary data

Table 6.18 Summary of correlation coefficients for different cognitive and informant and/or non-cognitive screening instruments examined in pragmatic diagnostic test accuracy studies in CFC (adapted from Larner 2015d:101)

	r	Performance	*t*	*p*
MMSE - IQCODE	−0.37	Low	4.49	< 0.001
MMSE - PHQ-9	0.01	Very low	0.08	> 0.5
MMSE - FCS	−0.10	Very low	0.45	> 0.5
MMSE - CSDD	0.12	Very low	1.85	$0.1 > p > 0.05$
MMSE - AD8	−0.23	Very low	2.62	≈ 0.01
MMSE - ZBI (full)	0.017	Very low	0.10	> 0.5
ACE-R - IADL	0.58	Moderate	6.25	< 0.001
ACE-R - IQCODE	−0.46	Low	5.46	< 0.001
ACE-R - PHQ-9	0.12	Very low	1.19	> 0.1
ACE-R - CSDD	0.26	Very low	3.62	< 0.001
MACE - ZBI (full)	−0.008	Very low	0.047	> 0.5
6CIT - AD8	0.37	Low	5.08	< 0.001

MMSE Mini-Mental State Examination; *IQCODE* Informant Questionnaire on Cognitive Decline in the Elderly; *PHQ-9* Patient Health Questionnaire-9; *FCS* Fluctuations Composite Scale; *CSDD* Cornell Scale for Depression in Dementia; *ZBI* Zarit Burden Interview; *ACE-R* Addenbrooke's Cognitive Examination-Revised; *IADL* Instrumental Activities of Daily Living (IADL) Scale; *MACE* Mini-Addenbrooke's Cognitive Examination; *6CIT* Six-Item Cognitive Impairment Test

correlated, indicating concurrent validity, whereas CSI and non-CSI scores are generally less well correlated, indicating that these tests may examine different constructs.

6.1.7 Cohen's Kappa Statistic: Test of Agreement

The "test of agreement" or Cohen's kappa statistic (Cohen 1960) compares observed diagnostic agreement with that expected by chance alone (i.e. chance corrected agreement; see Sect. 2.3.3). This metric has sometimes been used to compare diagnostic tests (Table 6.19), although it is a measure of precision rather than of accuracy.

6.1.8 Bland-Altman Limits of Agreement

As previously mentioned (Sect. 6.1.6), correlation between test scores may indicate concurrent validity, but correlation is not agreement and indeed high correlation may actually mask lack of agreement. Bland and Altman (1986) suggested a method which provides a measure of agreement between tests by estimating how far apart the two values are on average and putting an interval around this (see Sect. 2.3.3). The limits of agreement thus defined indicate how closely two methods agree, but what is accepted as "close" remains a clinical rather than a statistical judgement. The Bland Altman methodology is a simple way to evaluate bias between mean differences which avoids the potentially erroneous conclusions based on correlation analyses.

Table 6.19 Summary of Cohen's kappa statistic (test of agreement) for different cognitive screening instruments examined in pragmatic diagnostic test accuracy studies (adapted from Larner 2015d:102)

	κ	Agreement
MMSE - ACE-R	0.72 (0.63–0.81)	Substantial
MMSE - MACE	0.44 (0.29–0.59)	Moderate
MMSE - 6CIT	0.47 (0.29–0.63)	Moderate
MMSE - MoCA	0.39 (0.26–0.53)	Fair
MMSE - TYM	0.69 (0.58–0.80)	Substantial
MMSE - IQCODE	0.23 (0.07–0.39)	Fair
MMSE - AD8	−0.05 (−0.20–0.10)	None
ACE-R - TYM	0.69 (0.56–0.83)	Substantial
ACE-R - IQCODE	0.29 (0.11–0.46)	Fair
ACE-R - IADL	0.38 (0.18–0.58)	Fair
6CIT - AD8	0.10 (−0.08–0.28)	Slight

MMSE Mini-Mental State Examination; *ACE-R* Addenbrooke's Cognitive Examination-Revised; *M-ACE* Mini-Addenbrooke's Cognitive Examination; *6CIT* Six-Item Cognitive Impairment Test; *MoCA* Montreal Cognitive Assessment; *TYM* Test Your Memory (TYM) test; *IQCODE* Informant Questionnaire on Cognitive Decline in the Elderly; *IADL* Instrumental Activities of Daily Living (IADL) Scale

Table 6.20 Limits of agreement (with 95% confidence intervals) and Pearson's product moment correlation coefficients (*r*) for different cognitive screening instruments (adapted from Larner 2016c)

	n	Mean difference (d)	Standard deviation of difference (s)	Limits of agreement (d ± 2s)	*r*
MMSE-MoCA	147	3.61 (3.15–4.07)	2.83	−2.05 (−2.85 to 0.59) to 9.28 (8.48 to 10.1)	0.85
MMSE-MACE	244	4.00 (3.52–4.47)	3.77	−3.55 (−4.37 to −2.72) to 11.54 (10.7 to 12.4)	0.81
MACE-MoCA	193	0.61 (0.20–1.03)	2.92	−5.23 (−5.95 to −4.51) to 6.45 (5.73 to 7.17)	0.86

MMSE Mini-Mental State Examination; *MoCA* Montreal Cognitive Assessment; *MACE* Mini-Addenbrooke's Cognitive Examination

Bland Altman methodology was used to calculate limits of agreement for three brief CSIs (MMSE, MoCA, MACE) which were contrasted with Pearson product moment correlation coefficients between test scores (Larner 2016c). Mean differences between test scores were small (<1 for MACE versus MoCA, up to 4 for MMSE versus MACE) but the calculated limits of agreement were broad (>10 points for MMSE versus MoCA and MACE versus MoCA; and >15 points for MMSE versus MACE). Test scores were highly correlated ($r > 0.8$) in all the studies (Table 6.20). Bland-Altman plot of difference against mean for the comparison of MMSE versus MACE is shown in Fig. 6.5.

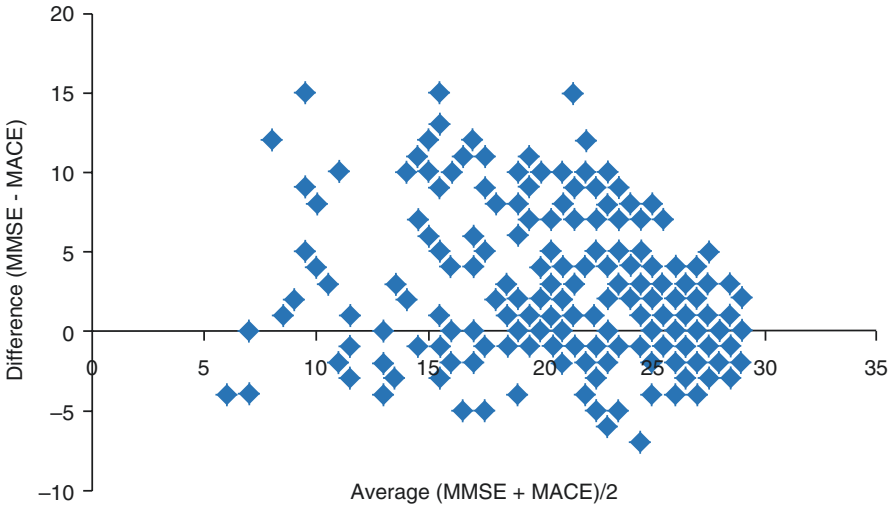

Fig. 6.5 Bland-Altman plot of difference against mean for MMSE versus MACE (Larner 2016c; data from Larner 2015a, b; n = 244) reprinted with permission

6.2 Combining Screening Instruments

The expectation that a single screening instrument might be entirely adequate for the diagnosis of a multidimensional construct such as the dementia syndrome, with the changes in symptomatology which occur in that syndrome over time, is likely to be wishful thinking. Different methods in staging dementia are recognised to give different results, with moderate to fair correlation of clinical scales and MMSE but a much greater dispersion of functional capacity as measured by the Instrumental Activities of Daily Living (IADL) Scale, indicating that factors other than dementia severity influence functional capacity (Juva et al. 1994). Hence combinations of tests, perhaps addressing the different domains (cognitive; functional, behavioural, global; see Chaps. 4 and 5 respectively) might be desirable, as may combinations of patient and informant information. Combinations of test results have been examined on occasion and found to give "added value" in some instances (e.g. Mackinnon et al. 2003; De Lepeleire et al. 2005).

As previously mentioned (see Sect. 2.3.2), when using screening instruments there is always a balance or trade-off to be struck between test sensitivity and specificity, with the chosen test cut-off being determined by the needs of the particular clinical situation. To optimise this trade-off, combinations of tests may be required. For example, ACE VLOM ratio showed poor sensitivity but

good specificity for the diagnosis of FTLD (see Sect. 4.1.5.2), principally because cases of bvFTD were missed (Bier et al. 2004), so combination with the Frontal Assessment Battery (FAB; see Sect. 4.2.1), which is highly sensitive for bvFTD, might be appropriate. FAB may therefore be useful as a situation-specific clinical assessment when a diagnosis of bvFTD is being considered. Use of the semantic index subscore of the ACE is appropriate if semantic dementia is being considered in the differential diagnosis (Sect. 4.1.5.2). Studies in CFC have not encouraged the view that the Ala subscore is useful prospectively for the diagnosis of DLB (Sect. 4.1.1.1), likewise the modified Ala (Sect. 4.1.5.2) and MoCA Ala (Sect. 4.1.8.1). The Mayo Fluctuations Questionnaire might be considered if DLB or PDD enters in the differential diagnosis (Ferman et al. 2004; Larner 2012d; see Sect. 5.4.3).

Following the methodology of Flicker et al. (1997), tests may be combined either in series (both tests required to be positive before a diagnosis of dementia is made: the "And" rule) or in parallel (either test positive sufficient for a diagnosis of dementia to be made: "Or" rule); in other words, respectively, sequency and simultaneity.

6.2.1 Combining Cognitive Screening Instruments: MMSE and MoCA

The combination of the MMSE and the Clock Drawing Test ("Mini-clock") has been reported to improve detection of mild AD and MCI (Cacho et al. 2010). Since MMSE (Folstein et al. 1975) has high specificity (see Sect. 4.1.1) and the Montreal Cognitive Assessment (MoCA; Nasreddine et al. 2005) has high sensitivity (see Sect. 4.1.8) for dementia diagnosis, the effect of combining these two cognitive screening instruments has been investigated (Larner 2012b).

In patients administered both MoCA and MMSE (n = 148), combining the tests in series ("And" rule) gave results almost identical to those using the MMSE alone, whilst combining tests in parallel ("Or" rule) gave results almost identical to those using the MoCA alone (Table 6.21; compare with Tables 4.23 and 4.24). In other words, MoCA "and" MMSE was less sensitive, missing a significant proportion of the dementia and MCI cases (35% of cases) but with few false positives, whereas MoCA "or" MMSE identified almost all the cases of dementia and MCI but with a large number of false positives (greater sensitivity).

The combination of these cognitive screening instruments therefore seems to offer little over and above their individual use (Larner 2012b). An item analysis of the MoCA and the MMSE (Damian et al. 2011) indicated that not all subtests were of equal predictive value, and that a selection of MoCA and MMSE items with high predictive value might engender a more useful hybrid test, although to the author's knowledge this has yet to be examined.

Table 6.21 Diagnostic parameters for MMSE + MoCA in both series and parallel paradigms for diagnosis of any cognitive impairment (dementia + MCI) vs. no cognitive impairment (adapted from Larner 2012b)

	MoCA	
N	150	
F:M (% female)	57:93 (38)	
Age range (years)	20–87 (median 61)	
Prevalence of cognitive impairment (dementia + MCI) (= pre-test probability)	0.43 (0.24 + 0.19)	
Pre-test odds = prevalence/(1 – prevalence)	0.75	
	Series: MoCA ≥ 26/30 + MMSE ≥ 26/30	**Parallel: MoCA ≥ 26/30 + MMSE ≥ 26/30**
Accuracy	0.80 (0.74–0.87)	0.75 (0.67–0.83)
Net reclassification improvement (NRI)	0.37	0.32
Sensitivity (Se)	0.65 (0.53–0.77)	0.97 (0.92–1.00)
Specificity (Sp)	0.92 (0.86–0.98)	0.59 (0.48–0.69)
Y	0.57	0.56
PPV (= post-test probability)	0.85 (0.75–0.95)	0.64 (0.54–0.73)
NPV	0.78 (0.70–0.86)	0.96 (0.91–1.00)
PSI	0.63	0.60
LR+	7.90 (3.79–16.5) = moderate	2.35 (1.82–3.04) = small
LR−	0.38 (0.18–0.79) = small	0.05 (0.04–0.07) = large
DOR	20.8 (9.97–43.2)	43.6 (33.7–56.4)
Post-test odds (= pre-test odds × LR+)	5.93	1.76
CUI+	0.56 (adequate)	0.62 (adequate)
CUI−	0.72 (good)	0.57 (adequate)

6.2.2 Combining Informant and Cognitive Screening Instruments

The Alzheimer Association has recommended the combined use of an informant interview with a performance measurement to detect dementia most efficiently (Cordell et al. 2013). Data from CFC which explore such combinations are presented here.

6.2.2.1 IQCODE and MMSE/ACE-R

The combination of an informant scale, the Informant Questionnaire on Cognitive Decline in the Elderly (IQCODE; see Sect. 5.4.1), and a cognitive scale, the MMSE (Sect. 4.1.1), has been previously reported in both community (Mackinnon et al. 2003) and clinical samples (Mackinnon and Mulligan 1998; Abreu et al. 2008;

Narasimhalu et al. 2008), some finding the combination helpful for detection of cases and non-cases (Mackinnon and Mulligan 1998; Mackinnon et al. 2003; Narasimhalu et al. 2008), others not (Abreu et al. 2008). This difference in findings may be related in part to the different casemix in these studies.

Many of the patients in the CFC/Brooker Centre IQCODE study (see Sect. 5.4.1) were administered the MMSE (n = 132) and/or the ACE-R (n = 114) at the same time that an informant completed the IQCODE (Hancock and Larner 2009). The IQCODE and MMSE scores showed a low negative correlation ($r = -0.37$; $t = 4.49$, df = 130, $p < 0.001$). Using the test of agreement (Cohen's kappa statistic; Cohen 1960), $\kappa = 0.23$ (95% CI = 0.07–0.39), where 1 is perfect agreement between tests and 0 is agreement purely due to chance alone. For IQCODE and ACE-R, tests scores showed a low negative correlation ($r = -0.46$; $t = 5.46$, df = 112, $p < 0.001$) with $\kappa = 0.29$ (95% CI = 0.11–0.46).

Results of using IQCODE in combination with either MMSE (n = 132) or ACE-R (n = 114) in series or in parallel (method of Flicker et al. 1997) showed the expected improvement in specificity in the series ("And" rule) paradigm, with some reduction in sensitivity but with improved overall accuracy, PPV, diagnostic odds ratio and positive likelihood ratio (Table 6.22). There was little difference between results combining IQCODE and MMSE versus IQCODE and ACE-R, with a marginal advantage for ACE-R. In the parallel ("Or" rule) paradigm, there was the expected improvement in sensitivity, but with no change in accuracy, specificity or PPV (Hancock and Larner 2009).

Table 6.22 Measures of discrimination for diagnosis of dementia for IQCODE, MMSE, ACE-R, IQCODE + MMSE in series or parallel, and IQCODE + ACE-R in series or parallel (adapted from Hancock and Larner 2009)

	IQCODE ≥ 3.6/5 + MMSE < 24/30 In series (n = 132)	IQCODE ≥ 3.6/5 + MMSE < 24/30 In parallel (n = 132)	IQCODE ≥ 3.6/5 + ACE-R < 73/100 In series (n = 114)	IQCODE ≥ 3.6/5 + ACE-R < 73/100 In parallel (n = 114)
Accuracy	0.75 (0.68–0.82)	0.68 (0.60–0.76)	0.77 (0.69–0.85)	0.65 (0.56–0.74)
Sensitivity (Se)	0.64 (0.51–0.78)	0.95 (0.89–0.99)	0.67 (0.55–0.79)	0.93 (0.87–0.99)
Specificity (Sp)	0.88 (0.80–0.96)	0.36 (0.23–0.48)	0.88 (0.79–0.96)	0.36 (0.23–0.48)
Y	0.52	0.31	0.55	0.29
PPV	0.87 (0.78–0.96)	0.64 (0.55–0.74)	0.85 (0.74–0.95)	0.60 (0.50–0.70)
NPV	0.67 (0.56–0.77)	0.84 (0.70–0.98)	0.72 (0.61–0.83)	0.83 (0.68–0.98)
PSI	0.54	0.48	0.57	0.43
LR+	5.43 (2.65–11.1) = moderate	1.47 (1.20–1.79) = unimportant	5.38 (2.63–11.0) = moderate	1.45 (1.18–1.78) = unimportant
LR−	0.40 (0.20–0.83) = small	0.15 (0.13–0.19) = moderate	0.37 (0.18–0.77) = small	0.19 (0.16–0.24) = moderate
DOR	13.4 (6.56–27.5)	9.53 (7.82–11.6)	14.4 (7.02–29.4)	7.50 (6.10–9.23)
CUI+	0.56 (adequate)	0.61 (adequate)	0.57 (adequate)	0.56 (adequate)
CUI−	0.59 (adequate)	0.30 (very poor)	0.63 (adequate)	0.30 (very poor)

These results were in some ways similar to those of Narasimhalu et al. (2008) who, in an Asian population with low education, found best sensitivity for combined test use with application of the "Or" rule. Overall they found that a "weighted sum" of MMSE and IQCODE produced statistically superior area under the ROC curve and specificity results.

6.2.2.2 AD8 and MMSE/6CIT/MoCA/MACE

The combination of the AD8 informant scale (Galvin et al. 2005, 2006; see Sect. 5.4.2) and a number of cognitive screening instruments has also been examined.

In the AD8 study (Larner 2015c; Table 5.10), AD8 was combined with MMSE and with 6CIT. Combining AD8 with MMSE in series (i.e. both tests required to be positive before a diagnosis of cognitive impairment is made: the "And" rule) showed the expected improvement in specificity (0.83) but with greatly reduced sensitivity (0.50), whereas in parallel (i.e. either test positive sufficient for a diagnosis of cognitive impairment to be made: "Or" rule), sensitivity was maximised (1.0) whilst specificity was very low (0.08). Combining AD8 with 6CIT in series showed reduced sensitivity (0.70) and specificity (0.13) whilst in parallel both sensitivity (0.99) and specificity (0.59) were improved (Table 6.23).

In a subsequent study (Connon and Larner 2017; Larner 2017c), AD8 was combined with either the Montreal Cognitive Assessment (MoCA) or the Mini-Addenbrooke's Cognitive Examination (MACE).

Over a 6-month period (May–October 2016), consecutive new outpatients attending CFC accompanied by a capable informant were administered MoCA whilst the informant completed AD8. Of 46 patient-informant dyads (F:M = 19:27, 41% female; age range 32–88 years, median 64), 13 were diagnosed with dementia (DSM-IV-TR criteria; dementia prevalence = 0.28), 22 had MCI (Petersen criteria; MCI prevalence = 0.67 of non-demented); the remainder (n = 11) were diagnosed with subjective memory complaints (Larner 2017c).

Using test cut-offs for cognitive impairment from index studies (AD8 ≥2/8; MoCA <26/30), standard measures of discrimination were calculated for individual tests and for combinations of AD8 with MoCA in series and in parallel (Table 6.24). Individually both tests were highly sensitive (>0.95) but with low specificity (all ≤0.45). In series combination maintained specificity for little loss of sensitivity. Conversely in parallel combination maintained sensitivity. Predictive values were ≥0.8 for both combinations, with predictive summary index better for parallel combinations.

In 67 patient-informant dyads seen over an 8-month period (May–December 2016; F:M = 33:34, 49% female; age range 26–88 years, median 64), the patients were administered MACE whilst the informants completed AD8 (Connon and Larner 2017). Fourteen patients were diagnosed with dementia (DSM-IV-TR criteria), 32 with MCI (Petersen criteria). Using cut-offs defined in index studies (AD8 ≥2/8; MACE ≤25/30), the measures of discrimination (Table 6.25) showed both instruments were very sensitive (≥0.98) but not specific (≤0.38) for diagnosis of cognitive impairment. In series ("And" rule) combination improved diagnostic specificity for little loss of sensitivity. In parallel ("Or" rule) combination

Table 6.23 Measures of discrimination for diagnosis of cognitive impairment for AD8, MMSE, 6CIT, AD8 + MMSE in series or parallel, and AD8 + 6CIT in series or parallel (adapted and corrected from Larner 2015c)

Test Cut-off N	AD8 ≥2/8 212	MMSE ≤24/30 125	6CIT > 4//28 169	AD8 + MMSE In series 125	AD8 + MMSE In parallel 125	AD8 + 6CIT In series 169	AD8 + 6CIT In parallel 169
Accuracy	0.67	0.62	0.66	0.64 (0.56–0.72)	0.61 (0.52–0.69)	0.49 (0.41–0.56)	0.84 (0.78–0.90)
Sens (Se)	0.97	0.53	0.72	0.50 (0.38–0.62)	1.00	0.70 (0.62–0.79)	0.99 (0.97–1.00)
Spec (Sp)	0.17	0.75	0.55	0.83 (0.73–0.93)	0.08 (0.004–0.15)	0.13 (0.04–0.21)	0.59 (0.47–0.71)
Y	0.14	0.28	0.27	0.33	0.08	−0.17	0.58
PPV	0.65	0.75	0.72	0.80 (0.68–0.92)	0.60 (0.51–0.68)	0.57 (0.48–0.65)	0.80 (0.73–0.87)
NPV	0.78	0.54	0.55	0.55 (0.44–0.66)	1.00	0.21 (0.08–0.33)	0.97 (0.92–1.00)
PSI	0.43	0.29	0.27	0.35	0.60	−0.23	0.77
LR+	1.17	2.15	1.60	2.94 (1.55–5.58) = small	1.08 (1.00–1.17) = unimportant	0.81 (0.69–0.94) = unimportant	2.44 (1.81–3.28) = small
LR−	0.17	0.63	0.51	0.60 (0.32–1.14) = unimportant	0 = large	2.36 (2.02–2.76) = unimportant	0.016 (0.011–0.022) = large
DOR	6.63	3.44	3.16	4.89 (2.58–9.26)	∞	0.34 (0.29–0.40)	152 (113–204.5)
CUI+	0.63	0.39	0.52	0.40 (poor)	0.60 (adequate)	0.40 (poor)	0.79 (good)
CUI−	0.13	0.41	0.30	0.46 (poor)	0.08 (very poor)	0.03 (very poor)	0.58 (adequate)

Table 6.24 Measures of discrimination for diagnosis of cognitive impairment for AD8, MoCA, and AD8 + MoCA (n = 46) in series or parallel (adapted from Larner 2017c)

Test Cut-off	AD8 ≥2/8	MoCA <26/30	AD8 + MoCA In series	AD8 + MoCA In parallel
Accuracy	0.78	0.87	0.85 (0.74–0.95)	0.80 (0.69–0.92)
Sens (Se)	0.97	1.00	0.97 (0.92–1.00)	1.00
Spec (Sp)	0.18	0.45	0.45 (0.16–0.75)	0.18 (0–0.41)
Y	0.15	0.45	0.42	0.18
PPV	0.79	0.85	0.85 (0.74–0.96)	0.80 (0.68–0.91)
NPV	0.67	1.00	0.83 (0.54–1.00)	1.00
PSI	0.46	0.85	0.68	0.80
LR+	1.19	2.20	1.78 (1.04–3.06) = unimportant	1.22 (0.93–1.61) = unimportant
LR−	0.16	0	0.06 (0.04–0.11) = large	0 = large
DOR	7.56	∞	28.3 (16.5–48.7)	∞
CUI+	0.77 (good)	0.85 (excellent)	0.83 (excellent)	0.80 (good)
CUI−	0.12 (very poor)	0.45 (poor)	0.38 (poor)	0.18 (very poor)

Table 6.25 Measures of discrimination for diagnosis of cognitive impairment for AD8, MACE, and AD8 + MACE (n = 67) in series or parallel (adapted from Connon and Larner 2017)

Test Cut-off	AD8 ≥2/8	MACE ≤ 25/30	AD8 + MACE In series	AD8 + MACE In parallel
Accuracy	0.72	0.81	0.81 (0.71–0.90)	0.72 (0.61–0.82)
Sens (Se)	0.98	1.00	0.98 (0.94–1.00)	1.00
Spec (Sp)	0.14	0.38	0.43 (0.22–0.64)	0.10 (0–0.22)
Y	0.12	0.38	0.41	0.10
PPV	0.71	0.78	0.79 (0.68–0.90)	0.71 (0.60–0.82)
NPV	0.75	1.00	0.90 (0.71–1.00)	1.00
PSI	0.46	0.78	0.69	0.71
LR+	1.14	2.63	1.71 (1.18–2.49) = unimportant	1.11 (0.96–1.27) = unimportant
LR−	0.15	0	0.05 (0.03–0.07) = large	0 = large
DOR	7.50	∞	33.8 (23.2–49.0)	∞
CUI+	0.70 (good)	0.78 (good)	0.77 (good)	0.71 (good)
CUI−	0.11 (very poor)	0.38 (poor)	0.39 (poor)	0.10 (very poor)

maximised sensitivity but with poorer specificity. Series combination had better Youden index and correct classification accuracy than parallel combination. Predictive values were >0.7 for both combinations, with predictive summary index marginally better for parallel combination (Table 6.25).

The data from these studies suggested that series combination of AD8 and either MoCA or MACE may improve the balance of sensitivity and specificity for diagnosis of cognitive impairment, principally by improving diagnostic specificity in comparison to the use of individual tests.

6.2.3 Combining Functional and Cognitive Screening Instruments: IADL Scale and ACE-R; Free-Cog

The Instrumental Activities of Daily Living (IADL) Scale and its derivative, the 4-IADL score (see Sect. 5.1.1), are reported to correlate strongly with measures of cognitive function such as the MMSE (Lawton and Brody 1969; Barberger-Gateau et al. 1992; De Lepeleire et al. 2004). MCI patients with impaired IADL have a higher percentage of conversion to AD than MCI patients with preserved IADL (Chang et al. 2011). Hence a combination of functional and cognitive scales might possibly assist in dementia diagnosis.

The combination of a functional scale, IADL Scale, and a cognitive scale, ACE-R, has been examined in a subgroup of patients (n = 79; M:F = 34:45; dementia prevalence = 57%) from the IADL study (see Sect. 5.1.1; Hancock and Larner 2007). Using the same IADL Scale cut-off (≤13/14) as used in that study, sensitivity and specificity for dementia diagnosis were comparable (Se = 0.91 vs. 0.87; Sp = 0.62 vs. 0.50). Using the same ACE-R cut-off (≥73/100) defined in the study of that instrument (see Sect. 4.1.5.3; Larner 2009, 2013a), sensitivity and specificity for dementia diagnosis were comparable (Se = 0.76 vs. 0.87; Sp = 0.91 vs. 0.91). 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) (Larner and Hancock 2012).

Results of using IADL in combination with ACE-R in series or in parallel (as per method of Flicker et al. 1997) showed the expected improvement in specificity in the series ("And" rule) paradigm, along with improved PPV, and positive likelihood ratio, but with loss of sensitivity, negative predictive value and negative likelihood ratio. In the parallel ("Or" rule) paradigm, there was the expected improvement in sensitivity, negative predictive value and negative likelihood ratio, but with loss of specificity, positive predictive value and positive likelihood ratio (Table 6.26). Parallel use might therefore be of possible advantage for increased sensitivity (case finding) (Larner and Hancock 2012).

The Free-Cog scale (Sect. 4.1.10) attempts to incorporate assessment of cognition and function in a single instrument. Preliminary study showed that subscores for the cognitive function and executive function components had only low correlation (r = 0.47; t = 2.24, df = 18, $p < 0.05$), as might be anticipated when testing different constructs.

Table 6.26 Diagnostic parameters for IADL + ACE-R, in both series and parallel paradigms (Larner and Hancock 2012)

	IADL < 14/14 + ACE-R < 73/100 In series	IADL < 14/14 + ACE-R < 73/100 In parallel
Accuracy	0.80 (0.71–0.89)	0.81 (0.72–0.90)
Sensitivity (Se)	0.69 (0.55–0.82)	0.98 (0.93–1.00)
Specificity (Sp)	0.94 (0.86–1.00)	0.59 (0.42–0.75)
Y	0.63	0.57
PPV	0.94 (0.86–1.00)	0.76 (0.65–0.87)
NPV	0.70 (0.56–0.83)	0.95 (0.86–1.00)
PSI	0.64	0.71
LR+	11.7 (3.01–45.6) = large	2.37 (1.59–3.56) = small
LR−	0.33 (0.08–1.29) = small	0.04 (0.03–0.06) = large
DOR	35.4 (9.10–137.9)	62.9 (42.0–94.2)
CUI+	0.65 (good)	0.74 (good)
CUI−	0.65 (good)	0.56 (adequate)

6.3 Converting Cognitive Screening Instrument Scores

The Mini-Mental State Examination (MMSE) has been available for over 40 years and has come to be regarded as the benchmark against which other simple cognitive CSIs are compared. The development of more sensitive CSIs may have reduced the utility of MMSE, as may concerns about infringement of copyright (e.g. Newman and Feldman 2011; Mitchell 2013). However, MMSE test scores may still be used as the indicator or determinant for important clinical decisions in cognitively impaired patients, such as the initiation of prescription of cholinesterase inhibitors and/or memantine.

Different screening instruments measure slightly different things, based on their different item content (Chaps. 4 and 5), but these are all aspects of the construct of cognitive function. Simple methods to convert test scores from one of the commonly administered CSIs to another might therefore be of clinical utility.

One method to do this involves deriving a conversion table of equivalent scores from equipercentile equating with log-linear smoothing (e.g. for MMSE and MoCA: Roalf et al. 2013; van Steenoven et al. 2014). Another method is the calculation of linear regression equations of the form y = a + bx. For example, Kalbe et al. (2004) reported MMSE = 19.997 + 0.567DemTect (other examples: for MMSE and ADAS-Cog, see Doraiswamy et al. 1997; for MMSE and one version of the clock drawing test, see Shua-Haim et al. 1997).

6.3.1 Linear Regression Equations

The datasets of several pragmatic diagnostic test accuracy studies undertaken in CFC (Abdel-Aziz and Larner 2015; Larner 2015c, 2016a, 2017a) were used to calculate regression equations of the form y = a + bx (Larner 2017d), where y, the

Table 6.27 Regression equations and correlation coefficients of some commonly used cognitive screening instruments (adapted and extended from Larner 2017d)

Compared CSIs (y vs. x)	N	Regression equation (y = a + bx)	Correlation coefficient (r)
MMSE vs. MoCA	147	y = 12.8 + 0.59x	0.85
MMSE vs. MACE	244	y = 12.8 + 0.58x	0.81
MMSE vs. 6CIT	150	y = 28.1–0.44x	−0.73
MMSE vs. AD8	125	y = 26.9–0.46x	−0.23
MACE vs. MoCA	260	y = 4.12 + 0.83x	0.83
MACE vs. s-MoCA	260	y = 10.4 + 1.18x	0.79
MoCA vs. s-MoCA	260	y = 7.53 + 1.43x	0.95

dependent or outcome variable, was approximate CSI score; x, the independent or explanatory variable, was score on a different CSI with which the first CSI was being compared; and a is the intercept and b the slope or gradient (regression coefficient) of the regression equation. Pearson product moment correlation coefficients were also calculated (Table 6.27).

As anticipated, since MoCA and MACE are scored positively and correlate positively with MMSE scores their regression coefficients with MMSE were positive, whereas for 6CIT and AD8, which are negatively scored and correlate negatively with MMSE scores, the slope of the regression line was negative, indicating lower MMSE scores for subjects with higher 6CIT and AD8 scores. Since MoCA, MACE, 6CIT and AD8 were all more sensitive than MMSE in the base studies, the intercept values of the regression equations were all high, indicating that many correct answers may be achieved on MMSE whilst the other tests remain at floor. MMSE is recognized to include relatively easy items which are of little value in patient assessment (Sect. 4.1.1). Greater coincidence of the various test scores occurred around ceiling.

Calculation and application of these regression equations is a relatively simple way to obtain approximate scores when converting between screening instruments (calculations can be easily done on a mobile phone calculator). Whether this approach might also be used outside of the secondary care clinic setting, whence the original data were generated, remains to be addressed. The regression equations derived here may be a simple way to generate approximate MMSE scores which may be used to inform clinical decision making without recourse to administering the MMSE per se and any potential copyright issues.

6.4 Summary and Recommendations

The various comparative metrics examined here suggest that a number of CSIs are suitable for the diagnosis of dementia. In the previous edition (Larner 2014a:140), ACE-R was noted to be at or near the top in most categories, so was recommended as eminently suitable for those requiring cognitive screening in a dedicated Cognitive Function Clinic (i.e. a high prevalence setting). The withdrawal of ACE-R because

of issues around MMSE copyright was regretted; it was hoped that ACE-III (Hsieh et al. 2013) might be a suitable replacement. Other options include MoCA and MACE, both of which appear to be highly acceptable, and certainly seem to be best for diagnosis of MCI. MMSE may still retain a place, acknowledging its shortcomings, in terms of both its neuropsychological limitations and questionable ecological validity (Larner 2007c). However, MMSE is certainly not good for identification of MCI, so if this frames the clinical question then MoCA or MACE are preferable.

Combinations of CSIs with informant scales or with functional instruments may have added diagnostic value compared to CSIs in isolation, and certainly pragmatic value in planning clinical interventions (Chap. 5). Conversion between test scores may also be useful; for example, if therapeutic decision making is to be based on MMSE scores, then conversion of other CSI scores to approximate MMSE scores by using linear regression equations might be used.

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Investigation

7

Contents

Abstract

This chapter examines the utility of various investigative techniques in the diagnosis of cognitive disorders including, in order of increasing invasiveness, neuroimaging, neurogenetics, neurophysiology, cerebrospinal fluid analysis, and tissue diagnosis.

Keywords

Dementia · Diagnosis · Investigation · Neuroimaging · Neurogenetics Neurophysiology · Cerebrospinal fluid

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The investigation of cases of suspected dementia has perhaps gained a higher profile in recent years. This may reflect a combination of the increasing availability of more sophisticated investigation methods and the search for disease biomarkers which might be used as surrogates for pathological confirmation of disease. For example, recent diagnostic criteria for Alzheimer's disease (AD; Dubois et al. 2007, 2014; Boxes 7.1 and 7.2; McKhann et al. 2011) enshrine investigation findings which examine potential AD biomarkers. Investigation findings are also integral to criteria

Box 7.1: Proposed diagnostic criteria for Alzheimer's disease (after Dubois et al. 2007; adapted from Larner 2010)

Probable AD: Diagnosis requires A plus one or more supportive features B-E	
Core criteria:	
A	Early significant episodic memory impairment that includes: 1. Gradual and progressive change in memory function over >6 months 2. Objective evidence of significantly impaired episodic memory on testing 3. Episodic memory impairment may be isolated or associated with other cognitive changes at AD onset
Supportive criteria:	
B	Medial temporal lobe atrophy on MRI
C	Abnormal CSF biomarker: $\downarrow A\beta_{42}$, ↑total tau, ↑phospho-tau
D	Specific pattern on functional neuroimaging with PET (NB not SPECT)
E	Proven AD autosomal dominant mutation in the immediate family
Definite AD: Requires clinical features + neuropathological confirmation, or clinical features + presence of deterministic genetic mutation	

Box 7.2: Proposed diagnostic criteria for typical Alzheimer's disease (after Dubois et al. 2014)

Typical AD: Diagnosis requires A plus B at any stage

A. Specific clinical phenotype:
Early and significant episodic memory impairment (with or without associated other cognitive or behavioural changes suggestive of a mild cognitive impairment or of a dementia syndrome) that includes the following features:
- gradual and progressive change in memory function reported by patient or informant over >6 months
- objective evidence of an amnestic syndrome of the hippocampal type based on significantly impaired performance on an episodic memory test with established specificity for AD

B. In vivo evidence of Alzheimer's pathology (one of the following):
- Decreased $A\beta_{1-42}$ together with increased T-tau or P-tau in CSF
- Increased tracer retention on amyloid PET
- AD autosomal dominant mutation present (in PSEN1, PSEN2, or APP)

for other dementing disorders, such as behavioural variant frontotemporal dementia (Rascovsky et al. 2011), Creutzfeldt-Jakob disease (Zerr et al. 2009), corticobasal degeneration (Armstrong et al. 2013), and dementia with Lewy bodies (McKeith et al. 2017; Liyanagedera et al. 2018). Nevertheless, at time of writing dementia remains a clinical diagnosis. Diagnostic errors based on over-reliance on investigations, particularly structural imaging reported to show brain atrophy, have been encountered (Larner 2004a; Davies and Larner 2009). As for the findings of screening instruments examining cognitive and non-cognitive domains (Chaps. 4, 5 and 6), interpretation of investigation findings must be set within the context of the patient and collateral history and examination (Chap. 3).

Despite these caveats, it is reasonable to consider pursuing a number of investigations over and above "bedside" neuropsychological assessment (see Chap. 4) in cases of cognitive complaint and/or suspected dementia, based in part on guidelines issued by the American Academy of Neurology (AAN; Anonymous 1994; Knopman et al. 2001) and the European Federation of Neurological Societies (EFNS: Waldemar et al. 2007, Box 7.3; Hort et al. 2010a; Sorbi et al. 2012).

Box 7.3: EFNS recommended investigations in dementia (after Waldemar et al. 2007; adapted from Larner 2010)

		Evidence level
Blood tests: "generally proposed as mandatory"	ESR, full blood count, electrolytes, calcium, glucose, renal and liver function tests, thyroid stimulating hormone	Good practice point
Blood tests: "often required"	Vitamin B_{12}, serology for syphilis, HIV, Borrelia	Good practice point
Neuroimaging: structural	CT: to identify surgically treatable lesions and vascular disease	A
Neuroimaging: structural	MRI: to increase diagnostic specificity	A
Neuroimaging: functional	SPECT and PET: may be useful in those cases where diagnostic uncertainty remains	B
Neurophysiology	EEG: useful adjunct, especially if CJD or transient epileptic amnesia suspected	B
Cerebrospinal fluid	Cell count, protein, glucose, protein electrophoresis in atypical presentations	Good Practice Point
Cerebrospinal fluid	Total tau, phospho-tau, Aβ42 as adjunct in cases of diagnostic doubt	B
Genetic testing: known pathogenic mutations	In patients with appropriate phenotype or family history of autosomal dominant dementia. Only to be undertaken in specialist centres, with appropriate counselling of patient and family caregivers and with consent	Good Practice Point
Genetic testing: ApoE	Not recommended as routine	B
Tissue biopsy	For specific diagnosis of some rare dementias. Only to be undertaken in specialist centres	Good Practice Point

7.1 Blood Tests

A variety of blood tests have sometimes been recommended as a "minimum dataset" for the investigation of suspected dementia cases. These include full/complete blood count, erythrocyte sedimentation rate (ESR), serum electrolytes, glucose, calcium, renal tests (urea, creatinine), liver-related blood tests (alkaline phosphatase, transaminases), red cell folate, serum vitamin B_{12} (cyanocobalamin), thyroid function and syphilis serology (Anonymous 1994; Bullock and Qizilbash 2002; Waldemar et al. 2007), although the rarity of positive syphilis serology and of low vitamin B_{12} in patients with cognitive impairment has long been recognised (Woolf and Kamerow 1990:2451). In practice, many of these blood tests will already have been performed by primary care physicians prior to referral to the cognitive clinic as part of their "dementia screen". If not, then it may be reasonable, following the AAN recommendations, to undertake measurement of vitamin B_{12} and thyroid function but reserve syphilitic serology for cases in which there are specific risk factors or a history of prior infection (Knopman et al. 2001). A counter argument has been made for syphilis screening in possible dementia cases in the developing world (Nitrini and Caixeta 2011). It is recognised that plasma VDRL is sensitive but not specific, hence at risk of false positives.

The EFNS guidelines of 2007 suggested that more extensive testing including vitamin B_{12} and serology for syphilis, HIV, and Borrelia might be required in individual cases (Waldemar et al. 2007). Arguments for (Nightingale et al. 2013) and against (Schott 2013) testing all dementia patients for HIV have been made.

A more recent EFNS guideline for AD seems to make vitamin B_{12} testing once again mandatory (Hort et al. 2010a), the various recommendations perhaps reflecting uncertainty about the diagnostic value of this test (its cost effectiveness is unproven: Marks 2011). Personally I am sceptical about vitamin B_{12} deficiency as a cause of cognitive impairment in anything other than very rare circumstances (Larner 2008a: 194–5; Larner 2013a:181–2), with only one unequivocal case seen in more than 30 years of neurological practice (Larner et al. 1999; Larner and Rakshi 2001). Low vitamin B_{12} levels may surely be an accompaniment of cognitive decline, perhaps related to poor dietary intake (weight loss is a common feature in early AD: Cronin-Stubbs et al. 1997), but without any anticipation of cognitive improvement with adequate repletion. This is, after all, often the situation with other complications of vitamin B_{12} deficiency, such as subacute combined degeneration of the spinal cord, peripheral and optic neuropathies (Larner 2002, 2004b; Larner et al. 1997). A trial of high dose vitamin B supplementation including vitamin B_{12} did not prevent decline in AD patients (Aisen et al. 2008).

The recommendations with respect to blood tests are prompted, at least in part, by the understandable desire to identify any potentially reversible cause(s) of cognitive decline, although in practice these are extremely rare (Clarfield 2003), with the possible exception of drug-related cognitive impairments, particularly related to the anticholinergic properties of some medications (Hejl et al. 2002).

Considering the large number of disorders which may result in cognitive impairment (Larner 2008a, 2013a), there are many other blood tests which may on

occasion need to be considered, dependent on clinical context. From the perspective of potentially reversible causes, the autoimmune non-paraneoplastic limbic encephalitides, though rare, loom large. These may be associated with antibodies directed against, for example, LGI1 (previously known as voltage-gated potassium channel [VGKC] antibodies), NMDA-receptors, and glutamic acid decarboxylase (GAD), examples of which have been seen in the clinic on occasion (Wong et al. 2010a; Bonello et al. 2014; Randall et al. 2018).

Blood tests for genetic mutations causing inherited disorders of cognitive function are considered in Sect. 7.3.

7.2 Neuroimaging

Structural and functional neuroimaging modalities have been increasingly used in clinical practice to supplement clinical and cognitive assessment of patients with memory or other cognitive complaints. A wide array of imaging modalities is available (Jagust and D'Esposito 2009; Barkhof et al. 2011), although many of these are currently confined to the research arena.

The original rationale for neuroimaging in this clinical situation was to exclude other possible, mostly structural, causes for cognitive decline, such as brain tumour, subdural haematoma, "normal pressure hydrocephalus", dural arteriovenous fistula, and white matter change. However the emphasis has now moved to the identification of markers of neurodegeneration in terms of the extent and location of brain atrophy and of pathological changes per se such as amyloid burden (e.g. PiB-PET, Klunk et al. 2004; florbetapir-PET, Clark et al. 2011).

7.2.1 Structural Neuroimaging: CT, MRI

Guidelines for the diagnosis of dementia have recommended the use of neuroimaging as a routine component of the initial evaluation of patients, as a supplement to clinical assessment in possible dementia cases (Knopman et al. 2001; Waldemar et al. 2007). The most recent EFNS guidelines recommended structural imaging in the evaluation of every patient affected by dementia (Filippi et al. 2012; Sorbi et al. 2012) whilst noting the difficulty of attributing clinical significance to evidence of cerebrovascular disease. Likewise national directives, such as the UK National Institute for Health and Clinical Excellence/Social Care Institute for Excellence (NICE/SCIE) guidelines (2006) stated that "Structural imaging should be used in the assessment of people with suspected dementia to exclude other cerebral pathologies and to help establish the subtype diagnosis" (paragraph 1.4.3.2).

Various structural pathologies have been reported to cause dementia or cognitive impairment (Larner 2013a:166–76), including brain tumour (Case Study 7.1; Ibrahim et al. 2009; Smithson and Larner 2013; Milburn-McNulty and Larner 2015), subdural haematoma, and various causes of hydrocephalus, including colloid cyst (Case Study 7.2), but these have very rarely been encountered in the Cognitive

Case Study 7.1: Clinical utility of structural brain imaging in diagnosis of dementia (1): brain tumour

A previously healthy 50 year-old man presented with a 4 month history of memory problems, word finding and naming difficulties, poor concentration, with associated anxiety and agitation. Neurological examination was normal. Neuropsychological assessment showed generalised intellectual loss (full scale IQ decline of 35 points). The patient was impaired on all measures of auditory and visual memory for immediate and delayed recall, recognition memory and working memory. He made dysphasic errors, performed poorly on copy of the Rey-Osterrieth figure, and was severely impaired on verbal fluency and the Stroop test. Based on these results, a diffuse dementing illness was suspected, possibly Creutzfeldt-Jakob disease. Subsequent brain imaging disclosed a large left temporoparietal, non-homogeneous, space-occupying lesion with a large cystic component with surrounding oedema and mass effect. At surgery this proved to be an atypical meningioma grade II which was completely resected. Repeat neuropsychological assessment 4 months post-operatively showed significant improvement with no evidence of intellectual or memory impairment.

Case Study 7.2: Clinical utility of structural brain imaging in diagnosis of dementia (2): colloid cyst

A 65 year-old lady presented accompanied by her son and he gave a 4 week history of declining memory and alertness in his mother such that his father had had to take over all the household duties. The patient was having difficulty walking, tending to shuffle, and had fallen on occasion. She was very sleepy during the day. A diagnosis of depression had been suspected in primary care and antidepressant medication started, without effect. Psychomotor retardation was evident on history taking and the head turning sign (Sect. 3.2.2) was present. In CFC a diagnosis of normal pressure hydrocephalus was mooted, but brain imaging (CT) showed a hyperdense lesion within the foramina of Monro representing a colloid cyst, with hydrocephalus and periventricular oedema, requiring prompt neurosurgical intervention.

Function Clinic (CFC) at the Walton Centre for Neurology and Neurosurgery (WCNN) in Liverpool, accounting for less than 0.5% of referrals over a 10-year period (Larner 2013b).

Because of the ready availability of structural neuroimaging, particularly computed tomography (CT), to primary care physicians as well as to cognitive neurologists, it might be argued that this investigation should be undertaken prior to referral, as is the case for "screening blood tests". A prospective observational study of 100 consecutive patients referred to CFC (March–August 2010) collected reports of

neuroimaging performed prior to and after referral (Larner 2011a). Referral source (Fig. 7.1) was predominantly from primary care (63). Of the cases referred from secondary care (37), there were equal proportions from other neurology consultants at the Walton Centre for Neurology and Neurosurgery (WCNN; 16) and from psychiatry/old age psychiatry services (16), with a handful from other sources (5), such as general physicians.

The majority of patients were not demented by DSM-IV criteria (67), although there was evidence for a neurological or neurodegenerative process causing cognitive impairment in some of these non-demented individuals (mild cognitive impairment [MCI] 10, progressive non-fluent aphasia [PNFA] 2, dementia with Lewy bodies [DLB] 2, HIV 1). One third of patients received a clinical diagnosis of dementia (33), the most frequent subtypes being AD/Down syndrome (15), frontotemporal lobar degeneration syndromes (FTLD; 8), DLB (3), and vascular dementia (2).

Patients who had undergone neuroimaging before referral to CFC were in the minority (28/100). Not unexpectedly, fewer primary care (7/63 = 11%) than secondary care (21/37 = 57%) referrals had undergone neuroimaging (Fig. 7.2), a statistically significant difference ($\chi^2 = 26.0$, df = 1, $p < 0.01$). In the group of referrals from secondary care, neuroimaging frequencies by referral source were: WCNN

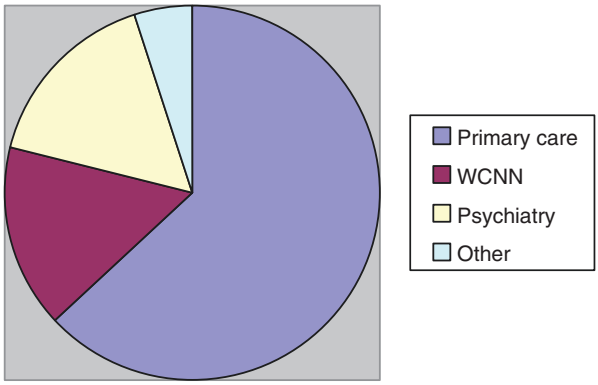

Fig. 7.1 Patient referral sources (n = 100), neuroimaging audit (Larner 2011a) reprinted with permission

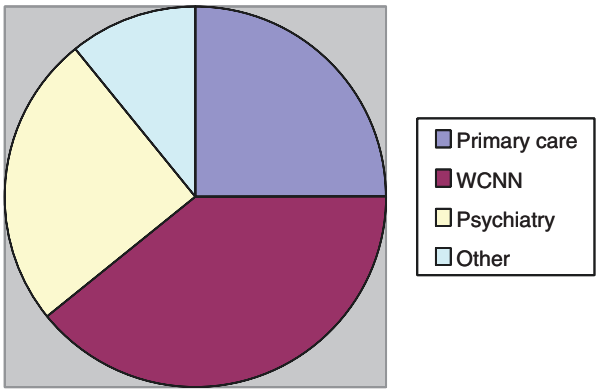

Fig. 7.2 Neuroimaging by referral source (n = 28), neuroimaging audit (Larner 2011a) reprinted with permission

consultant 11/16 (= 69%); psychiatry/old age psychiatry 7/16 (= 44%); and others 3/5 (= 60%).

Breakdown of the frequency of neuroimaging by patient diagnosis showed that patients ultimately receiving a diagnosis of dementia from CFC were significantly more likely to have been imaged (15/33 = 45%) than those not demented (13/67 = 19%; $\chi^2 = 8.14$, df = 1, $p < 0.01$), although notably the latter group included some of those patients with underlying neurological and/or neurodegenerative disease (PNFA 2, HIV, DLB, MCI).

Following CFC consultation, all remaining patients (72) underwent neuroimaging. These data indicated that CFC was compliant with NICE/SCIE (2006) guidelines on neuroimaging. The key question though is whether this compliance makes any difference in clinical management. To a certain extent this may be a subjective value judgment, but it was the case that no revision of clinical diagnosis (e.g. not dementia revised to dementia, or a change of dementia subtype) was forthcoming as a result of CFC neuroimaging in this study (Larner 2011a), although this has happened on occasion (see Case Studies 7.2 and 7.3). Finding potentially reversible causes of cognitive decline on neuroimaging is, sadly, exceedingly rare, the most common treatable structural causes seen in CFC being meningioma (3 cases in approximately 10 years; Larner 2013b) and intracranial dural arteriovenous fistula (4 cases; Wilson et al. 2010; Randall et al. 2015).

A second prospective observational study of neuroimaging practice prior to CFC referral was undertaken on consecutive patients over a 6-month period (September 2012–February 2013; Larner, unpublished observations). Of 127

Case Study 7.3: Clinical utility of structural brain imaging in diagnosis of dementia (3): diagnostic revision

A 64 year-old lady presented with an 18-month history of forgetfulness, such as leaving the cooker on, with some consequent reduction in her household activities. Her primary care physician thought she might be depressed and prescribed an antidepressant. On the MMSE she scored 26/30 dropping single points for orientation in date, serial 7 s, 5-min recall and intersecting pentagons. It was not clear whether these deficits related to depression or the early stages of a neurodegenerative disorder. Brain imaging with CT showed right frontotemporal atrophy, suggesting the possibility of FTLD. At reassessment, collateral history from her daughter indicated apathy and reduced personal hygiene. On the Frontal Assessment Battery (see Sect. 4.2.1) she scored 14/18 with impairments in lexical fluency, motor series, conflicting instructions, and go-no-go. MR brain imaging confirmed right frontotemporal atrophy and 1H-MR spectroscopy (Sect. 7.2.2) showed reduced N-acetyl aspartate and increased myoinositol in frontal but not occipital voxels. EEG was within normal limits. A diagnosis of behavioural variant frontotemporal dementia was therefore thought most likely. Neurogenetic testing for progranulin mutation (see Sect. 7.3.2) was negative.

patients (F:M = 57:70; 45% female; age range 19–89 years, median 61 years), the majority were not demented by DSM-IV criteria (86, = 68%), giving a dementia prevalence of 32%, but 32 had cognitive impairment short of dementia giving a prevalence of cognitive impairment of 57%. As before, patients who had undergone neuroimaging before referral to CFC were in the minority (51/127 = 40%), most initiated in secondary (46) care but a few (5) in primary care. However, the proportion imaged prior to referral had increased compared to the 2010 study (40% vs. 28%). Breakdown of the frequency of neuroimaging by patient diagnosis showed that patients receiving a diagnosis of dementia were significantly more likely to have been imaged (23/41 = 56%) than those not demented (28/86 = 33%; $\chi^2 = 7.38$, df = 1, $p < 0.01$). Patients with any cognitive impairment were significantly more likely to have been imaged (36/73 = 49%) than cognitively healthy individuals (15/54 = 28%; $\chi^2 = 6.56$, df = 1, $p < 0.01$).

So should neuroimaging be a prerequisite for referral to memory clinics, part of the minimum dataset available to the CFC clinician prior to assessment? Probably not.

A steady trickle of patients is referred to CFC because of "cortical atrophy", based on radiology reports of brain scans undertaken for other purposes, usually headache. (Twas ever thus: Allison (1962:257) reports a patient diagnosed with early AD because of symmetrical ventricular dilatation on air encephalography, an investigation now obsolete.) Although this label of "atrophy" may be technically correct according to neuroradiological terminology (Global Cortical Atrophy scale, grade 1 = opening of sulci), it is invariably a qualitative judgement. Moreover, experience indicates that it is seldom of clinical relevance, and serves only to generate significant (and understandable) anxiety in both patients and primary and secondary care physicians unfamiliar with the uses of neuroimaging in the assessment of cognitive problems. As with all imaging findings, clinical-radiological correlation is essential, which basically privileges the primacy of clinical assessment. A study of the diagnostic yield of CT scans done routinely in a UK memory loss clinic found "significant findings" in only 1% (Dawe 2012). Neuroimaging provided support for, but did not alter, clinical diagnosis in a large clinico-pathological case series (Snowden et al. 2011).

More common is the referral of patients with a radiological report of "normal pressure hydrocephalus". This is a clinical, not radiological, diagnosis (Sect. 7.5). Very few patients referred with this label actually prove to have the disorder, more usually having ex vacuo atrophy in the context of a neurodegenerative disorder.

With magnetic resonance imaging (MRI), the problem of incidental findings may be even more evident since they are very common (Morris et al. 2009). The presence of cerebrovascular disease in particular is problematic, as acknowledged in EFNS guidelines (Sorbi et al. 2012). Such changes seem often to be interpreted by psychiatrists and old age psychiatrists as commensurate with a diagnosis of vascular dementia, despite the clarity of diagnostic criteria which require such changes to be clinically and temporally relevant to cognitive decline (Román et al. 1993; van Straaten et al. 2003; Gorelick et al. 2011).

Case Study 7.4: Clinical utility of structural brain imaging in diagnosis of dementia (4): diagnostic confusion from incidental findings

A 48 year-old lady with Down's syndrome presented to intellectual disability services with a 3-year history of decline in her abilities as reported by her carers. Brain imaging (CT) was undertaken, and was reported by a general radiologist to show "Fahr's disease", prompting urgent referral to CFC. The scan showed extensive symmetrical calcification of the basal ganglia, a striking example of a phenomenon well-described in Down's syndrome (e.g. Takashima and Becker 1985; Mann 1988), without the need to invoke a diagnosis of Fahr's disease. Indices of calcium metabolism in this patient were within normal limits.

Another incidental finding occasionally seen is brain calcification, particularly of the basal ganglia, said to occur in perhaps 0.5–1% of normal CT scans, and in association with a variety of disorders (Larner et al. 2011:56–7), including Down's syndrome (Case Study 7.4).

Focal medial temporal lobe atrophy (MTA) on MR imaging is one of the supportive criteria for AD in some diagnostic criteria (e.g. Dubois et al. 2007; Box 7.1). MTA discriminates pathologically confirmed AD from DLB and vascular cognitive impairment (Burton et al. 2009). Visual assessment scales for MTA are available (Barkhof et al. 2011:22–3) although such assessment is not routinely undertaken at present in this centre. Structural neuroimaging is often unrewarding in suspected cases of FTLD, particularly early in the disease course. In a benign and good prognosis variant of behavioural variant frontotemporal dementia (bvFTD), or bvFTD phenocopy, neuroimaging may change little over time (Davies et al. 2006).

Other MR based modalities, such as diffusion weighted imaging (DWI), susceptibility weighted imaging (SWI), and diffusion tensor imaging (DTI) may possibly be of value in the assessment of cognitive disorders (Barkhof et al. 2011). DWI may be of particular value in suspected cases of sporadic Creutzfeldt-Jakob disease (e.g. Ali et al. 2013) and acutely in transient global amnesia (Larner 2017a:62–5); SWI in cerebral amyloid angiopathy (Charidimou et al. 2012); and DTI in white matter disorders (Filley 2012). Longitudinal volumetric MR imaging measuring rates of whole-brain and hippocampal atrophy has proved a sensitive marker of neurodegeneration and may well find increasing use as a diagnostic tool and as a surrogate marker to assess treatment effects (Frisoni et al. 2010).

7.2.2 Functional Neuroimaging: HMPAO-SPECT, 1H-MRS

Of the various functional imaging modalities, 99mTechnetium hexamethylpropylene amine oxime single photon emission computed tomography (99mTc HMPAO-SPECT) is probably the most widely available, although modern diagnostic criteria for AD specify functional brain imaging with positron emission tomography (PET) in preference to SPECT (Dubois et al. 2007, 2014; Boxes 7.1 and 7.2).

Use of HMPAO-SPECT in the assessment of cognitive problems has been standard practice in some centres, usually based on visual analysis of regional cerebral blood flow changes. Although more sophisticated analytical techniques are possible, such as statistical parametric mapping, these are not universally available. Hypoperfusion of posterior temporal and parietal regions with relative sparing of occipital blood flow is typical of AD as compared to normal controls (e.g. Talbot et al. 1998; Dougall et al. 2003), although in the visual variant of AD (posterior cortical atrophy) occipital hypoperfusion is seen. Otherwise, occipital hypoperfusion is more typical of dementia with Lewy bodies (e.g. Lobotesis et al. 2001). HMPAO-SPECT additionally has the facility for the differential diagnosis of AD and FTLD based on the frontal hypoperfusion in the latter (e.g. Talbot et al. 1998; Charpentier et al. 2000).

The most recent EFNS guidelines suggested that SPECT perfusion imaging is useful to distinguish DLB, corticobasal syndrome and Creutzfledt-Jakob disease from AD (Sorbi et al. 2012:1173).

There has been only limited experience of functional neuroimaging in CFC, perhaps surprisingly in light of the origins of isotope imaging in Liverpool (Ansell and Rotblat 1948). This has been for both logistic (no SPECT scanner on site, nearest facilities at Royal Liverpool University Hospital and Wrexham Maelor Hospital) and financial reasons. A study of the utility of HMPAO-SPECT was performed in a cohort of young cognitively-impaired patients in whom diagnostic uncertainty remained after standard clinical and neuropsychological assessment and structural brain imaging (Doran et al. 2005a). SPECT scans were visually assessed by five raters (2 consultant neurologists with a specialist interest in cognitive disorders, 3 nuclear medicine specialists) on two occasions 6 months apart, firstly without any clinical data ("blind"), secondly with brief pertinent clinical information ("informed"). SPECT diagnoses were compared with criterion diagnoses subsequently established by the two neurologists with access to all the clinical, neuropsychological and neuroimaging data. Despite reasonable intra- and inter-rater reliability, diagnostic accuracy ranged from 32 to 58%. SPECT scan normality or abnormality in blind and informed viewings gave respective sensitivities of 77% and 71%, specificities of 44% and 38%, positive predictive values of 88% and 87%, and negative predictive values of 27% and 18%. Calculating pairwise disease group comparisons, likelihood ratios suggested some diagnostic gain in differentiating AD from "not AD" (as also shown by Dougall et al. 2003), and in differentiating AD from FTD/focal syndromes (as also shown by Talbot et al. 1998; McNeil et al. 2007). SPECT scanning was of little help in establishing diagnoses in this (highly selected) cohort of patients, a finding which supported the conclusion of an AAN evidence-based review of SPECT imaging which concluded that SPECT could not be recommended for either the initial or the differential diagnosis of suspected dementia because it had not demonstrated superiority to clinical criteria (Knopman et al. 2001). That said, other studies in less selected cohorts than that examined in CFC have reached different, more positive, conclusions (Talbot et al. 1998; Salmon et al. 2009).

Dopaminergic SPECT imaging (FP-CIT, DATScan), for visualisation of the dopamine transporter, may be useful to differentiate AD from DLB (Hort et al.

2010a; Sorbi et al. 2012). However, it does not pick up all DLB cases (Colloby et al. 2012). Again, logistic and financial reasons have meant that this modality has been infrequently used in CFC patients with cognitive impairment (e.g. Ali et al. 2010).

Although 18F-fluoro-2-deoxyglucose-positron emission tomography (FDG-PET) has been used on occasion in cases of suspected paraneoplastic neurological syndrome (Ghadiri-Sani et al. 2016), there is currently no experience of PET in CFC.

In vivo biomarkers for diagnostic imaging may become of greater relevance in the future, such as fluorinated PET ligands for imaging amyloid (Klunk et al. 2004; Clark et al. 2011). There is increasing evidence of the utility of amyloid PET imaging for differential diagnosis of early onset dementia (Ossenkoppele et al. 2015) but currently there is experience in CFC of only a single patient submitted for amyloid PET, for financial and logistical reasons (Williamson et al. 2018). Tau PET imaging is still at the developmental stage (Hall et al. 2017).

Proton magnetic resonance spectroscopy (1H-MRS) is a form of functional neuroimaging which has been advocated as a possible tool for use in the evaluation and diagnosis of dementia (Kantarci 2007), based on changes in the neuronal marker N-acetyl aspartate (NAA) and in myoinositol (mI) relative to brain creatine (Cr). NAA:Cr ratios are typically decreased in disorders characterised by neuronal loss, such as AD and FTLD, and mI:Cr ratios are elevated in the presence of pathological gliosis, which may also be seen in AD and FTLD.

The utility of 1H-MRS in the diagnosis of dementia has been assessed in a highly selected population of patients attending CFC (Larner 2006). Single voxel 1H-MRS was performed on GE Signa 1.5 T Scanner (TE = 35 ms; TR = 1500 ms), measuring NAA and mI with Cr as reference, hence generating NAA:Cr and mI:Cr ratios. Comparison of mean NAA:Cr and mI:Cr ratios in occipital and frontal voxels in demented (n = 11; AD 8, FTLD 3) and non-demented (9) patients was performed. There was a statistically significant increase in mI:Cr ratio in occipital voxels in demented patients (t = 4.60, df = 15, $p < 0.001$), and a trend towards reduced NAA:Cr ratio in frontal voxels in demented patients ($t = 1.86$, df = 13, $0.05 < p < 0.1$). Acknowledging the small patient numbers and the clinical heterogeneity of cases, nonetheless this study suggested that a high occipital mI:Cr ratio may be useful in differentiating demented from non-demented patients, and a low frontal NAA:Cr may be suggestive of a diagnosis of dementia.

A subsequent study assessed the utility of 1H-MRS in the differential diagnosis of AD (n = 9) and FTLD (n = 6; bvFTD 4, semantic dementia 2) (Larner 2008b). Occipital NAA:Cr ratio was lower in AD than FTLD patients, the difference reaching statistical significance (t = 2.47, df = 13, $p < 0.05$), but occipital mI:Cr ratio showed no difference between the groups ($t = 0.81$, df = 12, $0.1 < p < 0.5$). Reduced occipital NAA:Cr ratio may reflect occipital neuronal loss occurring in AD, but not in FTLD, whilst the failure of occipital mI:Cr ratio to differentiate the two conditions may reflect either the absence of occipital gliotic change in FTLD or the equality of such change in both AD and FTLD (Larner 2008b). These latter findings contrast with the previously reported utility of mI:Cr ratio in differentiating cases of dementia (increased) from non-dementia patients (Larner 2006).

In a single case, extremely high frontal mI:Cr ratio, suggesting profound gliosis, prompted a clinical diagnosis of progressive subcortical gliosis of Neumann

(Neumann and Cohn 1967), in which prior structural neuroimaging had suggested a provisional diagnosis of vascular change (subcortical arteriosclerotic encephalopathy) (Larner et al. 2003). Neuroaxonal leukodystrophy also entered the differential diagnosis of this case. Case Study 7.3 provides a further example of the diagnostic utility of 1H-MRS.

7.3 Neurogenetics

There has been a huge expansion in the understanding of the genetic causes of dementia in the past two decades (Box 7.4). This has had an increasing impact on clinical practice, admittedly in selected cases (e.g. Adab and Larner 2006; Aji et al. 2013a, b, 2016; Connon and Larner 2017; Doran and Larner 2004a, b, 2006, 2009;

Box 7.4: Some monogenic Mendelian causes of dementia with deterministic genes and Online Mendelian Inheritance in Man (OMIM) numbers (see Larner 2013a:110–44)

Familial Alzheimer's disease:

- Amyloid precursor protein (APP): OMIM#104300
- Presenilin 1 (PSEN1): OMIM#607822
- Presenilin 2 (PSEN2): OMIM#606889

Frontotemporal lobar degenerations:

- Microtubule associated protein tau (MAPT): OMIM#600274
- Progranulin (GRN): OMIM#607485
- Valosin-containing protein (VCP): OMIM#167320
- Charged multivesicular body protein 2B (CHMP2B): OMIM#600795
- TAR-DNA binding protein 43 (TDP-43): OMIM#612069
- Fused in sarcoma (FUS): OMIM#608030
- C9orf72: OMIM#105550

Huntington's disease: IT15 gene, OMIM#143100

Familial prion diseases: all due to prion protein gene (PRNP) mutations:

- Familial Creutzfeldt-Jakob disease: OMIM#123400
- Gerstmann-Straussler-Scheinker disease: OMIM#137440
- Fatal familial insomnia: OMIM#600072
- Huntington's disease-like 1: OMIM#603218

CADASIL: Notch 3 gene, OMIM#125310

Nasu-Hakola disease (NHD), polycystic lipomembranous osteodysplasia with sclerosing leukoencephalopathy (PLOSL): DAP12 and TREM2, OMIM#221770

Familial British dementia: ITM2B, OMIM#176500

Familial Danish dementia: ITM2B, OMIM#117300

Doran et al. 2007; Larner 2003, 2004c, 2007a, 2008c, d, e, f, 2009a, b, c, 2011b, c, 2012a, b, c, 2013c, d; Larner and Doran 2006a, b, 2009a, b, c; Larner and du Plessis 2003; Larner et al. 2007; McCormick and Larner 2018; Milburn-McNulty and Larner 2018; Randall and Larner 2016; Sells and Larner 2011; St John and Larner 2015; Williamson and Larner 2018; Ziso et al. 2014, 2015a). The advent of next generation sequencing (NGS) panels, sequencing a wide variety of dementia related genes, is likely to increase this impact (Williamson et al. 2018).

In certain circumstances, neurogenetic testing may be indicated following appropriate genetic counselling, the exact nature of which is dependent upon whether testing is diagnostic (i.e. in a symptomatic individual) or predictive (i.e. in an asymptomatic individual with a suggestive family history). The latter may be best administered through the auspices of a clinical genetics service (Larner 2007b), perhaps using the model which is already well developed for families with Huntington's disease. All studies of the genetic basis of dementia should observe appropriate consensus statements and guidelines emanating from national and professional bodies regarding genetic counselling and informed consent (e.g. Olde Rikkert et al. 2008; Goldman et al. 2011a).

Due to allelic heterogeneity, genotype-phenotype correlations are in their infancy for a number of these genes (Larner 2004c, 2013c; Larner and Doran 2006a, 2009a, b). Few examples of dementia resulting from genetic (monogenic Mendelian) mutations have been encountered in CFC (Doran and Larner 2009).

Routine use of genetic tests is not recommended (Knopman et al. 2001), testing or screening being reserved for families with the appropriate phenotype or with a family history of dementia transmitted in an autosomal dominant pattern (Hort et al. 2010a; Sorbi et al. 2012). The latter may be defined as at least three affected individuals in at least two generations (Cruts et al. 1998). However, experience with eight families with either PSEN1 or MAPT mutations (see below) seen in CFC found that in only three was there a clear autosomal dominant pattern of disease transmission according to this definition; in four other families there was familial disease (i.e. at least one first degree family relative affected; Cruts et al. 1998); and one case was apparently sporadic, possibly due to *de novo* mutation (Larner and du Plessis 2003). All but one of these families had early onset dementia, defined as onset before 65 years of age (Doran and Larner 2009). The Goldman score (Goldman et al. 2005) or modified Goldman score (Rohrer et al. 2009) may be used to estimate the likelihood of an underlying mutation in FTLD cases dependent upon the family history: 1 = autosomal dominant family history defined as at least three affected individuals in two generations with one person being a first-degree relative of the other two; 2 = familial aggregation of 3 of more family members with dementia but not meeting criteria for 1; 3 = 1 other affected family member with dementia (modified to give a score of 3 only if there is a history of young-onset dementia within the family, i.e., <65 years, and 3.5 if onset >65 years); 4 = no or unknown family history. This metric has been used on occasion in CFC when considering the indication for genetic testing (Larner 2012b; Williamson and Larner 2018).

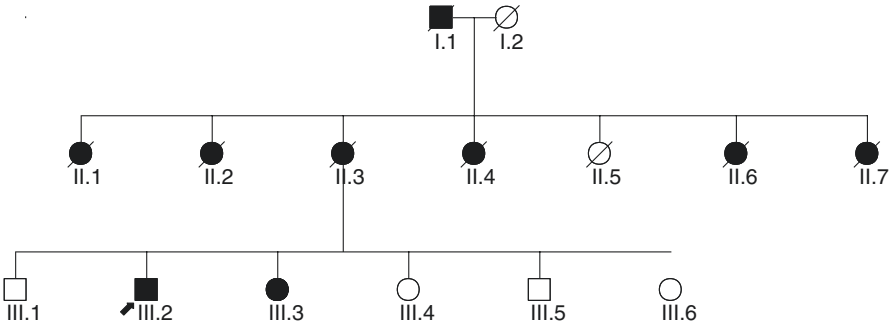

Fig. 7.3 Provisional family tree (genogram), R269H PSEN1 gene mutation; proband arrowed (Larner et al. 2007) reprinted with permission

7.3.1 Alzheimer's Disease

Mutations in three genes have been reported to be deterministic for AD (Box 7.4): amyloid precursor protein (APP), presenilin 1 (PSEN1), and presenilin 2 (PSEN2). Of these, the most commonly affected is PSEN1 (Alzheimer Disease and Frontotemporal Dementia Mutation Database 2017); indeed this is sufficiently familiar now to have become a topic for fictional discourse (Genova 2007:98). PSEN1 mutations are associated with a variable clinical phenotype which may encompass not only cognitive decline but also epileptic seizures, myoclonus, extrapyramidal features, spastic paraparesis, behavioural and psychiatric symptoms sometimes akin to those seen in bvFTD, aphasia, agnosia, and cerebellar ataxia (Larner 2011b, 2013c; Larner and Doran 2006a, b, 2009b).

Four families with PSEN1 AD have been seen in CFC, with the following mutations: p.Tyr115Cys (Doran and Larner 2006); p.Met139Val (apparently a *de novo* mutation; Larner and du Plessis 2003); p.Arg269Gly (with prominent behavioural and psychiatric symptoms; Doran and Larner 2004b); and p.Arg269His (with late age at onset; Fig. 7.3; Larner et al. 2007). It is recognised that there may be under-ascertainment of such families in the UK (Stevens et al. 2011). Concurrence of early- and late-onset AD in some families (Brickell et al. 2006) may indicate a PSEN1 mutation (Lladó et al. 2010).

Families with late-onset AD apparently transmitted as an autosomal dominant condition but without any of the known AD mutations have been reported on occasion (e.g. Jimenez-Escrig et al. 2005). One such family has been encountered in CFC, with seven affected individuals in two generations, all with onset after age 65 years as far as could be ascertained from oral family history (Hancock and Larner 2007).

AD phenotype has also been reported with some tau (MAPT) gene mutations (Sect. 7.3.2) including p.Arg406Trp (Rademakers et al. 2003; Tolboom et al. 2010) and the IVS10 + 16C > T splice site mutation (Doran et al. 2007).

No examples of APP or PSEN2 mutations have been encountered to date in CFC.

7.3.2 Frontotemporal Lobar Degenerations

Of the various mutations which may be deterministic for FTLD (Box 7.4), until around 2011–2012 those affecting MAPT and GRN genes were thought to be the most common (Seelaar et al. 2011; Rohrer et al. 2009), but the discovery of the C9orf72 hexanucleotide (GGGGCC) repeat expansion (DeJesus-Hernandez et al. 2011; Renton et al. 2011) has changed the clinical landscape of FTLD. Algorithms or flow charts for genetic testing in FTD pre- and post-dating this discovery have been presented (Goldman et al. 2011b; Le Ber et al. 2013).

MAPT mutations may be associated with a variable clinical phenotype encompassing cases defined as progressive supranuclear palsy (PSP), corticobasal degeneration, idiopathic Parkinson's disease (rarely), AD, FTLD with motor neurone disease (FTD/MND), progressive non-fluent aphasia, and respiratory failure, as well as bvFTD (Larner and Doran 2009a). Clinical heterogeneity is also recognised with GRN mutations. Whilst most cases present as bvFTD or progressive non-fluent aphasia, presentations resembling AD, DLB and CBS have been reported (van Swieten and Heutink 2008).

To date, seven families with MAPT mutations have been seen at CFC (e.g. Fig. 7.4), all with the splice site IVS10 + 16C > T mutation (Doran et al. 2007; Larner 2008d, 2009a, c, 2012a, 2017b Case 1, see Table 4.32; Larner and Doran 2009c; see also Case Studies 3.1 and 4.3). These families were not evidently connected to other IVS10 + 16C > T pedigrees reported from this region of northwest England and north Wales (Pickering-Brown et al. 2002) but presumably all derive from the same Welsh founder (Colombo et al. 2009).

In three of these families, the proband was initially diagnosed with AD (Doran et al. 2007; Larner 2008d, 2009a). Intrafamilial clinical heterogeneity has been observed, with other family members having a typical bvFTD phenotype from the outset, others having a parkinsonian syndrome (Larner 2009c). One patient developed a PSP phenotype (Larner 2009a). One patient underwent self-funded autologous stem cell transplantation at a commercial facility in Europe, without evident clinical improvement over the following 2 years, and with undoubted deterioration in his motor phenotype which eventually resembled PSP. He died from respiratory

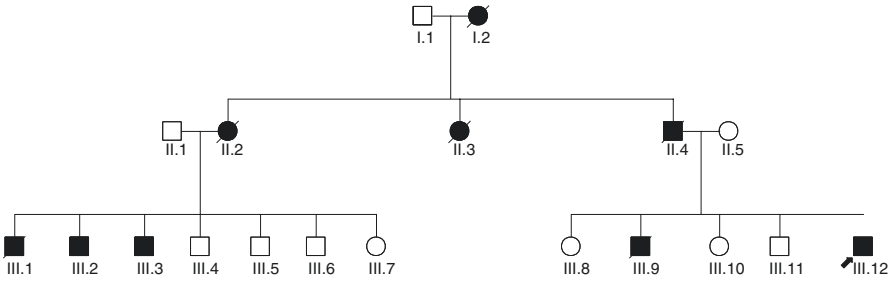

Fig. 7.4 Provisional family tree (genogram), IVS10 + 16C > T tau gene mutation, proband arrowed (Larner 2009c) reprinted with permission

Case Study 7.5: Clinical utility of neurogenetic testing in diagnosis of dementia: VCP mutation

A man developed proximal muscular weakness in his late-40s which was eventually diagnosed on the basis of clinical phenotype and muscle pathology as inclusion body myopathy. Because his father had had a similar illness complicated by a dementia, his cognitive function was monitored for a number of years, with no deficits seen. Neuropsychological assessment at the age of 60 was the first to show impairments, in immediate and delayed verbal free recall (<1st percentile), verbal fluency (semantic worse than phonemic), confrontation naming, and executive function as assessed by a sentence completion task. Visual recognition memory, attention/working memory, and recognition memory were relatively preserved. When VCP mutation testing became available this confirmed that he harboured a point mutation (p.Arg191Gln) in this gene, previously described in other cases of IBMPFD (e.g. Watts et al. 2004).

failure (Larner 2012a), which has been described in other MAPT mutations (Nicholl et al. 2003).

Although GRN mutations may be as common as MAPT mutations in FTLD (Rohrer et al. 2009), only one patient with a pathogenic mutation of the progranulin gene (p.Glu498fs, in exon 12) has been identified to date in CFC. The proband presented with a non-fluent aphasia, some years after her brother had been seen with typical bvFTD (Larner 2012b). Another patient with a GRN mutation (p.Arg547Cys in exon 11) has been reported from this centre, presenting with parkinsonism and an impulse control disorder (Wong et al. 2009a), but according to the Alzheimer Disease and Frontotemporal Dementia Mutation Database (2017) the pathogenic nature of this sequence change is unclear, no other examples having been reported.

Two patients with valosin-containing protein (VCP) mutations causing inclusion body myopathy associated with Paget's disease of bone and frontotemporal dementia (IBMPFD) have been seen in CFC, as referrals from the neuromuscular clinic (St John and Larner 2015; Case Study 7.5).

A small series of patients with FTD/MND or FTLD with a positive family history of MND have been encountered in CFC (e.g. Doran et al. 2005b; Hancock and Larner 2008; Larner 2008f, 2013d, 2017b; Sathasivam et al. 2008). Hexanucleotide repeat expansions in the C9orf72 gene in association with FTD, MND, and FTD/MND were first described in 2011 (DeJesus-Hernandez et al. 2011; Renton et al. 2011) and this seems to be the most common genetic cause of FTD, accounting for more than 20% of familial cases and 5% of sporadic cases. Patients with this expansion have been identified in CFC (Larner 2013d, 2017b Cases 2 and 3, see Table 4.32; Ziso et al. 2014; McCormick and Larner 2018; Case Studies 5.1 and 7.6).

No cases of FTLD with CHMP2B (Isaacs et al. 2011), TDP-43, or FUS gene mutations have been seen in CFC.

Nasu-Hakola disease (NHD), or polycystic lipomembranous osteodysplasia with sclerosing leukoencephalopathy (PLOSL), also known as presenile dementia with

Case Study 7.6: Clinical utility of neurogenetic testing in diagnosis of dementia: C9orf72 mutation

A man in his mid-60s presented with a 2–3 year history of change in personality, becoming less communicative and outgoing with resulting domestic upset. Dietary habits changed (eating quickly, predilection for chocolate) and he was upset if his routines were interrupted or changed. His father was said to have died with Alzheimer's disease aged 62 and his only brother with motor neurone disease aged 52. The patient was impaired on the Frontal Assessment Battery (see Sect. 4.2.1) scoring 10/18, with points dropped on tests of conflicting instructions, go-no-go, and motor series. Structural brain imaging showed global brain atrophy with frontotemporal preponderance and EMG showed some fasciculation in distal leg muscles without neurogenic change. When originally seen, only TDP-43 gene testing for FTD/MND was available, which proved negative. With the discovery of the C9orf72 hexanucleotide repeat expansion as a cause of FTD/MND, further genetic testing was undertaken and this proved positive.

bone cysts, is an autosomal recessive disorder characterised by large-scale destruction of cancellous bone resulting in bone cysts in the third decade of life which cause pain, swelling, and sometimes fracture of the wrists and ankles, with presenile dementia of frontal lobe type in the fourth decade, sometimes with epileptic seizures. MR brain imaging reveals frontal myelin loss and massive gliosis, "sclerosing leukoencephalopathy", as well as basal ganglia calcification. The condition is genetically heterogeneous, with homozygous mutations being identified in the Tyro protein tyrosine kinase binding protein (TYROBP), also known as DNAX-activation protein 12 or DAP12, gene on chromosome 19q13.12 in some families, and in the triggering receptor expressed on myeloid cells 2 (TREM2) protein on chromosome 6p21.1 in others (Klünemann et al. 2005). Homozygous and heterozygous *TREM2* mutations have been identified in cases of autosomal recessive behavioral variant frontotemporal dementia (bvFTD) without clinical or radiological evidence of bone involvement (Chouery et al. 2008; Giraldo et al. 2013; Guerreiro et al. 2013), including a case from CFC in which compound heterozygosity for a previously recognised *TREM2* missense mutation (p.Asp87Asn) and a novel *TREM2* frameshift mutation (p.Phe143fs) was found (Williamson and Larner 2018); the latter change was thought more likely to be pathogenic. TREM2 is exclusively expressed on immune cells, suggesting that white matter changes are likely to be inflammatory, rather than vascular, in origin. CSF oligoclonal bands were detected in our patient, perhaps reflecting an ongoing inflammatory process, which might ultimately have implications for treatment of patients harbouring *TREM2* mutations (Williamson and Larner 2018).

That monogenic mechanisms do not contribute to the aetiology of all FTLD cases may be illustrated by the observation of discordance for non-fluent progressive aphasia in a monozygotic twin pair over a 7-year period of follow up (Doran and Larner 2004a).

7.3.3 Other Genetic Disorders

A large number of genetic disorders may feature dementia or cognitive impairment as part of the phenotype (Larner 2008a:125–156; 2013a:110–144).

Of the cases of prion disease (Sect. 9.5) seen in CFC, all have been either sporadic or variant cases of Creutzfeldt-Jakob disease (CJD), with no examples of PrP mutations (Larner and Doran 2004).

Huntington's disease (HD) has been seen most frequently in general neurology clinics as a consequence of the movement disorder, but occasional cases have been identified *de novo* in CFC (Larner 2008c; Ziso et al. 2015a). This experience has also indicated that caudate atrophy on structural brain imaging may not be a prominent finding in HD.

Cognitive impairment sometimes amounting to dementia may be seen in cerebral autosomal dominant arteriopathy with subcortical infarcts and leukoencephalopathy (CADASIL), a form of vascular cognitive impairment (see Sect. 9.4). Patients with CADASIL resulting from mutations of the Notch gene have been seen in CFC (Doran and Larner 2009), two with p.Arg169Cys, one with p.Arg697Cys, two with p.Arg90Cys (one illustrated in Case Study 7.7). None had frank dementia, but one patient had progressive cognitive deficits over a 10 year period from diagnosis leading to some impairment of instrumental activities of daily living.

One family with X-linked adrenoleukodystrophy (X-ALD) has been encountered in CFC, in which the proband presented with a frontal-type dementia in his fifth decade (Larner 2003). He had been non-adherent with replacement treatment. Other family members with the same ABCD1 mutation (p.Arg152Cys), also identified in childhood by biochemical screening, were asymptomatic and showed no evidence of subclinical disease on either neuroradiological or neuropsychological assessment, having taken replacement therapy, unlike the proband (Larner 2008e).

Case Study 7.7: Cognitive Impairment in Neurogenetic Disease: CADASIL

A man in his 50s presented with a 2 year history of forgetfulness which had occasioned the loss of his job. Ten years earlier he had presented with severe headache with homonymous hemianopia and MR imaging changes in the white matter of the anterior temporal lobes, prompting consideration of the diagnosis of CADASIL. Neurogenetic testing showed a point mutation (p.Arg90Cys) in the Notch gene, a recognised cause of CADASIL (Utku et al. 2002). He was subsequently treated with aspirin.

On cognitive testing, he performed well on simple cognitive screening instruments (6CIT 2/28, MMSE 29/30) but on a more challenging test, the Hard TYM (H-TYM; Brown et al. 2014) his overall score was 10/30 (visual recall 3/15, verbal recall 7/15), below the cut-offs used for diagnosis of mild cognitive impairment (see Sect. 4.1.9.1: Larner 2015).

Perry syndrome comprises the sequential onset of depression, sleep disturbance, parkinsonism, and respiratory failure, and is inherited in an autosomal dominant manner (Perry et al. 1975). It has been regarded as a rare condition, with only seven families identified by a literature review published in 2008 (Wider and Wszolek 2008). Genome-wide linkage analysis identified disease-segregating mutations in the dynactin 1 (*DCTN1*) gene on chromosome 2p13.1 in families with Perry syndrome, all located in exon 2 (Farrer et al. 2009). Four patients with clinical and genetic evidence of Perry syndrome have been seen at this centre, three in CFC (Case Study 7.8).

Three of the patients were half-sisters from a large family with a history of parkinsonism suggestive of an autosomal dominant disorder, who were eventually shown to carry a *DCTN1* mutation (p.Lys68Glu; Sheerin et al. 2018). The CFC proband presented in her mid-60s with parkinsonism and mild cognitive impairment (MMSE 24/30), with a prior history of depression. Her parkinsonism showed moderate levodopa responsiveness. Another patient also had cognitive impairment (MMSE 22/30) at time of neurological presentation (Aji et al. 2013b). Central hypoventilation causing respiratory impairment has also been described with MAPT mutations (see Sect. 7.3.2; Nicholl et al. 2003; Larner 2012a). It may be that the pathological process in these two conditions affects common neuroanatomical substrates. The CFC experience has suggested that Perry syndrome may be more common than previously thought and that cognitive impairment may be an early feature in this condition (Aji et al. 2013b). Increasing numbers of cases are now seen worldwide, prompting the formulation of diagnostic criteria (Mishima et al. 2018).

Genetic testing for mitochondrial disorders may be undertaken on occasion, since these disorders can be associated with cognitive impairment. However, the

Case Study 7.8: Cognitive impairment in neurogenetic disease: Perry syndrome
This man initially presented to psychiatric services in his 40s with anxiety and depression before developing parkinsonism and cognitive impairment, with no family history of psychiatric, movement, or cognitive disorder. On cognitive testing using the Addenbrooke's Cognitive Examination-Revised (ACE-R; see Sect. 4.1.5.3) he scored 74/100 with problems particularly evident with memory (15/26) and fluency (2/14). Although visuospatial functioning seemed satisfactory on ACE-R, this was not the case when the Mini-Mental Parkinson (MMP; Sect. 4.1.2) test was administered, on which he scored 23/32 with impairments on tests of visual registration, visual recall and shifting. On the Frontal Assessment Battery (Sect. 4.2.1) he scored 8/18, failing the tests of lexical fluency (as in ACE-R), motor programming, and inhibitory control. His phenotype was thought to resemble progressive supranuclear palsy. The development of respiratory failure a few years later prompted consideration of the diagnosis of Perry syndrome and he was found to have a novel *DCTN1* mutation (p.Gly67Asp; Aji et al. 2013a).

multisystem nature of these disorders means that cognitive impairment is never an isolated finding; these patients are more likely to be seen in dedicated clinics, e.g. for neuromuscular problems. Mitochondrial disorders have rarely been encountered in CFC, but include a patient with NARP syndrome (Rawle and Larner 2013) and with the TWINKLE mutation (Larner, unpublished observations).

Other occasional genetically determined conditions seen in CFC include one patient with spinocerebellar ataxia type 17 (SCA17; Randall and Larner 2016) and one with Sotos syndrome (Milburn-McNulty and Larner 2018). One patient from a celebrated local pedigree with porphyria (Youngs 1998) due to a mutation in the porphobilinogen deaminase gene (Poblete-Gutierrez et al. 2006) has also been seen but this condition was not thought relevant to the subjective cognitive complaints.

Chromosomal abnormalities may also produce syndromes which result in cognitive impairment. Down syndrome (trisomy 21) is the most common of these (Larner 2007a, 2011c; Sect. 9.6) but 18q deletion has also been encountered (Adab and Larner 2006; Larner 2009b; Sect. 9.6).

All patients described hitherto in this section have undergone diagnostic genetic testing, rather than predictive testing. Following the diagnosis of AD with a deterministic presenilin 1 gene mutation (p.Arg269His) in their father (Fig. 7.3, III:2; Larner et al. 2007), two of the patient's daughters presented to CFC for cognitive assessment and both had normal performance on cognitive screening instruments and normal structural brain imaging. They were both referred to clinical genetics services for genetic counselling since both wished to consider predictive genetic testing. It was over 5 years later before one of the siblings (Larner 2011d, Case 35), without further cognitive assessment, finally opted for testing and was found to be negative (see also Case Study 3.1).

7.4 Neurophysiology

7.4.1 Electroencephalography (EEG)

Electroencephalography (EEG) is recommended by EFNS guidelines in the differential diagnosis of atypical AD or when CJD or transient epileptic amnesia is suspected (Hort et al. 2010a). EEG use in CFC has been largely restricted to these clinical scenarios. An evidence-based evaluation found insufficient evidence for routine resting EEG in the initial evaluation of subjects with cognitive impairment (Jelic and Kowlaski 2009).

The EFNS recommendation with respect to CJD presumably applies only to sporadic forms (sCJD) since the EEG may remain relatively normal in variant CJD (vCJD). The characteristic change in sCJD, sometimes evolving over time, is of periodic sharp wave complexes (PSWC). Similar changes may be seen on occasion in other neurodegenerative disorders, for example dementia with Lewy bodies (as has been encountered in two cases in CFC; Doran and Larner 2004c), potentially causing diagnostic confusion, although application of rigorous criteria

for the definition of PSWC (Steinhoff et al. 2004) may reduce this possibility. CSF 14–3-3 protein (see Sect. 7.5) may be superior to EEG in identifying CJD (Knopman et al. 2001).

EEG changes in AD are non-specific, so there is little diagnostic gain from routinely performing EEG in suspected AD cases. EEG remains relatively normal in FTLDs, a point enshrined in some diagnostic criteria (Neary et al. 1998), although many patients do in fact have abnormalities (Chan et al. 2004).

7.4.2 Electromyography and Nerve Conduction Studies (EMG/NCS)

Both the AAN and EFNS guidelines are silent about use of EMG/NCS in the assessment of dementia, but these investigations certainly do have a place if a diagnosis of FTLD with motor neurone disease (FTD/MND) is suspected on clinical grounds, for example if fasciculation is observed around the shoulder girdle, or wasting of intrinsic hand muscles is seen (Doran et al. 2005b; Hancock and Larner 2008; Larner 2008f, 2011e; Larner and Gardner-Thorpe 2012; Sathasivam et al. 2008).

A significant proportion of FTLD patients without such clinical evidence may nevertheless harbour subclinical EMG changes suggestive of anterior horn cell disorder (Lomen-Hoerth et al. 2002), but there are no recommendations that EMG should be routinely performed in such cases, even though this finding might have prognostic significance in view of the limited survival of FTD/MND patients (Hodges et al. 2003).

Neurophysiological findings consistent with anterior horn cell involvement may also be seen in neuronal intermediate filament inclusion disease (NIFID) or FTLD-FUS (Roeber et al. 2006; Menon et al. 2011).

7.5 Cerebrospinal Fluid (CSF)

EFNS guidelines recommend cerebrospinal fluid (CSF) analysis as mandatory when vasculitic, inflammatory, haematologic or demyelinating disease is suspected as a cause of cognitive impairment, and in cases of suspected CJD in the differential diagnosis of AD (Hort et al. 2010a), in other words to identify disorders other than AD. It should be noted here, in passing, that primary neurodegenerative disorders have on occasion been reported with CSF oligoclonal bands (Janssen et al. 2004; Jesse et al. 2011), including Nasu-Hakola disease (Sect. 7.3.2; Williamson and Larner 2018).

Much research in recent years has examined the potential value of CSF biomarkers for the diagnosis of AD, especially reduced Aβ42, increased total tau and phospho-tau, or combinations thereof (Blennow et al. 2010), and their use is becoming more widespread. These markers certainly look to have some utility, and hence are incorporated in recent diagnostic criteria for AD (Dubois et al. 2007, 2014), albeit there are issues around standardisation of laboratory assays and use of

different cut-offs (Hort et al. 2010b). To date there has been only very limited experience of CSF AD biomarkers in CFC patients (Wojtowicz et al. 2017).

The value of CSF 14–3-3 protein, a marker of acute neuronal loss, in the diagnosis of sporadic CJD is now well established, and incorporated in guidelines (Knopman et al. 2001; Hort et al. 2010a), although it is not of value in diagnosis of vCJD. It may be elevated in any rapidly progressive neurological disorder (e.g. Jayaratnam et al. 2008).

It is recognised that CSF VDRL is specific but not sensitive for a diagnosis of neurosyphilis, hence at risk of false negatives (cf. blood tests).

Whipple's disease is often mentioned as a potentially reversible form of dementia, though extremely rare in practice. It may be identified using CSF PCR for the causative organism, *Tropheryma whippelii*. No cases have been seen in CFC, the only local case diagnosed in recent times presenting with cerebrovascular pathology (Peters et al. 2002).

CSF analysis is not routinely undertaken in patients referred to CFC, but there are two clinical situations in which it is considered: to exclude an inflammatory, potentially steroid-responsive, condition (as per guidelines); and to assist in the diagnosis of idiopathic normal pressure hydrocephalus (iNPH).

iNPH remains a contentious construct. It is perhaps a more popular diagnosis with neurosurgeons than with neurologists. The CSF tap test, namely assessment of cognition and gait after removal of a significant volume (perhaps 20–30 ml) of CSF, has been advocated to assist in the diagnosis and to determine patient suitability for shunting procedures, but both false positive and false negative tap tests occur (Marmarou et al. 2005; Malm and Eklund 2006). The former may occur in patients later established to have neurodegenerative pathologies, such as PSP (e.g. Schott et al. 2007; Magdalinou et al. 2013). One patient responsive to CSF tap but not to shunting (Larner and Larner 2006) was later found to have a marked response to levodopa preparations, leading to a provisional diagnosis of PSP-parkinsonism (following the nomenclature of Williams et al. 2005).

The diagnosis of iNPH is sometimes suggested, particularly by non-neuroradiologists, on the basis of brain imaging showing ex vacuo atrophy, but these appearances may be due to a neurodegenerative process such as AD. AD has been reported as a common "comorbidity" of iNPH (Golomb et al. 2000). However, the possibility remains that such individuals have AD, with no "NPH": presence of AD pathology in suspected iNPH has been associated with lack of response to shunting (Hamilton et al. 2010).

7.6 Tissue Diagnosis: Brain Biopsy and Autopsy

Brain biopsy is sometimes undertaken in patients with cognitive decline, often with the hope of identifying a potentially remediable (e.g. inflammatory) disorder rather than a neurodegenerative disease. However, such a diagnosis is rarely uncovered (Warren et al. 2005), and there are usually some peripheral indicators of this possibility (e.g. CSF markers) which might have prompted an empirical trial of steroids

without recourse to biopsy. That said, the absence of a tissue diagnosis may leave matters uncertain, which impacts on decisions about how long to continue with immunomodulatory therapies which are not without adverse effects.

Brain biopsy for patients with cognitive decline has been used extremely sparingly at WCNN, with only a handful of biopsies performed (Pulhorn et al. 2008; Wong et al. 2009b, 2010b). Even in a national tertiary referral centre, only 90 biopsies for dementia disorders were performed in a 14 year period (Warren et al. 2005). At WCNN, biopsies for cognitive decline have generally revealed untreatable conditions (AD, prion disease, tauopathy, cerebral amyloid angiopathy) and so have not altered patient management, although they may provide important prognostic information (Wong et al. 2009b, 2010b), specific examples being two cases of prion disease with unusual phenotypes (Ali et al. 2013; Williamson and Larner 2016). Tissue diagnosis has on occasion been available for other cerebral mass lesions associated with cognitive deficits (Ibrahim et al. 2009).

Tonsil biopsy for variant CJD (Hill et al. 1999) has not been undertaken at this centre.

Autopsy diagnosis, although of no use to the individual patient, may be of importance for a number of reasons, ranging from continuing clinician education in clinico-pathological correlation to informing relatives about their loved ones ultimate diagnosis. In provincial centres, neuropathology services may be dominated by biopsy work (brain tumour, muscle, nerve) which may leave little opportunity for post-mortem work. Post mortem brain tissue may sometimes need to be sent to other centres of excellence for diagnostic purposes. There have been a number of examples of autopsy diagnosis of neurodegenerative disorders in CFC patients over the years (Doran and Larner 2004c; Doran et al. 2003, 2005b, 2007; Du Plessis and Larner 2008; Larner and Doran 2004; Larner and du Plessis 2003; Menon et al. 2011; Murray et al. 2008; Sathasivam et al. 2008; Ziso et al. 2015b).

7.7 Other Investigations

A number of other investigations may be contemplated for patients with cognitive complaints dependent upon the specific clinical situation. For example, suspicion of a sleep-related disorder may prompt sleep studies such as overnight pulse oximetry or polysomnography, to identify conditions such as obstructive sleep apnoea or periodic leg movements of sleep which may impair sleep quality and result in cognitive impairment (see Sect. 8.2.4).

7.8 Summary and Recommendations

What investigations should be undertaken in cases of cognitive decline or suspected dementia? Is there an appropriate minimum dataset? Considering the heterogeneity of the clinical population seen, a tailored approach is perhaps more appropriate than any prescriptive guidelines. Prototypical cases of AD, as defined by clinical presentation

based on history and neuropsychological assessment, may require little in the way of additional investigation; structural brain imaging may be performed, if only to reassure (particularly relatives) that there is no other disease process, but even here there is risk. For example, the finding of changes indicative of cerebrovascular disease may prompt a diagnosis of "vascular dementia" in some quarters even though diagnostic criteria for the latter are not met (Román et al. 1993; van Straaten et al. 2003). This is not merely an academic point, since a patient labelled with "vascular dementia" may not qualify for treatment with cholinesterase inhibitors in some dispensations, unlike AD (see Sect. 10.2.1). All investigations have the potential to be "a sword in a blind man's hands" (as the seventeenth century physician Thomas Willis, inventor of the word "neurology", described the treatment dispensed by unlicensed practitioners; Rose 2012:21), the moreso the easier their availability, particularly when those ordering them having little or no competence in their interpretation (e.g. just read the report of a brain scan).

In younger people, where the potential differential diagnosis of cognitive impairment is broader, investigations may consequently be more extensive, especially if inherited metabolic conditions are considered (Doran 1997; Rossor et al. 2010; Davies et al. 2011). Clinical acumen, based in part on clinician experience, will therefore be the most important guide to investigation, rather than a cookbook or shopping list approach. It is perhaps also worth pointing out 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 (Landau et al. 2010).

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Diagnosis (1): Cognitive Syndromes, Comorbidities, No Diagnosis, and Wrong Diagnosis

8

Contents

Abstract

This chapter examines the various cognitive syndromes (e.g. amnesia, aphasia, agnosia) which may be defined by clinical assessment and investigation, as a prelude to establishing aetiological diagnosis. It also examines various comorbidities which may be encountered in dementia disorders, including behavioural and neuropsychiatric features, delirium, epilepsy and sleep-related disorders.

Keywords

Dementia · Diagnosis · Cognitive syndromes · Comorbidities

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8.1 Cognitive Syndromes

The diagnosis of specific disorders causing cognitive impairment or dementia (see Chap. 9) may be facilitated by the definition of cognitive syndromes. In other words, diagnosis of a clinical syndrome may inform the aetiological diagnosis, although the mapping is far from 1:1 because of the heterogeneity of pathological entities, with clinical phenotype depending on the exact topographic distribution of disease (Larner 2013a:1–22).

Cognitive neuropsychology often depends on unusual cases with highly circumscribed deficits for the development of ideas about brain structure/behaviour functional correlations (Shallice 1988). The messy contingencies of clinical practice seldom correspond to these archetypal cases, but nonetheless specific cognitive syndromes can often be delineated, which may facilitate differential diagnosis. The classical deficits, corresponding to the recognised domains of cognitive function examined by cognitive screening instruments (see Chap. 4), are amnesia, aphasia, agnosia, apraxia, and a dysexecutive syndrome. In turn, specific clinical diagnoses (see Chap. 9) may be arrived at based on these deficits and informed by investigation findings (see Chap. 7).

8.1.1 Memory: Amnesia

Amnesia is an acquired syndrome of impaired encoding of information resulting in impaired recall. Amnesic syndromes may be classified according to variables such as onset (acute, subacute, chronic), duration (transient, persistent), pattern (anterograde, retrograde), and course (fixed, progressive) (Fisher 2002; Papanicolaou 2006; Larner 2016:20–1). Many causes of amnesia are recognised (Box 8.1), some of which have been encountered in CFC.

Box 8.1: Causes of amnesia

Chronic/persistent:

Alzheimer's disease, amnestic mild cognitive impairment (aMCI)
Other neurodegenerative disorders: FTLD, DLB
Wernicke-Korsakoff syndrome, alcohol-related dementia
Limbic encephalitis (paraneoplastic or non-paraneoplastic)
Sequela of herpes simplex encephalitis
Hypoxic brain injury
Bilateral paramedian thalamic infarction/ posterior cerebral artery occlusion ("strategic infarct dementia")
Structural lesions: third ventricle tumour, colloid cyst; fornix damage; temporal lobectomy (bilateral; or unilateral with previous contralateral injury, usually birth asphyxia)

Inflammatory disorders, e.g. multiple sclerosis
Focal retrograde amnesia (rare)

Acute/transient:

Traumatic brain (closed head) injury
Adverse drug effect
Transient global amnesia (TGA)
Transient epileptic amnesia (TEA)
Migraine
Hypoglycaemia

8.1.1.1 Chronic/Persistent Amnesias

A chronic/persistent amnesic syndrome is the most common presentation of Alzheimer's disease (AD) often with evidence of mild dysfunction in other cognitive domains (e.g. perception, language, executive function), but sometimes occurring in isolation (Larner 2006a, 2008a), as enshrined in diagnostic criteria (Dubois et al. 2014; Boxes 7.1 and 7.2). A temporal gradient is often evident in the amnesia of AD, with more distant events being more easily remembered than recent happenings, often characterised by the patient's relatives as a defect in "short term memory" with preserved "long term memory". Verbal repetition ("repetitive questioning") regarding day to day matters, reflecting the anterograde amnesia, is one of the most common and, for relatives, most troubling symptoms of AD (Rockwood et al. 2007; Cook et al. 2009).

Mild cognitive impairment (MCI) was initially proposed as a term to describe cognitive impairment which did not amount to dementia, and in which activities of daily living were essentially preserved (Petersen 2003). For some this is a heterogeneous category (Sects. 2.2 and 9.1), whereas others, defining MCI by a score of 0.5 on the Clinical Dementia Rating scale, envisage MCI to be early-stage AD (Morris et al. 2001). However defined, MCI may be exclusively amnestic (single-domain amnestic MCI; aMCI) or show deficits in other domains (multi-domain amnestic MCI; Winblad et al. 2004).

All the multidomain cognitive screening instruments used in patient assessment (see Sect. 4.1) have memory testing paradigms, usually of the registration/recall type, sometimes with an added recognition paradigm, and specific (single domain) cognitive tests for memory are also available (e.g. Buschke et al. 1999). The hippocampal origin of the AD/amnestic MCI memory deficit may be examined by controlling for the encoding phase (e.g. the "5 words" test of Dubois et al. 2002). This may also help in the differentiation from physiological age-related memory complaints, the growing difficulty (lessening efficiency) in encoding new information which afflicts us all as we age.

Memory complaints may be evident in neurodegenerative disorders other than AD/aMCI, but are often accompanied by other more prominent symptoms which assist in differential diagnosis. Although a complaint of memory difficulties is not

infrequent from relatives of patients with frontotemporal lobar degeneration (FTLD) syndromes, this is more often related to behavioural and linguistic problems rather than amnesia per se, although amnesic presentations of pathologically confirmed FTLD have been described on occasion (e.g. Graham et al. 2005; Papageorgiou et al. 2016), and may be a particular feature in FTLD of late onset (Baborie et al. 2012, 2013). Diagnostic errors in which clinical overlap causes confusion between FTLD with AD may therefore occur (Davies and Larner 2009a), and some genetically-determined FTLD cases (Sect. 7.3.2) undoubtedly do present with an AD-like phenotype (Doran et al. 2007; Larner 2008b, 2009).

Dementia with Lewy bodies (DLB) may also be mistaken for AD, but typically there is more attentional disturbance and visuospatial dysfunction with relative preservation of memory (Sect. 9.3).

Alcohol-related memory problems, both Wernicke-Korsakoff syndrome (described before Korsakoff by Lawson in 1878; Larner and Gardner-Thorpe 2012) and alcohol-related dementia, have been seen only rarely in CFC, presumably because local services for alcohol problems absorb these patients, even though it is more prevalent amongst patients with early onset dementia. This situation may change in the future if binge drinking habits in youth translate into an epidemic of alcohol-related dementia in the future (Sachdeva et al. 2016; Cheng et al. 2017).

Autoimmune (also sometimes known as limbic) encephalitis is a syndrome of subacute or chronic amnesia, often accompanied by anxiety and depression, epileptic seizures, hypersomnia, and hallucinations, with active CSF (pleocytosis, raised protein). The syndrome may be viral, paraneoplastic, or non-paraneoplastic in origin (Schott 2006). Non-paraneoplastic limbic encephalitis may be associated with serum (and CSF) antibodies directed against neuronal antigens located either on the cell surface or intracellularly (Graus et al. 2016; Pollak et al. 2017).

First to be described were serum antibodies thought to be directed against voltage-gated potassium channels (VGKC-NPLE; Thieben et al. 2004; Vincent et al. 2004), but the underlying antigens in the VGKC complex were latterly shown to be leucine-rich glioma inactivated 1 (LGI1) and contactin-associated protein-like 2 (CASPR2) (Binks et al. 2018). A number of VGKC-NPLE patients have been reported from CFC (S Wong et al. 2008, 2010; Ahmad and Doran 2009; Ahmad et al. 2010). In a consecutive series, immunosuppressive therapy with plasma exchange, intravenous immunoglobulin, and intravenous followed by oral steroids was associated with prompt remission of epileptic seizures and correction of hyponatraemia (1 week), improvement in cognitive function as assessed with the Addenbrooke's Cognitive Examination and its revision (ACE and ACE-R; see Sects. 4.1.5.1 and 4.1.5.3) (3 months), and improvement in neuroradiological appearances (9 months) (S Wong et al. 2008, 2010). Some patients with VGKC-NPLE have been reported to develop a profound retrograde amnesia as a sequela of the acute disease (Chan et al. 2007), prompting speculation that some cases of "focal retrograde amnesia" (see below; Kapur 1993) may in fact be recovered episodes of VGKC-NPLE (Lozsadi et al. 2008). Hence, though rare, VGKC-NPLE must be considered in cases of subacute amnesia because of its potential reversibility.

An autoimmune encephalitis associated with antibodies directed against the NMDA receptor (anti-NMDAR encephalitis) was first described in young women with ovarian teratoma (Vitaliani et al. 2005), and subsequently in other patient groups. CFC experience has included a patient on long-term immunosuppression for a renal transplant who was unresponsive to standard treatment regimes (Titulaer et al. 2013) and who was eventually discovered to have an underlying lymphoma (Randall et al. 2018).

Autoimmune encephalitis associated with antibodies against glutamic acid decarboxylase (GAD) has also been seen in CFC (Bonello et al. 2014). Unlike VGKC-NPLE, this is a chronic non-remitting disorder, with antibody titres remaining high after immunosuppression, and patients often continue to have seizures despite intense anti-epileptic drug therapy (Malter et al. 2010). Sequential cognitive assessment of one patient with the Repeatable Battery for the Assessment of Neuropsychological Status (RBANS; Randolph et al. 1998; see Sect. 4.1.11) showed no evidence for cognitive improvement over 30 months of follow-up (Bonello et al. 2014).

Structural damage to anatomical areas involved in memory function (Papez circuit) is an occasional cause of amnesia. Anterograde amnesia associated with damage to the fornix, a fibre bundle which connects the hippocampus to the mamillary bodies within the limbic system, has been described (Sweet et al. 1959), particularly following removal of third ventricle colloid cysts (Aggleton et al. 2000; Case Study 7.2). A patient with persistent anterograde amnesia with some additional executive dysfunction following removal of an isolated subependymal giant cell astrocytoma which invaded the left fornix has been seen in CFC (Ibrahim et al. 2009). Amnesia did show some improvement over a follow up period of 12 months, suggesting that tissue swelling secondary to traumatic surgical tissue dissection may have contributed to the clinical presentation and course.

Although cognitive impairment has been increasingly recognised as a clinical feature of multiple sclerosis (MS) in recent years (e.g. LaRocca 2011; Jongen et al. 2012), this is usually of subcortical type with impaired executive function and slowed processing speed as a consequence of progressive acquisition of white matter damage, whilst cortical cognitive syndromes such as amnesia are relatively rare: hence a typical "white matter dementia" (Filley 2012). An attempt to characterise isolated cognitive relapses has been made (Pardini et al. 2014). Prominent amnesia has been described in a cortical variant of MS, with or without aphasia, alexia and agraphia (Zarei et al. 2003). Acute presentation of MS with amnesia appears to be rare (Vighetto et al. 1991), particularly as a proven consequence of demyelination (Shanmugarajah et al. 2017). Other potential causes for this syndrome occurring in MS should always be considered. One patient with an acute onset of demyelinating disease, probably relapsing-remitting MS, and with the clinical phenotype of amnesia has been encountered in CFC (Larner and Young 2009). Cognitive impairment as a prominent early symptom of MS has also been encountered (Young et al. 2008). The rarity of amnesia in MS may perhaps explain the relatively lack of efficacy of cholinesterase inhibitors for cognitive impairment in MS (Larner 2010b:1701). Cognitive impairment may on occasion be encountered in other CNS inflammatory disorders, such as relapsing polychondritis (Ellis et al. 2017).

Focal retrograde amnesia is a rare syndrome in comparison with anterograde amnesia, in which recent events can be more easily recalled than distant ones, a reversal of the usual temporal gradient of amnesia (Kapur 1993). In one case of focal retrograde amnesia seen in CFC, the Autobiographical Memory Interview (Kopelman et al. 1989) showed autobiographical amnesia for childhood, teenage and adult life but the patient was able to give a reasonable account of current news events and auditory delayed recall was preserved. MR brain imaging showed some left temporal lobe atrophy (Larner et al. 2004a). The aetiology of focal retrograde amnesia is uncertain; in this case it may possibly have been related to prior alcohol misuse. Functional amnesias are typically retrograde in nature (Markowitsch and Staniloiu 2013).

8.1.1.2 Acute/Transient Amnesias

Probably the most commonly encountered acute/transient amnesia in CFC is transient global amnesia (TGA), although even this is rare (Fig. 8.1). TGA consists of an abrupt attack of impaired anterograde memory, often manifest as repeated and circular questioning, with a variably severe retrograde amnesia, but with intact working memory, semantic memory, and other cognitive domains (language, perception) and without clouding of consciousness or focal neurological signs (Bender 1956; Guyotat and Courjon 1956; Fisher and Adams 1958, 1964; Hodges 1991; Quinette et al. 2006; Bartsch and Deuschl 2010). Episodes are of brief duration (<24 h by definition, and usually 4–6 h), with no recollection of the amnesic period following resolution. Clinical diagnostic criteria have been formulated (Hodges and Warlow 1990). Recognised precipitating factors for TGA include emotional upset or physical exercise, including sexual activity (Larner 2008c). Predisposing factors include age (typically affects those in their 50s or 60s; Fig. 8.1), migraine (a population-based cohort study found that females with migraine aged 40–60 had a

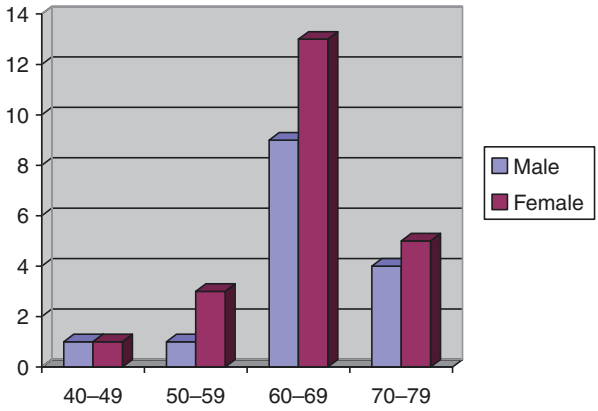

Fig. 8.1 Age and gender distribution of consecutive cases fulfilling diagnostic criteria for TGA (n = 37) seen in author's clinic over 16-year period (2002–2017) (adapted from Larner 2017b:98) reprinted with permission

greater risk of developing TGA: Lin et al. 2014) and possibly those with a familial history (Larner 2017a). Aetiology is uncertain but temporary deactivation or functional ablation of memory-related neuroanatomical substrates seems likely. The CFC experience of TGA has been described in detail elsewhere (Larner 2017b).

Transient epileptic amnesia (TEA) is a distinctive epilepsy syndrome, characterised by brief amnesic episodes, typically occurring on waking, and associated with accelerated long-term forgetting and autobiographical amnesia (Zeman et al. 2012). TEA enters the differential diagnosis of TGA (Ung and Larner 2014), but differs in a number of respects, including the timing and frequency of attacks. Only very occasional cases of TEA have been encountered in CFC (Larner 2017b:35–7). In one possible case, episodes initially diagnosed as parasomnias but typical of TEA had approximately the same age at onset as a more pervasive memory problem which evolved to AD (Krishnan and Larner 2009). Epileptic seizures in AD may take a number of forms, and may occur at onset of cognitive decline (although they become more frequent with disease duration; see Sect. 8.2.3), so this concurrence might possibly reflect shared pathogenic processes involving synaptic network pathology in the medial temporal lobes (Larner 2010a, 2011a). TEA has also been suggested as a cause of wandering behaviours observed in AD patients (Rabinowicz et al. 2000).

Other causes of acute/transient amnesia which have been seen on occasion in CFC, and which may need to be considered in the differential diagnosis of TGA and TEA (Larner 2017b:27–55), include profound hypoglycaemia (Cox and Larner 2016; Larner et al. 2003a) and migraine (Larner 2011b).

Amongst the many transient phenomena that may be encountered in the context of migraine attacks, amnesia is sometimes prominent. A patient who drove apparently safely for several miles, missing her turning, without awareness of her journey ("unconscious driving phenomenon") developed a headache typical of migraine, which she had suffered from since teenage years, at the end of her journey (Larner 2011b). A syndrome of acute confusional migraine is recognised in children (Pacheva and Ivanov 2013) which has some features akin to TGA (Sheth et al. 1995; Schipper et al. 2012); both may be examples of "cognitive migraine" (Larner 2013b).

Profound hypoglycaemia is a recognised cause of acute amnesia (Fisher 2002), but relatively few cases with longitudinal neuropsychological data have been reported. A patient seen in CFC (Case Study 8.1) illustrated a focal pattern of deficit, selective for anterograde memory and learning, probably reflecting hippocampal vulnerability to the effects of neuroglycopaenia, which gradually, though incompletely, reversed over a period of months (Larner et al. 2003a). However, at long-term follow up the patient had developed a dementia, with particular decline during a period of repeated profound hypoglycaemic episodes (Cox and Larner 2016).

Case Study 8.1: Acute amnesia due to hypoglycaemia, evolving to dementia
A 61-year old man with long-standing (ca. 50 years) insulin-dependent diabetes mellitus type 1 which was being treated with continuous subcutaneous insulin infusion was found collapsed with blood glucose of 1.0 mmol/L. After correction of hypoglycaemia, he noted difficulty remembering names of friends and content of recent conversations, necessitating use of external memory aids. Neuropsychological assessment showed normal attention, concentration, language and working memory function, but impaired verbal and visual immediate and delayed recall (WMS III, Camden Memory Tests). MR brain imaging was normal. There was gradual improvement in his memory function: at 4 months he continued to have impairments in short term verbal memory and learning but there was improvement in visual memory. Scores on MMSE at 1, 4 and 10 months were 27, 28, and 30/30, and on Addenbrooke's Cognitive Examination were 82, 93, and 93/100 respectively.

He was then lost to follow up, and not seen again until aged 75, by which time he was resident in a nursing home with a diagnosis of dementia (MoCA 12/30, MACE 11/30), presumed to be of vascular origin. Review of previous records showed repeated admissions for hypoglycaemia prior to nursing home placement, with MMSE 25/30 and 17/30 at age 65 and 67 (Fig. 8.2). Whether this decline was a consequence of repeated hypoglycaemic episodes was not clear: MR brain imaging at age 75 showed global brain atrophy but only minor ischaemic changes.

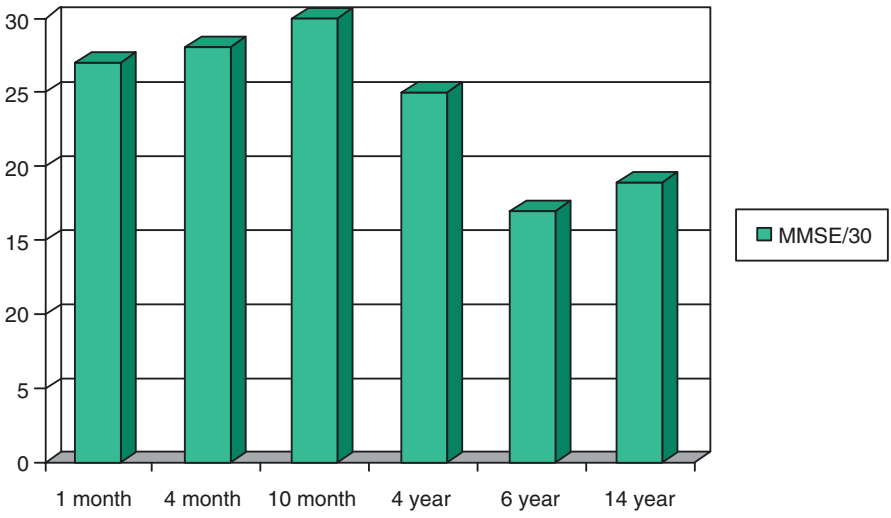

Fig. 8.2 Evolution of cognitive performance following recurrent episodes of profound hypoglycaemia: sequential MMSE scores plotted against period of follow up, to 14 years (adapted from Larner et al. 2003a; Cox and Larner 2016) reprinted with permission

8.1.2 Language: Aphasia, Alexia

Aphasia is an acquired syndrome of impaired language function affecting the spoken word. The symbolic code of language may also be impaired in the context of its written form, either in reading (alexia) or writing (agraphia), difficulties in which (e.g. fluency, comprehension) generally mirror those in the spoken form. Various causes of aphasia are recognised (Benson and Ardila 1996; Rohrer et al. 2008; Larner 2016:30–1). The possibility that linguistic structure may either determine or influence cognition is at the core of the so-called Sapir-Whorf hypothesis (linguistic relativity).

8.1.2.1 Aphasia

Various disorders may present with a primary complaint of aphasia in a cognitive disorders clinic.

Linguistic impairment is one of the commonly recognised presentations of FTLD (cf. behavioural presentation; Sect. 8.1.5). The aphasic phenotype may be either non-fluent or fluent, the syndromes of progressive non-fluent aphasia and semantic dementia, respectively (Neary et al. 1998; McKhann et al. 2001), now sometimes denoted as the agrammatic and semantic variants of primary progressive aphasia (Gorno-Tempini et al. 2011; see Sect. 9.2). Speech apraxia, the impaired articulation of speech sounds especially with increasing articulatory complexity, may be seen as a component of progressive non-fluent aphasia (Grossman 2012).

Aphasic presentations of Alzheimer's disease are well-recognised but rare (Caselli and Tariot 2010:91–9). Clinically these may sometimes have the phenotype of progressive non-fluent aphasia (PNFA) or, much less commonly, semantic dementia (Davies et al. 2005; Alladi et al. 2007). Gorno-Tempini et al. (2004) delineated a third type of progressive aphasia, logopenic progressive aphasia (LPA), characterized by slow speech with long pauses, impaired syntactic comprehension and anomia, in which AD pathology is the most common neuropathological substrate (Gorno-Tempini et al. 2008). LPA has been incorporated into modern clinicobiological AD diagnostic criteria (Dubois et al. 2014).

Aphasic presentations accounted for around 4.5% of new AD cases seen in CFC over a 6-year period (2000–2005) (Larner 2006a). Great care must be taken with this diagnosis, however, because of the possible confusion with linguistic presentations of FTLD; instances requiring diagnostic revision following the passage of time have been encountered (see Sect. 9.1; Davies and Larner 2009a).

Overlap between the linguistic features of PNFA and clinically diagnosed corticobasal degeneration (CBD) has been noted (Graham et al. 2003). However, the frequent occurrence of CBD phenocopies, the corticobasal syndrome (CBS; Doran et al. 2003), may possibly jeopardise this conclusion (Larner and Doran 2004).

Occasional unusual cases with linguistic presentations have been seen in CFC (Larner 2005a, 2006b, 2012a; Larner and Lecky 2007; Larner et al. 2004b). Acute aphasia is most often due to stroke in the middle cerebral artery territory of the dominant hemisphere. Occasional atypical, acute aphasic, presentations of

neurodegenerative disease, both FTLD and AD, have been seen in CFC following cardiac surgery, and initially mistaken for cerebrovascular disease (Larner 2005a). Presumably, an acute cerebral insult may render manifest a previously slowly progressing subclinical neurodegenerative disorder. Cerebrovascular disease is recognised to lower the threshold for the clinical manifestation of underlying AD pathology (Snowdon et al. 1997).

Aphasia is a rare presentation in multiple sclerosis (Lacour et al. 2004), in contrast to dysarthria which is common. The possibility of a second pathology should be considered when a patient with established MS develops acute aphasia, for example cases of partial seizures or non-convulsive status epilepticus causing aphasia ("status aphasicus") have been presented (e.g. Trinka et al. 2002). In a case of acute aphasia in a patient with long-standing MS seen in CFC, CT brain imaging showed a heterogeneous, partially calcified, lesion in the left lateral temporal lobe with an area of high density anterolaterally, suggesting an acute haemorrhage, confirmed on MR imaging, which also showed typical MS periventricular white matter changes. A second lesion returning heterogeneous signal was also observed in the left occipital lobe. These lesions were thought most likely to be cavernomas, hence entirely incidental to the MS (Larner and Lecky 2007).

8.1.2.2 Alexia

Various causes of alexia are recognised (Leff and Starrfelt 2014; Larner 2016:13–5). The classical disconnection syndrome of alexia without agraphia, also known as pure alexia or pure word blindness, is a form of peripheral alexia in which patients lose the ability to recognise written words quickly and easily. Although patients can write at normal speed, they are unable to read what they have just written. Some authorities classify this syndrome as a category-specific agnosia. Alexia without agraphia often coexists with a right homonymous hemianopia, a particular problem in a patient who passed through CFC (reported by Imtiaz et al. 2001) who sustained at least one accident because of his visual field defect.

Reading may be achieved through the tactile, as well as the visual, modality, as in Braille reading. The nineteenth century American physician Oliver Wendell Holmes (1809–1894) in his *Prelude to a volume printed in raised letters for the blind* (1885) noted Braille readers to be:

> … - you whose finger-tips
> a meaning in these ridgy leaves can find
> Where ours go stumbling, senseless, helpless, blind.

Alexia for Braille reading has rarely been reported (e.g. Birchmeier 1985; Signoret et al. 1987 [translated by Fisher and Larner 2008]; Hamilton et al. 2000), with an additional patient encountered in CFC (Larner 2007a; Case Study 8.2).

Case Study 8.2: Acute Braille alexia
A septuagenarian, blind from birth, a proficient Braille reader with her left index finger, found that she could not read following apparently uncomplicated coronary artery bypass graft surgery. On examination, her spoken language was fluent with no evidence of motor or sensory aphasia. There was no left-sided sensory neglect or extinction, and no finger agnosia. Testing stereognosis in the left hand, she was able to identify some objects (pen, ring, paper clip, watch) but was slow to identify a key, could not decide on the denomination of a coin (50 pence piece, heptagonal; or 10 pence piece, circular) and thought a £1 coin was a badge, although she identified this immediately with the right hand. Two-point discrimination was 3 mm on the pulp of the right index finger (minimum spacing possible between tines) but 5 mm on the pulp of the left index finger. MR imaging of the brain showed a few punctate high signal lesions on T_2-weighted and FLAIR sequences in subcortical white matter, thought to be ischaemic in origin, including one subjacent to the right motor cortex in the region of the internal watershed between anterior and middle cerebral artery territories.

Braille alexia may be viewed as the tactile homologue of pure alexia (alexia without agraphia), and may result from disruption of different, possibly overlapping, psychoperceptual mechanisms, some analogous to those postulated in pure alexia. It may reflect problems integrating tactile information over the temporal or spatial domains, hence an associative form of agnosia (Signoret et al. 1987; Fisher and Larner 2008). A frontal-parietal network may contribute to the integration of perception with action over time, and right hemisphere lesions may be associated with impaired integration of spatial information from multiple stimuli. Tactile agnosia (and astereognosis) may arise from lesions of the parietal area of the cerebral cortex (Luria 1980:168). Alternatively, Braille alexia may reflect a perceptual impairment, hence an apperceptive form of agnosia (Larner 2007a). Since Braille characters are close to the limits of normal perceptual resolution, impaired light touch perception following damage to primary sensorimotor cortex or its connections may result in degraded tactile identification and slowed Braille reading speed.

8.1.3 Perception: Agnosia

Agnosia is a syndrome, most usually acquired, of impaired higher sensory function leading to a failure of recognition, occurring most often in the visual modality but also in other sensory domains (Farah 1995; Ghadiali 2004; Larner 2016:8–9). As mentioned, Braille alexia may in fact be a form of tactile agnosia (see Sect. 8.1.2; Larner 2007a).

Agnosic presentations of Alzheimer's disease are well-recognised, sometimes described as posterior cortical atrophy (PCA; although this syndrome may on occasion have pathological substrates other than AD) or the visual variant of AD (Caselli and Tariot 2010:84–91; Dubois et al. 2014; Crutch et al. 2017). These accounted for around 3% of new AD cases seen in CFC over a 6-year period (2000–2005) (Larner 2006a). Although deficits in other cognitive domains, particularly memory, may be evident from the history or cognitive testing, sometimes the agnosic deficit is isolated, constituting an example of single domain non-amnestic MCI (Winblad et al. 2004); this has been encountered on occasion in CFC (Larner 2004a). Typically these individuals have already been seen by optometrists and/or ophthalmologists prior to referral with no cause for their visual complaint identified. Four patients with PCA were unable to differentiate between a normal and a backward clock (see Sect. 4.1.3.1; Larner 2007b).

Although FTLDs are classically associated with behavioural and linguistic problems with preserved visuoperceptual function, semantic dementia (SD; semantic variant of primary progressive aphasia) is recognised to encompass an associative agnosia, with impairment of object identification on both visual and tactile presentation, presumably a part of the semantic deficit in these patients. SD patients with predominantly non-dominant hemisphere degeneration may present with prosopagnosia (Thompson et al. 2003), a circumscribed form of visual agnosia characterised by an inability to recognise previously known human faces or equivalent stimuli (Larner 2016:261–2).

Agnosia for faces accompanying lesions of the right hemisphere was originally described by Charcot (Luria 1980:378). The term prosopagnosia was coined by Bodamer in 1947, although the phenomenon had been described toward the end of the nineteenth century by Quaglino in 1867 (Della Sala and Young 2003) and Hughlings Jackson in 1872 and 1876, as well as by Charcot in 1883. Brief accounts thought to be suggestive of prosopagnosia have been identified in writings from classical antiquity by Thucydides and Seneca (De Haan 1999). A developmental form of prosopagnosia is also described, which may cause significant social difficulties, as demonstrated by a patient seen in CFC (Larner et al. 2003b; Case Study 8.3).

Case Study 8.3: Developmental prosopagnosia

Assessed in his thirties, this man gave a history of lifelong difficulty identifying people by their faces, despite otherwise normal physical and cognitive development. Examples included failure to identify the faces of fellow pupils when a schoolboy, to identify familiar customers in the work environment, to recognize his wife in the street unless she was wearing familiar clothes, and to identify his children when collecting them from school. However, in his work as an optician, he was easily able to recognize different makes of spectacle frame. His neurological examination was unremarkable, with normal visual acuity, visual fields (confirmed by automated perimetry) and

fundoscopy, and there was no achromatopsia. His reading was fluent, and there were no obvious perceptual difficulties.

Neuropsychological assessment included: the WAIS-R (above average intelligence: Verbal IQ 128; Performance IQ 113, but impaired on Object Assembly subtest); Visual Object and Space Perception (VOSP) battery, on which all subtests (incomplete letters, silhouettes, object decision, progressive silhouettes) were above relevant 5% cut-off scores; the Birmingham Object Recognition Battery (BORB), on which all subtests were above relevant 5% cut-off scores; Warrington Recognition Memory Test, on which words were normal but faces impaired; the Graded Naming Test and the Boston Naming Test on both of which scores were in the normal range. On the Benton Facial Recognition Test (matching faces according to identity) he scored 40/54 (borderline impaired; excessively slow performance). On the Young and Flude Face Processing Tasks he was impaired on the identity matching task (39/48; >3 SD below control mean) and on gender identification (39/48; 2 SD below control mean), but normal on identification of emotional expression (47/48) and eye gaze direction (16/18). He had no subjective awareness that animals might have faces, a possible example of zooagnosia (Larner 2016:347).

Akinetopsia is the name given to a specific inability to see objects in motion whilst perception of other visual attributes remains intact, which may reflect lesions of area V5 of visual cortex (Zeki 1991; Larner 2016:13). Rarely described, a possible example of akinetopsia has been seen in CFC (Larner 2005b; Case Study 8.4). Neuropsychological deficits following carbon monoxide poisoning may be very focal, as for example in a renowned case of visual form agnosia (Goodale and Milner 2004).

Auditory agnosia is one of the clinical features of the semantic variant of primary progressive aphasia, manifesting with impaired word comprehension. As for visual agnosia, this auditory agnosia may be interpreted as a primary sensory abnormality, interlocutors suspecting a "hearing problem" when patients ask for auditory material to be repeated, sometimes prompting investigation with audiometry (McCormick and Larner 2018).

Macdonald Critchely described personification of paralysed limbs in hemiplegics following an initial anosognosia (unawareness of deficit), reporting patients who called their hemiplegic limbs "George", "Toby", "silly billy", "floppy Joe", "baby", "gammy", "the immovable one", "the curse", "lazy bones", and "the nuisance". Patients often showed a detached attitude towards their deficit which was treated with insouciance and cheerful acceptance. Most cases occurred in the context of left hemiplegia (Critchley 1955). A case of personification of a presumed functional neurological disability has been seen in CFC, although it was not apparent whether this was an anosognosic problem (Larner 2010c).

Case Study 8.4: Possible akinetopsia
A male patient in his twenties attempted suicide by deliberate carbon monoxide poisoning (acute carboxyhaemoglobin = 44.6%). On recovery from his acute illness, he complained of difficulty seeing, was unable to fixate or follow visual targets such as the examiner's face, but had normal voluntary saccadic eye movements in both amplitude and velocity. He had "leadpipe" rigidity in all four limbs but there was no tremor. He could walk only with assistance because of his visual difficulty. A diagnosis of delayed parkinsonism with visual agnosia secondary to carbon monoxide poisoning was made. Eventually he could ambulate without assistance but still found it difficult to perceive moving as opposed to stationary objects. Subsequent neuropsychological assessment confirmed an apperceptive visual agnosia. Magnetic resonance imaging of the brain showed bilateral high signal intensity in the caudate and putamen, accounting for his parkinsonism, as well as some subtle bilateral parieto-occipital cortical signal change more rostrally, perhaps accounting for his visual agnosia.

8.1.4 Praxis: Apraxia

Apraxia is an acquired syndrome of impaired voluntary movement despite an intact motor system with preservation of automatic/reflex actions (Larner 2016:32–3).

Of the neurodegenerative disorders, corticobasal degeneration (CBD) was typified in its early descriptions, emanating from movement disorders specialists, as showing unilateral limb apraxia, sometimes with the alien limb phenomenon (e.g. Gibb et al. 1989). However, it has become increasingly apparent that CBD phenocopies, labelled as corticobasal syndrome (CBS), are relatively common, with the underlying pathology often being Alzheimer's disease (e.g. Boeve et al. 1999, 2003; Alladi et al. 2007) and sometimes Pick's disease. Occasional cases of CBS with underlying AD or Pick-type pathology have been seen in CFC (Doran et al. 2003). Apraxic presentations of Alzheimer's disease are now well-recognised (Caselli and Tariot 2010:96–104), but rare: only one apraxic presentation was seen amongst new AD cases seen in CFC over a 6-year period (2000–2005) (Larner 2006a).

8.1.5 Executive Function: Dysexecutive Syndrome

Executive function is a broad umbrella term which may encompass a number of complex thought processes including functions such as problem solving, planning, goal-directed behaviour, and abstraction. In view of the heterogeneity of this construct, no one test can adequately probe "executive function", but a variety of neuropsychological tests may address elements of it, including the Wisconsin Card Sorting Test, word and design fluency tasks, proverb interpretation, cognitive estimates, Stroop task, and gambling tasks (Iowa, Cambridge). Dysexecutive syndrome

is an acquired syndrome of deficits or impairments in these various cognitive tasks which may be accompanied by (and indeed result from) behavioural dysfunction, ranging from disinhibition with loss of social mores to abulia, apathy and social withdrawal (Larner 2016:102). The variety of behavioural (or neuropsychiatric) features seen in this syndrome means that these patients may present initially to psychiatric services, with suspected manic or depressive disorders. Because of the overlap of neurologic and psychiatric symptomatology, these patients are often referred to the CFC by psychiatrists (see Sect. 1.2.2).

Executive dysfunction is typical of the behavioural variant of frontotemporal dementia (bvFTD; Rascovsky et al. 2011), and may emerge with time in the other, linguistic, FTLD phenotypes (Sect. 9.2). The executive impairments found may facilitate the differential diagnosis of bvFTD from AD (Bozeat et al. 2000), and their assessment is incorporated into certain screening instruments such as the Cambridge Behavioural Inventory (see Sect. 5.2.1). In contrast to the impulsiveness which compromises the performance of bvFTD patients on gambling tasks, a patient with semantic dementia has been seen who was still able to bet regularly on horse racing with moderate success despite being essentially mute (Larner 2007c).

The question as to whether a frontal variant of AD (fvAD) exists has been approached in two different ways. Some have defined such a variant based on neuropsychological assessments suggesting a disproportionate impairment of tests sensitive to frontal lobe function. For example, Johnson et al. (1999) reported a group of 63 patients with pathologically confirmed AD, of whom 19 were identified with greater neurofibrillary pathology in frontal as compared to entorhinal cortex, of whom three had disproportionately severe impairment on two neuropsychological tests of frontal lobe function (Trail Making Test A, FAS letter fluency test) at the group level. No details of the clinical, as opposed to the neuropathological and neuropsychological, phenotype of these patients were given, for example whether they presented with behavioural dysfunction akin to that seen in bvFTD. Woodward et al. (2010) defined cases of fvAD as AD subjects scoring in the lowest quartile of scores on the Frontal Assessment Battery (Dubois et al. 2000; see Sect. 4.2.1). Using other assessment scales, these fvAD patients appeared to be simply more severely affected AD patients. In contrast to this approach based on neuropsychological test performance, others have defined a frontal AD variant based on a clinical picture suggestive of bvFTD but with additional investigation evidence suggestive of AD (Larner 2006c; Caselli and Tariot 2010:104–8), although neuropathological confirmation of such cases is rare (e.g. Alladi et al. 2007; Taylor et al. 2008). Clinico-biological diagnostic criteria recognise the fvAD variant (Dubois et al. 2014). Some AD patients with presenilin 1 gene mutations (Sect. 7.3.1) may have a phenotype suggestive of bvFTD (Larner and Doran 2006, 2009; Larner 2013c). One PSEN1 mutation (G183V) has been reported in which there was not only the clinical but also the neuropathological phenotype of bvFTD (Dermaut et al. 2004). One family with the R269G PSEN1 mutation with prominent behavioural and psychiatric symptoms has been seen in CFC (Doran and Larner 2004).

Marked executive dysfunction producing a frontal type of dementia has also been encountered in a patient with X-linked adrenoleukodystrophy (X-ALD),

confirmed on clinical, biochemical and neurogenetic grounds, who was inadequately compliant with his treatment regime (Larner 2003a). Cases of X-ALD presenting with adult onset dementia have only rarely been reported, some with prominent frontal lobe dysfunction (e.g. Powers et al. 1980) and some with behavioural features ("manic-depressive psychosis") which might possibly have been indicative of frontal lobe involvement (Angus et al. 1994).

Behavioural disturbance sufficient to prompt legal redress (antisocial behaviour order, or ASBO, issued by a court) may result from brain disease; this has been seen in a possible case of neuroacanthocytosis (Doran et al. 2006; Larner 2007d).

8.2 Comorbidites

The comorbidities of cognitive disorders, both psychiatric and physical, have attracted greater attention in recent times (Kurrle et al. 2012). Their presence may be apparent on history taking (see Chap. 3) but may require the use of dedicated screening instruments for their identification (see Chap. 5).

8.2.1 Behavioural and Neuropsychiatric Features

The ubiquity of behavioural and psychological symptoms of dementia (BPSD; Finkel et al. 1996) has been increasingly recognised, not least because they, rather than cognitive impairments, are the most common antecedents of nursing home placement, the most costly aspect of dementia care. Since the assessment and treatment of BPSD lies outwith the training and expertise of most neurologists, and because of the close links between CFC and local old age psychiatry facilities, patients developing BSPD have typically been referred on rather than managed in house. Moreover, because some antipsychotic medications used to treat BPSD have been associated with an excess mortality secondary to cerebrovascular disease, behavioural rather than pharmacological therapeutic approaches are now recommended (Cerejeira et al. 2012; Kales et al. 2015).

The FTLDs are often accompanied by non-cognitive neuropsychiatric manifestations such as apathy, disinhibition, loss of insight, transgression of social norms, emotional blunting, and repetitive and stereotyped behaviours (Mendez et al. 2008a; Box 10.3). In a series of FTD/MND patients reported from CFC, over two-thirds were under the care of a psychiatrist at time of diagnosis, some with provisional diagnoses of hypomania or depression, and all of whom were receiving either antidepressant or neuroleptic medications, sometimes in addition to anti-dementia drugs, suggesting that neuropsychiatric symptoms are not uncommon in this condition (Sathasivam et al. 2008). Psychotic symptoms including delusions and hallucinations are, however, rarely seen in FTLDs (Mendez et al. 2008b). FTD/MND may be an exception to this generalisation, sometimes manifesting an early psychotic phase characterised by hallucinations and delusions which may be dramatic and bizarre but transient. This may be related to presence of the C9orf72 hexanucleotide

repeat expansion (Sect. 7.3.2) which has been associated with a number of neuropsychiatric features. For example, in a patient cohort from the United Kingdom it was noted that 38% of mutation carriers presented with florid psychotic symptoms, for which initial psychiatric diagnoses of delusional psychosis, somatoform psychosis, and paranoid schizophrenia had been made. An additional 28% had paranoid, delusional and irrational thinking. Delusions were much more common than hallucinations (Snowden et al. 2012). However, in a large series of FTD patients, Le Ber et al. (2013) reported that hallucinations were indicative of GRN rather than C9orf72 mutations.

A patient with delusion of pregnancy related to the C9orf72 hexanucleotide repeat expansion has been seen in CFC (Larner 2008d, 2013d; Case Study 5.1). This mutation has also been associated with presentations as obsessive-compulsive disorder (Calvo et al. 2012) and bipolar disorder (Floris et al. 2013). A schizophrenia-like psychosis has been reported on occasion as the presenting feature of early-onset FTLD (Velakoulis et al. 2009) but there does not seem to be an association between C9orf72 repeat expansions and schizophrenia (Huey et al. 2013). A patient with a provisional diagnostic label of "undifferentiated schizophrenia" who eventually developed neurological signs and proved to have this mutation has been seen in CFC (Ziso et al. 2014). A bvFTD patient with Cotard syndrome (delusion of negation), a phenomenon previously reported in SD (Mendez and Ramirez-Bermudez 2011), has also been seen in CFC (Larner 2016:83).

Visual hallucinations are included amongst the core criteria in the diagnostic criteria for dementia with Lewy bodies (McKeith et al. 1996, 1999, 2005, 2017). These are usually complex images of people or animals, although the sensation of a presence, someone standing beside the patient (*anwesenheit*; Larner 2016:28–9), is also relatively common in parkinsonian syndromes (Fénélon et al. 2000). A pathologically confirmed case of sporadic Creutzfeldt-Jakob disease (CJD) was initially mistaken for DLB because of the presence of visual hallucinations as well as motor features of parkinsonism and orthostatic hypotension, but the very rapid progression prompted diagnostic re-evaluation. Of note, the visual hallucinations in this case took the form of simple colours rather than complex shapes. Post mortem neuropathology was consistent with the MV1 subtype of CJD (Parchi et al. 1999; Du Plessis and Larner 2008). The Heidenhain variant of sporadic CJD, accounting for perhaps 20% of cases, is characterized by visual disorders throughout the disease course which may include blurred vision, diplopia, visual field restriction, metamorphopsia, cortical blindness, and visual hallucinations (Kropp et al. 1999; Armstrong 2006).

Progressive psychiatric disturbances are one of the typical and often early features of variant CJD (vCJD; Spencer et al. 2002) but these may also occur on occasion in sporadic CJD. Psychiatric features are the presenting feature in around 20% of sCJD patients (Wall et al. 2005; Rabinovici et al. 2006), although not mentioned in current diagnostic criteria. We have experience of a patient with a psychiatric prodrome diagnosed as depression for many months before progressive cognitive decline and investigation features typical of sCJD became apparent (Ali et al. 2013), likewise in a young patient suspected to have vCJD but which proved to be a rare phenotype of sCJD (Williamson and Larner 2016).

8.2.2 Delirium

Delirium is a clinically heterogeneous syndrome characterised by cognitive and behavioural features, diagnostic criteria for which require disturbance of consciousness (which may take the form of subtle attentional deficits only), change in cognition, and onset over a short period of time with fluctuation during the course of the day (Larner 2004b). It is a richly varied syndrome ranging from hypoactive to hyperactive states, with a number of recognised precipitating factors (infection, metabolic derangement, various medications) and predisposing factors (age, medical comoribidty, visual and hearing impairment). Dementia is one of the recognised predisposing factors for delirium (Davis et al. 2012), and the differential diagnosis may be difficult, since the two may coexist ("delirium superimposed on dementia"; Morandi et al. 2012).

It is exceptionally unusual for delirium per se to present in an outpatient setting, such as CFC, rather than acutely, although a history of previous episodes of unexplained confusion may be obtained in patients presenting to the clinic with cognitive impairments or dementia. Use of the Confusion Assessment Method may assist with the diagnosis of delirium (CL Wong et al. 2010), but it may sometimes be necessary to institute empirical therapy for presumed delirium (i.e. review medications, treat underlying infection, correct metabolic abnormalities, reduce sensory impairments).

8.2.3 Epilepsy

The concurrence of epileptic seizures and cognitive decline has a broad differential diagnosis (Lozsadi et al. 2008; Larner 2010a, 2011d). Epileptic seizures may either be a cause of cognitive dysfunction (generalised and complex partial seizures are usually characterised by amnesia for the event) or be associated with cognitive disorders. In the former category, occasional cases of repeated seizures producing a phenotype akin to AD have been reported (e.g. Høgh et al. 2002; Tombini et al. 2005). More commonly, however, AD may be accompanied by epileptic seizures.

Alzheimer did not mention seizures in his original reports. Allison (1962:118) claimed that Solomon Carter Fuller (1912) noted, in what is probably the first paper on Alzheimer's disease to be published in English, convulsive fits in a pathologically confirmed case in the later stages. However, a reading of Fuller's lengthy case report leads to the assumption that Allison was referring to the "short periods of unconsciousness or dream-like states" which occurred in the two years before the patient's "final breakdown" (Fuller 1912:441), but no account of convulsion was found (Larner 2013e). However, Fuller noted in his summary of previously published cases that "In a few of the cases motor disturbances have been noted as residua of epileptiform convulsions. Convulsions with loss of consciousness, however, have not been observed, save in the terminal stage, epileptiform attacks and muscular twitchings being recorded" (Fuller 1912:554). An early, definite, report of epileptic seizures in pathologically confirmed AD is that of Hannah (1936).

Epileptic seizures in AD have become a subject of increasing interest in recent times (Larner 2010a, 2011a; Irizarry et al. 2012; Pandis and Scarmeas 2012; Chin and Scharfman 2013; Vossel et al. 2017). This has been prompted, at least in part, by laboratory observations of transgenic animals harbouring pathogenic AD mutations. Such animals have been shown not only to have high brain levels of amyloid beta-peptides and to develop AD pathological changes and cognitive deficits, but also to have spontaneous non-convulsive seizure activity in cortical and hippocampal networks (Palop et al. 2007). GABAergic sprouting, with enhanced synaptic inhibition and deficits in synaptic plasticity, was observed in the dentate gyrus in these mouse models. It has also been shown in experimental animals that amyloid beta-peptides may induce neuronal hyperexcitability and trigger progressive epilepsy (Minkeviciene et al. 2009). These animal models have been used to investigate possible treatments with anti-epileptic drugs (Ziyatdinova et al. 2011).

These animal studies have raised the possibility that epileptiform activity, with or without clinical seizures, is an integral part of the AD phenotype, rather than being merely an epiphenomenon. High rates of subclinical epileptiform activity have been reported in early-onset AD patients (Vossel et al. 2016) and epidemiological studies have reported clinical seizures particularly in early-onset disease (e.g. Mendez et al. 1994; Amatniek et al. 2006; Bernardi et al. 2010). Epileptic seizures have been reported in around 20% of reported presenilin-1 mutations causing early-onset AD, prompting the suggestion that this may be a genetic epilepsy syndrome (Larner 2011c).

It has been repeatedly observed that seizure prevalence increases with disease duration in AD (Larner 2010a) although a study in CFC showed that a small percentage of newly diagnosed AD patients (6.8%) had seizures at the time of AD diagnosis and that in half of these (3.4% of the whole cohort) no explanation for seizures other than AD could be identified (Lozsadi and Larner 2006). The NINCDS-ADRDA clinical diagnostic criteria for AD stated that epileptic seizures in advanced disease are consistent with a diagnosis of probable AD, whereas epileptic seizures at onset or early in the course of the illness make the diagnosis of probable AD uncertain or unlikely (McKhann et al. 1984); early occurrence of seizures remains an exclusion criterion for typical AD in modern criteria (Dubois et al. 2014). However, this study (Lozsadi and Larner 2006) clearly indicated that early seizures should not entirely rule out the diagnosis of AD. Seizures may occasionally precede cognitive symptoms (Picco et al. 2011).

Treatment of seizures in AD remains largely empirical (e.g. Belcastro et al. 2007; Cumbo and Ligori 2010; Jenssen and Schere 2010; Lippa et al. 2010; Vossel et al. 2013); the need for controlled clinical trials is evident (Larner and Marson 2011). Clearly drugs with potential for adverse cognitive effects (e.g phenobarbitone, primidone, phenytoin, topiramate) are best avoided. With their better adverse effect profile, newer anti-epileptic medications such as lamotrigine and levetiracetam may be preferred (Belcastro et al. 2007; Cumbo and Ligori 2010; Lippa et al. 2010; Vossel et al. 2013). Interestingly, there is some evidence that levetiracetam may decrease neuropathological burden and reverse spatial memory deficits in a transgenic animal model of AD (Shi et al. 2013).

Epileptic seizures have long been recognised as part of the phenotype of Down syndrome (DS), particularly with increasing age (e.g. Veall 1974; Puri et al. 2001). A syndrome of senile myoclonic epilepsy in Down syndrome (De Simone et al. 2010) or late-onset myoclonic epilepsy in Down syndrome (LOMEDS) has been delineated and seems to be common (Li et al. 1995; Möller et al. 2001). This has been observed in the small numbers of patients with DS seen in CFC (Larner 2007e, 2011d). Aetiopathogenesis is uncertain, but may be related to constitutive overexpression of amyloid beta-peptides derived from the APP gene, present in an extra copy in trisomy 21. Epileptic seizures also appear to be frequent in rare families with AD due to APP locus duplication (Cabrejo et al. 2006).

Epileptic seizures may be seen in a number of other neurodegenerative disorders (Larner 2007f, 2010d). In prion disease, seizures have been reported in sporadic CJD, sometimes as the presenting feature, with focal motor seizures, nonconvulsive status epilepticus, and generalised status epilepticus all reported. Localization-related seizures have been reported as the first presentation of variant CJD (Silverdale et al. 2000) but this would seem to be a rare or even exceptional event (Spencer et al. 2002). Epileptic seizures are rarely encountered in FTLDs, and if present should probably give pause as to the correctness of the diagnosis, likewise in synucleinopathies (DLB, PDD) and late-onset Huntington's Disease, although seizures are said to be more common in the juvenile onset (Westphal variant) form of HD. It would be anticipated that seizures are common in vascular and mixed dementia, since cerebrovascular disease is a recognised risk factor for late-onset seizures. Patients with stroke who have epileptic seizures may be at increased risk of dementia. In a cohort of stroke patients without pre-existing dementia, the occurrence of epileptic seizures was an independent predictor of new-onset dementia within 3 years of stroke (Cordonnier et al. 2007).

8.2.4 Sleep-Related Disorders

The importance of sleep for cognitive function, particularly for memory consolidation, has become increasingly apparent (Yang et al. 2014). The link between amyloid pathology and impaired hippocampal-dependent memory consolidation in AD may be mediated through non-REM sleep disruption (Mander et al. 2015).

Sleep-related disorders may be a signature of neurodegenerative disease, as for example REM sleep behaviour disorder (see Case Study 5.2) and synucleinopathies such as DLB. Sleep disturbance is a feature of AD which worsens with advancing disease. Insomnia may be a characteristic feature of some prion diseases, familial and sporadic fatal insomnia (Max 2007). Aspects of sleep may be assessed with screening instruments such as PSQI and SDI (see Sect. 5.3).

Even in the absence of neurodegenerative disease, sleep disturbance may be relevant to complaints reported in the cognitive clinic. Poor sleep quality correlates with subjective memory complaint (see Sect. 5.3.1; Hancock and Larner 2009a). This may reflect an underlying affective disorder such as depression, but other

Case Study 8.5: Obstructive sleep apnoea-hypopnoea syndrome
Following a stroke of undetermined aetiology affecting his right side, a male patient in his late twenties developed tiredness, weight gain and excessive daytime somnolence. By the time of his referral to CFC, one year poststroke, he had still not returned to work and was described as hard to motivate. His sleep was described as restless, with loud snoring and witnessed apnoeas. He was obese (weight 140 kg; BMI 40 kg/m^2). On the Epworth Sleepiness Scale his score was abnormally high (18/24). Neuropsychological assessment showed mild impairment of cognitive function, with slight reductions in verbal reasoning and verbal comprehension performance, poor performance on tests of short term memory and learning, reduced verbal fluency and mild attentional problems. Non-verbal reasoning, language, visuospatial and constructional functions were intact. The pattern of deficits was thought typical of a subcortical process. Overnight home oximetry showed severe cyclic fluctuations in oxygen saturation with a desaturation index (i.e. decrease in oxygen saturation by ≥4% per hour of sleep) of >60, indicative of severe obstructive sleep apnoea-hypopnoea syndrome (Larner 2003b:151 [Case 2], 2008e:198).

sleep-related disorders should be borne in mind since they may have specific treatments. Sleep-related disorders presenting with cognitive complaints which have been seen on occasion in CFC include obstructive sleep apnoea (Larner 2003b; Lim and Larner 2008; Case Study 8.5), central sleep apnoea (Larner and Ghadiali 2008), restless legs syndrome (Davies and Larner 2009b), and shift-work sleep disorder (Larner 2010e). With regard to the latter, poor sleep quality is commonplace in shift workers (Akerstedt 2003) and sleep deprivation is recognised to have adverse consequences on cognitive function (Durmer and Dinges 2005). Poor sleep quality is associated with amnestic and non-amnestic function in older patients (Miller et al. 2014).

8.2.5 Diabetes Mellitus

The relationship between diabetes mellitus (DM) and cognitive function has attracted significant research attention, not least because of the increasing prevalence of type 2 DM in the population. Cognitive dysfunction in general, and Alzheimer's disease with or without cerebrovascular disease in particular, may be chronic complications of DM, but the pathophysiology is uncertain. Possible mediating and modulating factors may include the effects of glycaemic control: hyperglycaemia, hyperinsulinaemia (with subsequent insulin resistance), and failure of insulin degrading enzyme (protease) activity (Cheng et al. 2012; McCrimmon et al. 2012; Koekkoek et al. 2015; Schilling 2016). Treatment-induced hypoglycaemia might also be a factor (Larner 2013a:177–8; Case Study 8.1).

A survey of 235 consecutive new outpatients attending CFC over a 10-month period (September 2012–April 2013; F:M = 107:128; age range 18–89 years, median 59 years) found 18 with type 2 DM (= 7.7%; F:M = 4:14; age range 38–84 years, median 62 years). Of those with DM, only 5 had dementia, but 10 of the 13 non-demented DM patients were adjudged to have MCI, giving a prevalence of cognitive impairment of 0.83 in this group, as compared to 0.49 in the whole group (dementia 71, MCI 43). The relative risk or risk ratio for cognitive impairment in patients with DM compared to non-diabetics (n = 217) was 1.83 (95% CI = 1.57–2.08). Of the whole group with cognitive impairment, 15 out of 114 had DM, whilst only 3 of the 121 cognitive healthy individuals had DM. The relative risk or risk ratio for DM in patients with cognitive impairment compared to cognitive healthy individuals was 5.31 (95% CI = 4.09–6.52). These data prompt the question as to whether screening of cognitive function in patients with DM should be considered (Price and Larner 2013).

8.3 No Diagnosis; Functional Cognitive Disorders

Many patients attending CFC are found, following clinical, neuropsychological, and neuroimaging assessment, to have no evidence for the presence of an underlying cognitive disorder to account for their symptoms. Indeed, longitudinal evidence from 2002 to the present suggests that the proportion of demented patients seen in CFC has gradually decreased over the years (see Sect. 1.4; Fig. 1.8), although the proportions of all patients referred to CFC with either dementia or cognitive impairment over the period 2009–2016 have not changed significantly. The proportion of patients with no evidence of cognitive impairment or cognitive disorder has remained between 50 and 60% (Table 8.1; Fig. 8.3). These changes may possibly be a consequence of national directives, such as the National Dementia Strategy of 2009 in England (Department of Health 2009), which has raised awareness of the diagnosis of dementia amongst both primary care practitioners and the general public, causing more patients with memory symptoms to present.

Table 8.1 Referral numbers and diagnoses, CFC 2009–2016 (compare with Table 1.3; see Fig. 8.3)

Year	N	Any cognitive disorder/cognitive impairment (% of N)	No cognitive disorder/cognitive impairment (% of N)
2009	249	106 (42.6)	143 (57.4)
2010	233	96 (41.2)	137 (58.8)
2011	227	92 (40.5)	135 (59.5)
2012	245	107 (43.7)	138 (56.3)
2013	323	154 (47.7)	169 (52.3)
2014	323	153 (47.4)	170 (52.6)
2015	328	139 (42.4)	189 (57.6)
2016	340	145 (42.6)	195 (57.4)
Total (%)	2268	992 (43.7)	1276 (56.3)

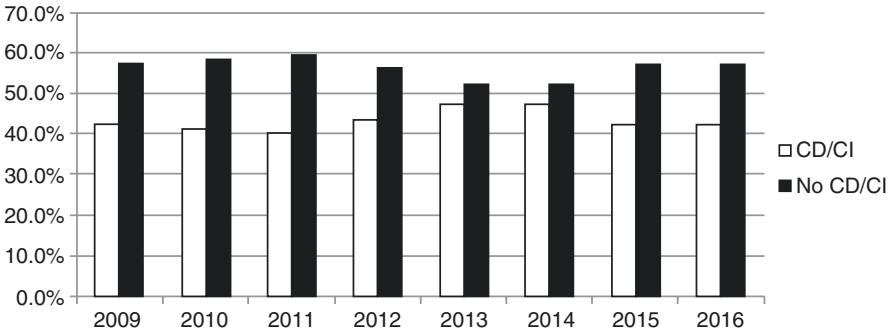

Fig. 8.3 Proportion of patients with or without cognitive disorder (CD) or cognitive impairment (CI) presenting to CFC, 2009–2016 (courtesy of Dr. V Bharambe)

The UK National Institute for Health and Clinical Excellence (NICE) suggested a memory clinic base rate for dementia of 54% (2010). However, a report from 30 Alzheimer's Centers in the USA reported 50% of patients seen were diagnosed as having normal cognition (Steenland et al. 2010). These figures may greatly overestimate current CFC experience, where over the past decade rates between around 20–30% have been seen (Table 1.3). This predominance of subjective memory complaint should not surprise us: in the seventeenth century La Rochefoucauld (1613–1680) noted that "Everybody complains of his memory, but nobody of his judgement" (*Maxims*, 89). Identification and reassurance of those individuals with purely subjective memory complaint is an important function of cognitive and memory clinics, a task which may also be facilitated by use of cognitive screening instruments (Larner 2017c).

The exact nature of this non-demented non-diagnostic group remains unclear, but it is probably heterogeneous, as reflected in the various diagnostic labels which have been applied, including "memory complainers", "worried well", subjective memory impairment, mild cognitive dysfunction, and functional memory disorder (Schmidtke et al. 2008; Blackburn et al. 2014). Stone et al. (2015) have proposed that a positive diagnosis of "functional cognitive disorder", analogous to other functional (e.g. movement, epilepsy) disorders, may be made based on inconsistency or incongruence of symptoms. The typology of functional cognitive disorders may be broad, encompassing mood disorder (depression/anxiety), normal cognitive experience, dementia health anxiety (e.g. in the context of a positive family history), other functional disorders (e.g. fibromyalgia, chronic fatigue syndrome), dissociative amnesia, medication effects, and malingering (Stone et al. 2015). In this context, it should be noted that memory complaints and cognitive impairment feature among the functional neurological symptoms seen in clinics dedicated to these disorders (e.g. Fig. 1 in Reuber et al. 2007:628). Memory complaints may be as common following non-head injury as in mild traumatic brain injury (Lees-Haley et al. 2001), as one feature of the post-trauma syndrome.

Some non-demented individuals attending the clinic have the kind of simple memory lapses which are common to many (Jónsdóttir et al. 2007), such as going

into a room and not recalling why, particularly if distracted by another task, suggesting an attentional rather than a mnemonic dysfunction. Difficulty in naming individuals (as opposed to objects) is a particularly common complaint (Kapur and Pearson 1983) but in isolation this is seldom cause for concern: naming is a challenging test from the neuropsychological perspective, being an example of cross-modal non-contextual paired associate learning. A lack of correlation between subjective and objective memory impairment is often found in such cases (Kapur and Pearson 1983). Memory lapses which are recalled in great detail during clinical consultation are seldom pathological, reflecting as they do an absence of source amnesia. Cognitive anosognosia, as manifested by many AD patients, is far more worrying. The importance of the clinical history in trying to differentiate between these possibilities cannot be overemphasized (Larner 2011e).

Some memory complainers may simply be intuiting the decline in cognitive efficiency which comes to us all as a feature of the physiological change in memory function with age (Larner 2006d, 2012b): physiological cognitive decline may be evident in early middle age, between 45–49 years (Singh-Manoux et al. 2012). Hypervigilance to physiological memory lapses may be one cause of subjective memory complaints. It may also be pertinent to point out that forgetting may sometimes be physiological rather than pathological (e.g. the quote attributed to Friedrich Nietzsche [1844–1900] that "Many a man fails as an original thinker simply because his memory is too good"). Many other neurological disorders may also be accompanied with cognitive impairment (Larner 2008e, 2013a; Larner et al. 2011), so evidence of a neurological disorder other than a dementia syndrome may be evident.

Some memory complainers may harbour brain disease insufficient to mandate a diagnosis of dementia (i.e. MCI). It is recognised that older people with subjective memory complaints (SMC; see Sects. 3.1.1.2 and 3.1.1.3) are more likely than those without SMC to progress to dementia (Mitchell et al. 2014); absence of SMC may be a marker excluding dementia and MCI (Mitchell 2008).

The factors which contribute to subjective memory complaints prompting attendance for clinical consultation are complex (i.e. many factors interacting which cannot be reliably predicted with mathematical analysis). Differentiating worried well patients from those with amnestic mild cognitive impairment may be difficult, even using screening instruments for memory complaints (Ahmed et al. 2008). However, some clues may be gleaned from empirical analysis of clinical cohorts and calculation of relative risks or risk ratios (Table 8.2). The presence of a positive family history of dementia may sensitize individuals to physiological memory lapses and/or exacerbate anxieties sufficient to prompt referral (Sect. 3.1.2; Larner 2013f). Sleep-related disorders (Sect. 5.3) which may or may not be part of an affective disorder (anxiety, depression; Sect. 5.2), may also contribute to memory difficulties. Simple screening instruments such as the Pittsburgh Sleep Quality Index (PSQI; Sect. 5.3.1; Hancock and Larner 2009a) and the Patient Health Questionnaire-9 (PHQ-9; Sect. 5.2.2; Hancock and Larner 2009b) may identify those individuals who might benefit from interventions to tackle poor

Table 8.2 Summary of relative risks or risk ratios from CFC studies (>1 = increased risk; with 95% confidence intervals)

(a) Risk of no dementia vs. dementia:		
	Relative risk or risk ratio	Reference
Impaired ADL (IADL Scale score ≤13/14)	0.57 (0.48–0.68)	Hancock and Larner (2007)
Depression (PHQ-9 score >9/27)	3.32 (1.48–7.43)	Hancock and Larner (2009b)
Poor sleep quality (PSQI score ≤5/21)	1.79 (1.38–2.31)	Hancock and Larner (2009a)
(b) Risk of no cognitive impairment vs. any cognitive impairment (dementia + MCI)		
	Relative risk or risk ratio	Reference
+ve family history of dementia	1.72 (1.00–2.96)	Larner (2013f)
Attended alone sign	6.75 (4.17–10.9)	Larner (2014)
Head turning sign (HTS+)	0.08 (0.02–0.32)	Ghadiri-Sani and Larner (2013)
(c) Risk of dementia vs. no dementia:		
	Relative risk or risk ratio	Reference
Any referral from primary care	0.55 (0.40–0.74) and 0.66 (0.49–0.89)	Fearn and Larner (2009)
Patient age ≤ 65 years	0.22 (−0.12–0.56),	Price and Larner (2013)
(d) Risk of any cognitive impairment (dementia + MCI) vs. no cognitive impairment:		
	Relative risk or risk ratio	Reference
Patient age ≤ 65 years	0.38 (0.17–0.59)	Price and Larner (2013)
Diabetes mellitus as comorbidity	1.83 (1.57–2.08)	Price and Larner (2013)

sleep and/or affective disorder. Conversely, attending CFC alone (Sect. 3.2.1; Larner 2014), absence of the head turning sign (Sect. 3.2.2; Ghadiri-Sani and Larner 2013), *la maladie du petit papier* (Sect. 3.2.4; Randall and Larner 2018), and preservation of activities of daily living (Sect. 5.1.1; Hancock and Larner 2007) may all point towards preserved cognitive health. Referrals from primary care have a lower risk of dementia diagnosis than those from secondary care (Sect. 1.2.1).

Management in the absence of evidence of any neurological disorder is based on reassurance. Sometimes this may be all that is required, but scheduled longitudinal assessment to see what, if any, change has occurred may be necessary, for example the prognosis of functional cognitive disorders is not well defined. To avoid practice effects on cognitive testing, reassessment should be no more frequent than 6 monthly and preferably longer (Heilbronner et al. 2010). Longitudinal volumetric neuroimaging techniques may also be useful to detect advancing brain atrophy. There is no compelling evidence yet available to suggest that "brain training" games or puzzles such as Sudoku have any utility in these circumstances to improve memory function.

8.4 Wrong Diagnosis

It is debatable which is the greater clinical evil, making no diagnosis or making a wrong diagnosis; making a possible error of omission or an error of commission. In terms of the matrix of confusion (Fig. 2.1), this may be characterised in terms of false negative or false positive diagnosis, the (relative) costs associated with which are difficult to determine (see Sect. 6.1.1).

As previously mentioned (Chap. 7), diagnostic errors based on over-reliance on investigations, particularly structural imaging reported to show brain atrophy, have been encountered (Larner 2004c; Davies and Larner 2009a). Contextualising all investigation results in terms of the clinical history and neurological examination is paramount in all neurological diagnosis (Larner et al. 2011), and hence the optimal (though not infallible) way to avoid diagnostic error.

When (not if!) diagnostic errors occur, the clinician should reflect on their potential salutary heuristic value, as cogently described by Sir William Gowers (1894):

> It is always pleasant to be right, but it is generally a much more useful thing to be wrong … if you are wrong you generally gain in knowledge and gain perception of the way in which your method of diagnosis needs improvement.

8.5 Summary and Recommendations

The differential diagnosis of cognitive syndromes is very broad, and hence potentially daunting to the uninitiated. However, the number of syndromes commonly encountered in CFC is relatively circumscribed, with amnesia accounting for the majority of cases. Definition of specific cognitive syndromes (e.g. amnesia, aphasia, dysexecutive syndrome) may guide differential diagnosis of specific dementia syndromes (see Chap. 9). The presence of defined comorbidities may assist in differential diagnosis, as well as having implications for management.

Failure to establish a specific syndrome or diagnosis in those attending a neurological cognitive clinic is not uncommon (as in other spheres of neurological practice), and does not seem to be simply a consequence of clinician incompetence. The uncertainty attendant upon "no diagnosis" may be the most difficult thing for patients and other clinicians, in both primary and secondary care, to deal with, and potentially risks exacerbating the situation through increased anxiety. Therefore, putting in place some sort of management plan (e.g. interval assessment, or onward referral to other services as appropriate) is essential to try to assuage these concerns.

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Diagnosis (2): Disorders Causing Dementia and Cognitive Impairment

9

Contents

Abstract

This chapter examines the various cognitive disorders (e.g. Alzheimer's disease, frontotemporal lobar degenerations, parkinsonian disorders, cerebrovascular disorders) which may be defined by clinical assessment and investigation, emphasizing their clinical heterogeneity.

Keywords

Dementia · Diagnosis · Cognitive disorders · Alzheimer's disease · Frontotemporal lobar degeneration · Parkinsonian disorders · Vascular dementia

The delineation of cognitive syndromes (see Chap. 8) may narrow differential diagnostic considerations for specific dementia disorders. There are many causes of the dementia syndrome and of cognitive impairment (e.g. see Mendez and Cummings 2003; Kurlan 2006; Larner 2008a, 2010a, 2013a, 2014; Filley 2012; Dickerson and Atri 2014). Only those most often encountered in practice at the Cognitive Function

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Clinic (CFC) at the Walton Centre for Neurology and Neurosurgery (WCNN) in Liverpool are discussed here; evolving diagnostic criteria are listed in Chap. 2 (Box 2.2). Other disorders, such as delirium (Sect. 8.2.2) and depression (Sects. 5.2.2 and 5.2.4), may need to be considered in the initial differential diagnosis, as independent or superimposed causes of cognitive impairment.

9.1 Alzheimer's Disease and Mild Cognitive Impairment

Alzheimer's disease (AD) is by far the most common neurodegenerative disorder seen in CFC, the relatively young age of the casemix notwithstanding. Around 95% of these AD cases have presented with the typical amnesic syndrome, the remainder comprising the focal cortical variants presenting with agnosia, aphasia, apraxia, or dysexecutive syndrome (Larner 2006a, 2008b). These variant presentations (Caselli and Tariot 2010) are acknowledged in updated AD diagnostic criteria (McKhann et al. 2011; Dubois et al. 2014).

Errors in the diagnosis of AD sometimes occur, even in the best centres. Patients diagnosed with AD in other clinics but who have proved not to have dementia on longitudinal follow up at CFC have been encountered on occasion. Over-reliance on structural brain imaging reported to show "atrophy" may have been instrumental in the misdiagnosis of these cases (see Sect. 7.2.1; Larner 2004).

An examination of the CFC database of patients in whom either an initial diagnosis of AD was made and/or cholinesterase inhibitors were prescribed, covering the period January 2000 to end June 2008 (8½ years), was interrogated to identify those in whom diagnostic revision was required, based on disease progression with emergence of new features during follow-up (Davies and Larner 2009). Of 300 patients on the database, 289 (= 96.3%) were initially clinically diagnosed with probable AD using NINCDS-ADRDA criteria (McKhann et al. 1984). From this group, 8 patients initially diagnosed with AD in whom subsequent diagnostic revision was required were identified (= 2.8%; F:M = 1:7, age range at diagnosis 52–63 years, median 58 years). In all cases, diagnosis was revised from AD to FTLD due to the emergence, in isolation or combination, of behavioural (7), linguistic (2), and motor (1) features more typical of the FTLD phenotypes (Sect. 9.2). Onset of these changes was noted between 12 months and 5 years (median 18 months to 2 years) after initial diagnosis. Two patients were eventually shown to harbour tau gene mutations (Larner 2008c, 2009a); both had a family history of early-onset dementia (parent or siblings affected), but in neither case did the available details permit the conclusion of autosomal dominant inheritance of disease (i.e. ≥3 affected in individuals in 2 generations; Cruts et al. 1998). One of these patients developed prototypical FTLD behavioural features, the other a phenotype of progressive supranuclear palsy, 3 and 4 years after initial diagnosis respectively. Of the six other patients, all with early-onset disease (i.e. onset ≤65 years of age), none had a family history of dementia and hence all were initially diagnosed with sporadic probable AD. Two were initially thought to have aphasic presentations of AD, since they had apparent amnesia in addition to aphasia, but both gradually developed behavioural

features requiring their reclassification as FTLD. A further two patients also evolved behavioural features after amnesic presentations. The two remaining patients with amnesic presentations developed progressive impoverishment of language function suggestive of the progressive non-fluent aphasia phenotype, as well as behavioural features. In one of these cases, English was not the patient's first language, thereby confounding initial assessment. That FTLD may on occasion have been misdiagnosed as AD is perhaps not surprising, as symptom overlap between AD and FTLD was evident in definitions then used in widely accepted clinical diagnostic criteria (Varma et al. 1999). In clinical practice initial assessment is essentially cross-sectional, whilst longitudinal assessment may reveal new features mandating diagnostic revision. The adoption of more modern diagnostic criteria for AD (Dubois et al. 2007, 2014; McKhann et al. 2011) and FTLDs (Gorno-Tempini et al. 2011; Rascovsky et al. 2011) may obviate the problem of symptom overlap.

Genetically determined AD has been rarely encountered (see Sect. 7.3.1), all those detected harbouring presenilin 1 gene mutations (Larner and du Plessis 2003; Doran and Larner 2004a, 2006; Larner et al. 2007), and none with either APP or presenilin 2 mutations. Patients with Down syndrome invariably harbour AD pathology after the age of 50 years (Mrak and Griffin 2004), presumably because of the extra copy of the APP gene in trisomy 21. The neuropathological features may have the clinical correlate of cognitive decline and dementia, but such cases have rarely been seen in CFC (see Sect. 9.6; Larner 2007, 2011a; Case Study 7.4).

Mild cognitive impairment (MCI) was initially proposed as a term to describe cognitive impairment which did not amount to dementia, which might purely affect the domain of memory (amnestic MCI) or multiple domains of cognition (Petersen 2003). This may represent prodromal AD, and some authors have used these terms almost interchangeably (Burns and Morris 2008), whereas others have used the term "MCI" to denote a more heterogeneous concept encompassing cognitive impairment associated with other brain disorders which can progress to dementia, including Parkinson's disease (Litvan et al. 2012) and cerebrovascular disease (vascular cognitive impairment; Gorelick et al. 2011), and possibly also frontotemporal dementia (De Mendonca et al. 2004). This may explain the varying estimates of rate of MCI progression to dementia (Mitchell and Shiri-Feshki 2009). Dubois et al. (2007) eschewed the category of mild cognitive impairment altogether, whereas the 2011 National Institute on Aging-Alzheimer's Association criteria have retained MCI, four categories of which are described (Albert et al. 2011). Whatever terminology may be used, the early symptomatic phases of dementing disorders might represent a significant opportunity for treatment, particularly if disease-modifying therapies can be discovered and brought to the clinical arena.

9.2 Frontotemporal Lobar Degenerations

Frontotemporal lobar degenerations (FTLD) are less common than AD overall but in the presenile age group they may be as prevalent as AD (Ratnavalli et al. 2002), although other population based studies find AD to be more prevalent in this age

group (Harvey et al. 2003). Hence FTLDs make up a significant component of CFC work, in part because of the relatively young age at onset of patients seen in this setting (see Sect. 1.3.1). In addition, patients referred to CFC from psychiatrists (see Sect. 1.2.2) have an increased frequency of FTLD, mostly the behavioural variant. FTLD in the elderly may be underreported, and may differ in clinical and pathological phenotype from early-onset disease (Baborie et al. 2012, 2013).

FTLDs are heterogeneous at the clinical, neuropsychological, neuropathological and genetic level (Snowden et al. 1996; Hodges 2007; Warren et al. 2013; Dickerson 2016). Of the various clinical phenotypes encompassed by the FTLD rubric (Neary et al. 1998), behavioural variant (bvFTD; Rascovsky et al. 2011) and the agrammatic variant of primary progressive aphasia (avPPA; formerly known as progressive non-fluent aphasia) are more common than the semantic variant of primary progressive aphasia (svPPA; also known as semantic dementia; Gorno-Tempini et al. 2011). This has been the experience in CFC (Larner et al. 2005a; Davies and Larner 2010; Larner 2012a, b; Case Studies 4.2, 4.3, 5.1, 7.3, 7.5 and 7.6), consistent with reports from other centres seeing larger numbers of FTLD cases.

Cases of FTLD with motor neurone disease (FTD/MND) have also been seen (see Sect. 1.2.2; Doran et al. 2005; Hancock and Larner 2008; Larner 2008d, 2013b; Sathasivam et al. 2008; Larner and Gardner-Thorpe 2012; Ziso et al. 2014; Case Study 7.6). Many of the cases have been referred from psychiatry clinics or are under concurrent care of psychiatrists, but it is of note that FTD/MND is not mentioned in DSM-IV-TR (American Psychiatric Association 2000), either as a specific cause of dementia or in the catch-all category of "Dementia due to other general medical conditions". This omission is surprising in light of the fact that FTD/MND may present with neuropsychiatric symptoms (Sect. 8.2.1), leading to referral to psychiatrists rather than neurologists in the first instance. These neuropsychiatric symptoms include disinhibition, which may be mistaken for hypomania, and self-neglect and poverty of speech which may be mistaken for depression (Sathasivam et al. 2008), as well as florid delusions (Larner 2008d, 2013b; Ziso et al. 2014). Disinhibition was presumed to be the substrate for the "animal-like behaviour" seen in one patient with bvFTD who, according to his wife, used to bark like a dog, a behaviour which may fall under the rubric of lycanthropy (Larner 2010b).

As far as genetically determined cases of FTLD are concerned (Sect. 7.3.2), it was formerly the case that large centres reported either a preponderance of tau compared to progranulin mutations (Seelaar et al. 2008) or roughly equal numbers (Rohrer et al. 2009). However, following the discovery of the C9orf72 hexanucleotide repeat expansion (DeJesus-Hernandez et al. 2011; Renton et al. 2011), this has superseded both tau and progranulin mutations in frequency (Boeve et al. 2012; Dobson-Stone et al. 2012; Hsiung et al. 2012; Mahoney et al. 2012; Majounie et al. 2012; Simon-Sanchez et al. 2012; Snowden et al. 2012).

Families with tau gene mutations (FTDP-17) have been seen on occasion in CFC (see Sect. 7.3.2). In some of these cases the proband received an initial diagnosis of probable AD, with features more typical of FTLD only emerging at a later

stage of disease. This clinical heterogeneity has also been observed with some of the other tau gene mutations (Larner and Doran 2009a), such as R406W (Lindquist et al. 2008). This diagnostic error, FTLD confused with AD, has also been noted in sporadic FTLD patients (Davies and Larner 2009), perhaps related to the overlap of older diagnostic criteria (Varma et al. 1999). Occasional FTLD cases with progranulin and C9orf72 mutations have also been seen in CFC (Sect. 7.3.2; Larner 2012b, 2013b, 2017 Cases 2 and 3 [Table 4.32]; Ziso et al. 2014; McCormick and Larner 2018).

Unusual forms of FTLD have also been seen, defined on neuropathological grounds. Neuronal intermediate filament inclusion disease (NIFID) was initially defined by intraneuronal cytoplasmic inclusions of variable morphology which immunostained for all class IV intermediate filament (IF) proteins, namely NF-H, NF-M, NF-L, and alpha-internexin (Cairns et al. 2004). More recently it has been shown that a much larger proportion of the inclusions in NIFID are immunoreactive with the *fused in sarcoma* (FUS) protein than with IF (Neumann et al. 2009), leading to changes in the suggested nomenclature to FTLD-FUS (Mackenzie et al. 2010). These cases have a broad phenotype which may overlap with both corticobasal degeneration and motor neurone disease, and the pathological diagnosis may be unsuspected ante mortem (Menon et al. 2011).

Late diagnosis of FTLD is a common problem, even following contact with medical services, with an average delay of nearly 3 years in a Scandinavian series in which nearly three-quarters of patients initially received a non-dementia diagnosis (Rosness et al. 2008). Such delays are of particular frustration to caregivers who are often sure something is wrong. An integrated care pathway (ICP) has been developed in the hope of hastening FTLD diagnosis (see Sect. 10.6; Davies and Larner 2010).

9.3 Dementia with Lewy Bodies, Parkinson's Disease Dementia, REM Sleep Behaviour Disorder, and Other Parkinsonian Disorders (PSP, CBD)

Dementia with Lewy bodies (DLB) is claimed by some authors to be the second most common of the neurodegenerative dementias, but has been encountered relatively rarely in CFC, in contrast to other centres, although this low prevalence does appear to fall within the range of prevalence estimates for the general population (Zaccai et al. 2005).

Based on the greater impairment of attentional and visuospatial function, and the relative preservation of orientation and memory function, in DLB as compared to AD (e.g. Salmon et al. 1996; Downes et al. 1998; Ballard et al. 1999; Calderon et al. 2001), Ala et al. (2002) derived a weighted subscore from the Mini-Mental State Examination (MMSE) for DLB diagnosis. Prospective use of the Ala subscore (and its modifications derived from the ACE and MoCA) has not proved of particular use in CFC for prospective diagnosis (see Sects. 4.1.1.1, 4.1.5.2, and 4.1.8.1).

DLB may sometimes be mistaken for CJD (e.g. Haïk et al. 2000; Tschampa et al. 2001; Van Everbroeck et al. 2004; Larner 2006b; Du Plessis and Larner 2008), not least because rapidly progressive instances of DLB have been described (Momjian-Mayor et al. 2006; Gaig et al. 2011). One differential diagnostic clue is that the visual hallucinations of DLB are generally well formed (animals, people) compared with the rather elemental visual hallucinations (colours, shapes) which may occur in CJD (Du Plessis and Larner 2008). EEG findings of periodic sharp wave complexes may sometimes be found in DLB, adding to the phenotypic overlap (see Sect. 7.4.1; Doran and Larner 2004b). Orthostatic hypotension may be a feature of DLB, sometimes occurring initially in isolation and prompting a diagnosis of pure autonomic failure (Larner et al. 2000). Orthostatic hypotension may predispose to repeated syncope, one of the supporting features in DLB diagnostic criteria (McKeith et al. 2005, 2017). A case of fragile X-associated tremor/ataxia syndrome (FXTAS) which was mistaken for DLB (parkinsonian signs, possible REM sleep behaviour disorder, and frontal executive type cognitive impairments) has also been seen (Connon and Larner 2017, Case 2).

Parkinson's disease dementia (PDD) is likely to become an increasing problem, since most patients with PD followed longitudinally develop some evidence of cognitive decline over time (Reid et al. 2011; Williams-Gray et al. 2013). Few patients with PDD have been seen in CFC presumably because they are managed in either dedicated movement disorder clinics or, because of the neuropsychiatric problems, psychiatry clinics. Instruments such as the MMP and MoCA (see Sects. 4.1.2 and 4.1.8) may be useful for the detection of cognitive impairments in PDD.

REM sleep behaviour disorder (REMBD) occasionally presents to the cognitive clinic (Case Study 5.2). Presence of REMBD, sometimes referred to as "dream enactment", may be a useful clue to the diagnosis of synucleinopathies such as DLB, PDD, and multiple system atrophy (MSA), often preceding by years the diagnosis of the underlying neurological disorder (Boeve et al. 2007). REMBD has now been incorporated amongst the core clinical features in diagnostic criteria for DLB (McKeith et al. 2017). A diagnosis of REMBD should always prompt clinical and cognitive assessment for an underlying condition. REMBD is often amenable to treatment with clonazepam (Larner et al. 2005b).

DLB and PDD are sometimes referred to as "Lewy body dementias" (Walker et al. 2015), in distinction from other parkinsonian syndromes which may be accompanied by neuropsychological impairment as well as movement disorder (Larner 2013a:48–51), but which are characterised pathologically as tauopathies, rather than synucleinopathies, in particular progressive supranuclear palsy (PSP) and corticobasal degeneration (CBD). Occasional cases of PSP have been seen in CFC; the phenotype has also been seen in association with tau gene mutations (Larner 2009a, 2012c; Larner and Doran 2009a) and in a case of Perry syndrome (Aji et al. 2013a, b), as well as being mistaken for normal pressure hydrocephalus (Schott et al. 2007). PSP has also been reported in patients with the C9orf72 hexanucleotide repeat expansion (Le Ber et al. 2013). Cases of suspected CBD but with other pathological substrates, so called corticobasal syndrome (CBS; Boeve et al. 2003; Doran et al. 2003), are well-recognised (e.g. Menon et al. 2011).

9.4 Vascular Dementia, Vascular Cognitive Impairment

Vascular dementia (VaD) and vascular cognitive impairment (VCI) are recognised to be heterogeneous entities with respect to both pathology and pathogenesis (Wahlund et al. 2009; Gorelick et al. 2011), including vasculopathic and thrombotic disorders. Mixed dementia, defined as the coexistence of AD and VaD (Langa et al. 2004), may be the most common neuropathological substrate of dementia (Neuropathology Group of the Medical Research Council Cognitive Function and Ageing Study 2001; Schneider et al. 2009). Cerebrovascular disease may modulate the clinical expression of AD pathology (Snowdon et al. 1997). The old dichotomy of AD and VaD is now superseded by an integrative approach to aetiology with a continuum or spectrum running from pure boundary cases through entities such as "AD with vascular lesions" and "VaD with AD changes". VCI is analogous to MCI, representing a syndrome of cognitive impairment short of dementia as a consequence of vascular brain injury (Bowler and Hachinski 2003). A category of mild cognitive dysfunction, MCD, has also been proposed for cognitive impairment short of dementia in white matter disorders such as SLE (Kozora and Filley 2011; Filley 2012:391–2).

Cases of pure vascular dementia, such as subcortical ischaemic vascular dementia (Román et al. 2002), have rarely been encountered in CFC. Cerebral autosomal dominant arteriopathy with subcortical infarcts and leukoencephalopathy (CADASIL) has been seen on occasion (see Sect. 7.3.3; Case Study 7.7; Doran and Larner 2009).

Though unusual, intracranial dural arteriovenous fistula (dAVF) must also be considered amongst reversible causes of vascular cognitive impairment and dementia. Experience with intracranial dAVF seen at CFC (Wilson et al. 2010; Randall et al. 2015) has shown impairments in attention, memory and executive functioning. One common clinical feature which was not fully captured by the standard neuropsychological and cognitive tests administered was the impairment in cognitive processing speed, suggestive of subcortical involvement. This may be a reflection of the marked prolongation of cerebral transit time seen with radiological contrast studies, late angiographic views indicating that venous drainage of brain parenchyma may be considerably delayed. Of note, despite marked cognitive improvement after endovascular fistula embolisation, residual deficits were evident in some cognitive domains even up to 2 years after treatment, presumably related to irreversible structural changes in the brain, such as complete or partial venous infarction of tissues subjected to chronic venous hypertension.

9.5 Prion Disease (Prionoses)

Prion diseases have attracted much attention in recent years, not least because of their novel biology as sporadic, inherited, and iatrogenic conditions (Collinge 2001), and despite their clinical rarity. Variant Creutzfeldt-Jakob disease (CJD) has been viewed as a major public health issue.

Case Study 9.1: Clinical diagnosis: sporadic CJD
A 75 year-old lady was brought to CFC by ward staff from another hospital; she was unable to give any history. Previously very fit and active, she had apparently developed cognitive problems over a 5-month period. A month or so after symptom onset her MMSE was 21/30 and a CT brain scan was reported to be normal. However her decline was relentless, requiring hospital admission because of failure to cope at home. Aside from some myoclonic jerks her neurological examination was normal. A diagnosis of sporadic CJD was suspected on the basis of the rapid decline and the myoclonic jerks. Subsequent EEG was abnormal with a non-specific slow background but no triphasic waves were seen. CSF analysis was positive for 14–3-3 protein.

In addition to the classical presentation of rapidly progressive cognitive decline with myoclonus (Case Study 9.1), prion disorders can present with multifocal symptoms including cerebellar, visual cortical, extrapyramidal, pyramidal, and psychiatric symptoms (Nakatani et al. 2016), some examples of which have been seen in CFC, including visual hallucinations (Du Plessis and Larner 2008), psychiatric presentations (Ali et al. 2013; Williamson and Larner 2016), stroke-like symptoms (Ghadiri-Sani et al. 2015), and myelopathy (Ziso et al. 2017).

An audit of prion disease cases seen at CFC over a 12-year period (1990–2001 inclusive) (Larner and Doran 2004) found that 82 patients with suspected CJD were referred from the Mersey Region to the National Creutzfeldt-Jakob Disease Surveillance Unit (NCJDSU) in Edinburgh; 65 referrals were made after 1995 when the UK epidemic of variant CJD (vCJD) began (Will et al. 1996). Sixty-six patients (80%) presented initially to non-neurologists. Forty-four referrals were of in-patients at WCNN, usually transferred from district general hospitals by visiting neurologists. Thirty-eight cases were referred to NCJDSU directly from district general hospitals or from Alder Hey Children's Hospital, Liverpool. Prion disease was confirmed pathologically in 43 of 82 referrals, giving an overall diagnostic accuracy of 0.52. Of the confirmed prion disease cases, 33 had sporadic CJD, 8 had vCJD (e.g. Silverdale et al. 2000; Lorains et al. 2001), and 2 had iatrogenic disease; there were no familial cases. Of the non-prion cases (39), eight were found to have alternative diagnoses only at postmortem, principally AD and DLB (see Sects. 9.1 and 9.3). Autoimmune encephalitides may also mimic CJD (Schott et al. 2003; Geschwind et al. 2008).

Although diagnosis of prion disease may be straightforward (e.g. Case Study 9.1), there may be difficulties if the phenotype is unusual, for example with prominent parkinsonism and orthostatic hypotension (Du Plessis and Larner 2008), or there is a long prodrome of psychiatric symptoms (Ali et al. 2013; Williamson and Larner 2016). Neuropsychiatric features, once claimed to be a distinguishing feature of vCJD, are in fact quite common in sCJD, even early in the disease course (Wall et al. 2005; Rabinovici et al. 2006). They were also prominent in another patient seen in CFC whose non-identical twin was discordant for the disease. Patient

age may also confuse diagnostic thinking: although sporadic CJD is usually a disorder of older people some variants may occur in young people (e.g. Williamson and Larner 2016), and although variant CJD typically occurs in younger patients it may also affect older individuals (Lorains et al. 2001; el Tawil et al. 2015). Rapidly progressive cognitive decline from causes other than CJD may sometimes lead to diagnostic confusion, including on occasion brain tumour (Case Study 7.1), dural AV fistula (Randall et al. 2015), and rapidly progressive DLB (Sect. 9.3) or AD (Jayaratnam et al. 2008; Schmidt et al. 2010). Some forms of CJD may progress slowly (Ali et al. 2013).

Whether subclinical vCJD, which may be more common than previously thought (Gill et al. 2013), might manifest with different clinical features, particularly in patients valine homozygous at PRNP gene codon 129, remains to be seen.

9.6 Learning Disability; Down Syndrome

The assessment of individuals with learning disability remains problematic for most neurologists, since generally they have received little or no training in this area, far less developed any claims to expertise. Most patients with learning disability are referred to neurology services because of episodes of loss of or impaired consciousness which may reflect epileptic seizures (see Sect. 8.2.3) (Adab and Larner 2006; Larner 2007, 2009b, 2011a; Sells and Larner 2011; Milburn-McNulty and Larner 2018), although occasional patients are sent to CFC with possible progression of cognitive dysfunction. Cases of learning disability in the context of neurofibromatosis-1 (NF1), fragile X syndrome, infantile Refsum disease, and Sotos syndrome have sometimes been seen (Larner 2008e; Milburn-McNulty and Larner 2018).

Many forms of learning disability are inadequately understood at the pathological or aetiological level, but some are better characterised. For example, in those with Down syndrome (trisomy 21), cognitive decline often reflects the inevitable development of Alzheimer type pathology, first reported by Struwe in 1929 (see also Mrak and Griffin 2004; Prasher 2005). Down syndrome patients have on occasion been seen in CFC (Larner 2007; Case Study 7.4). A syndrome of myoclonic epilepsy may be typical of Down syndrome (De Simone et al. 2010), and examples have been seen in CFC (Larner 2011a). The exact place of cholinesterase inhibitors in the management of cognitive decline in Down syndrome remains to be defined, but it would seem likely that their greatest benefit, if any, might be in the early stages of cognitive decline (Larner 2010c).

9.7 Other Causes of Dementia and Cognitive Impairment

Although some form of cognitive impairment is thought to be common in multiple sclerosis (MS), few patients have been seen in CFC other than with an unusual phenotype (Case Study 9.2: Young et al. 2008), presumably because most MS patients with cognitive issues are managed within dedicated clinics (as for cognitive

Case Study 9.2: Clinical diagnosis: Multiple sclerosis

A patient presented in his early 30s with poor visual acuity, eye movement disorder, spastic quadriparesis and cognitive impairment characterised by poor memory and lack of insight. MR brain imaging showed typical periventricular white matter changes of multiple sclerosis but CSF oligoclonal bands were absent. Over a 10-year period of follow-up, cognitive impairment progressed with a subcortical pattern of dementia; MR showed brain atrophy as well as white matter changes. Secondary generalised tonic-clonic seizures developed at age 40, requiring escalating doses of antiepileptic drugs. Interictal EEG showed generalised slow wave activity but no focal changes.

Three of the patients four siblings were also diagnosed with MS (age range at diagnosis 28–35 years), all complicated with cognitive impairment progressing to dementia; one also had epilepsy from childhood. All siblings died (age at death 35–42 years); one had a post-mortem examination of the brain which showed definite MS and no other pathological changes.

The proband was negative for PTPRC (CD45) mutation reported in familial MS (Nicholas et al. 2003) and also for presenilin-1 (PSEN1) mutations which are associated with early-onset Alzheimer's disease, sometimes complicated with spastic paraparesis, white matter changes and epilepsy (Larner and Doran 2006, 2009b; Larner 2011b, 2013c).

impairment in the context of cerebrovascular disease and movement disorders). Currently there seems to be no compelling evidence for cognitive benefit in MS for cognitive rehabilitation, symptomatic drugs, or disease modifying treatments (Amato et al. 2013).

As previously mentioned (see Sect. 8.1.1.1), alcohol-related cognitive problems have rarely been seen in CFC. Likewise, cognitive disorders associated with HIV infection have rarely been referred. Presumably this reflects local availability of dedicated services for these conditions. There has been a dramatic decline in HIV dementia incidence since the advent of highly active antiretroviral therapy (HAART) with nucleoside and non-nucleoside reverse transcriptase inhibitors and protease inhibitors, but prevalence of HIV-associated neurocognitive disorders has increased because of improved life expectancy. In addition to viral burden, persistent neuroinflammation and AD-like neurodegenerative changes may contribute to HIV-associated cognitive problems, requiring additional therapeutic approaches (Clifford 2017).

Structural brain lesions causing potentially reversible dementia or cognitive decline have rarely been seen (Larner 2013d; Case Study 7.1). There have been occasional cases of brain tumour (though not always relevant to cognitive decline: Abernethy Holland and Larner, 2008) and dural arteriovenous fistula (see Sect. 9.4), but no instances of subdural haematoma or normal pressure hydrocephalus (see Case Study 7.2). Indeed, two patients diagnosed elsewhere with, and shunted for,

"normal pressure hydrocephalus" eventually proved to have frontotemporal lobar degeneration (Davies and Larner 2010).

Other causes of dementia and cognitive impairment have occasionally been encountered in CFC. Because of the relatively young age of the patients referred (see Sect. 1.3.1), genetic and metabolic causes of dementia may be seen, since these are much more common in younger cohorts (Doran 1997; Rossor et al. 2010; Davies et al. 2011). Huntington's disease (HD) has very rarely been seen in CFC, most cases presenting to general neurology or movement disorders clinics (Larner 2008e; Ziso et al. 2015). Other conditions seen on occasion in CFC include X-linked adrenoleukodystrophy (X-ALD) (Larner 2003), Perry syndrome (Aji et al. 2013a, b), and relapsing polychondritis (Ellis et al. 2017).

9.8 Summary and Recommendations

The differential diagnosis of disorders causing cognitive symptoms is potentially very broad (Larner 2013a), as with cognitive syndromes (Chap. 8), and hence potentially daunting. However, the number of commonly encountered conditions is relatively circumscribed, with AD accounting for the majority of cases (many more will have subjective memory complaints or functional cognitive disorder; Sect. 8.3). Definition of specific cognitive syndromes (e.g. amnesia, aphasia, dysexecutive syndrome) may guide differential diagnosis of specific dementia syndromes. This is preferable to the old binary, probabilistic diagnostic strategy (e.g. McKhann et al. 1984), which was dependent on the presence of dementia before a diagnosis of AD could be made. Newer criteria (e.g. Dubois et al. 2007, 2014; Albert et al. 2011; Sperling et al. 2011) seek to establish AD diagnosis earlier in the disease course at a time when intervention with disease-modifying treatment might stand a greater chance of success (Aisen et al. 2011). As robust biomarkers of disease are defined, a biological or pathogenetic definition of disease may be possible, as is already the case for those few families harbouring deterministic genetic mutations. Specific diagnosis is the first step to specific therapy, although currently available treatment modalities have limited efficacy (see Chap. 10).

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Management

10

Contents

Abstract

This chapter examines various aspects of the management of cognitive disorders, including provision of information and pharmacotherapy, both licensed and novel treatments. The effects of a number of policy directives issued under the auspices of the United Kingdom government in recent years are examined: none appears to contribute to closure of the dementia diagnosis gap. The place of neurology-led services for dementia within an integrated dementia care pathway is considered.

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Dementia · Treatment · Cholinesterase inhibitors · National Dementia Strategy · Integrated care pathway

The management of dementia syndromes is a broad topic, encompassing not only pharmacotherapies and behavioural therapies for cognitive deficits and physical comorbidities but also the social care context (e.g. Scharre 2010; Curran and Wattis 2011; Kurrle et al. 2012; Lipton and Marshall 2013; Rabins et al. 2016). Dementia transcends medical, social, economic and political boundaries, hence the need for enunciation of management strategies at national and international political levels (Larner 2018a). The National Dementia Strategy for England as originally conceived (Department of Health 2008, 2009; Sect. 10.5.3) included amongst its objectives an information campaign to raise awareness of dementia and reduce stigma, and improvement of community personal support services, housing support and care homes. Clearly many of these objectives fall largely or entirely outwith the sphere of neurological expertise or influence (Larner 2009a). Those with a neurological training will obviously focus on pharmacotherapy, and since Alzheimer's disease (AD) is the most common dementia syndrome much of the emphasis here will be on the treatment of this condition. Symptomatic treatment of complicating factors (e.g. behavioural and psychological symptoms, epileptic seizures) is not discussed here (for epilepsy, see Sect. 8.2.3). It has been suggested that the term "dysmentia" be used in place of dementia both to counter therapeutic nihilism and to emphasize the potential for treatment in these syndromes (Chiu 1994).

10.1 Information Seeking

With the onset of cognitive problems, and with the establishment of a diagnosis of dementia, patients and their carers may wish to seek additional information, over and above that communicated to them in clinical settings. Such sources of information include self- or relative-directed searches of the internet, and contact with patient support organisations such as the Alzheimer's Society.

10.1.1 The Internet

The Internet is a vast resource for medical information, albeit unregulated. Studies of new referrals to general neurology outpatient clinics ($n > 2000$) over the decade 2001–2010 (Larner 2006a, 2011a) have shown increasing internet access and use by patients to search for medical information prior to clinic attendance. Both access to and use of the internet was highest in younger patients, maximal in the 31–40 years age group, with least access and use in older people (i.e. those at greatest risk of dementia; Larner 2011a:29–30; b, c).

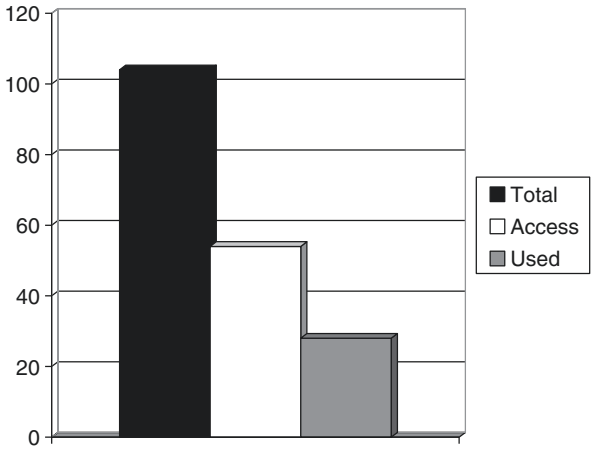

Fig. 10.1 Internet access and use by patients and carers, Cognitive Function Clinic, October 2001–March 2002 (Larner 2011a:34) reprinted with permission

Similar studies have been undertaken to examine how often patients with cognitive problems, or more usually their relatives, use the internet to access information (Larner 2003a, 2007a, 2011a:33–4). In a study of 104 patients seen in the Cognitive Function Clinic (CFC) at the Walton Centre for Neurology and Neurosurgery (WCNN) in Liverpool over a 6-month period (73 new patients, 31 follow-ups), 54 (52%) acknowledged internet access, of whom 28 had searched for medical websites with relevant information (52% of those with access, or 27% of all cases). Eighty-five patients (82%) said that they would definitely or probably access websites suggested by the clinic doctor if they had internet access (Fig. 10.1; Larner 2003a).

In a study of awareness and use of complementary and alternative therapies for dementia (Larner 2007a; see Sect. 10.3.1), internet searches for information about AD had been undertaken in 49/84 cases (= 58%), most commonly by patients' children. The data suggested an increase in spontaneous searching for information by people diagnosed with dementia and their carers over the years (27% in 2003; 58% in 2007).

Reflecting the desire for information, and perhaps also the limited clinical resources available to meet the need, many web-based programmes for dementia caregiver support and education have been developed. These are designed to provide dementia caregivers with the knowledge, skills, and outlook needed to undertake and succeed in the caregiving role. Such studies generally indicate that participants feel more confident in caregiving skills and communication with family members, and that caregivers can benefit from receiving professional support via e-mails and dedicated information websites. An internet-based video conferencing support group may be associated with lower stress in coping with a care recipient's cognitive impairment and decline in function than an Internet-based chat support group. Combined internet and telephone delivery of multicomponent interventions may give more positive outcomes in reducing depression, burden and increasing self-efficacy than using either modality alone (Jackson et al. 2016). Suggestions for

online resources have been provided to patients with dementia and their carers in CFC (Larner and Storton 2011).

The Internet has been described as a psychoactive medium, and clearly there are potential harms, as well as benefits, from internet use for those with neurodegenerative disease (e.g. Larner 2006b).

10.1.2 The Alzheimer's Society

The Alzheimer's Society is a charitable patient organisation which operates throughout the United Kingdom to support patients with dementia and their carers (www.alzheimers.org.uk). Amongst its various activities, it sponsors research and publication of reports into various aspects of dementia in the UK (e.g. Alzheimer's Society 2007, 2011, 2013, 2014; Royal College of Psychiatrists/Alzheimer's Society 2006). Despite the name, support is available to patients with dementia diagnoses other than AD, for example a number of patients with frontotemporal lobar degenerations referred from CFC have been supported through the local Alzheimer's Society branch (Storton et al. 2012).

Only one-third of patients/carers questioned in the CFC AD outpatient follow-up clinic (July–December 2006) were aware of the Alzheimer's Society and its work. This increased to 100% following regular attendance of a Family Support Worker from the Alzheimer's Society at the clinic (Culshaw and Larner, unpublished observations). Patient cohorts for studies of screening instruments may be successfully recruited through the auspices of the Alzheimer's Society (see Sect. 5.3.2).

10.2 Pharmacotherapy

Currently the only medications licensed for the treatment of dementia are cholinesterase inhibitors and memantine (Rodda and Carter 2012). Such licensing is based on the outcomes of randomized controlled trials, systematic reviews and meta-analyses (e.g. van de Glind et al. 2013) although the methodology of clinical trials assessing medications for the treatment of dementia has been criticised (Thompson et al. 2012).

10.2.1 Cholinesterase Inhibitors (ChEIs) and Memantine

The existing evidence base suggests that cholinesterase inhibitors (ChEIs) do have effects, albeit modest, on both cognitive and behavioural symptoms of AD (e.g. Lanctôt et al. 2003; Ritchie et al. 2004; Whitehead et al. 2004; Birks 2006; Raina et al. 2008) although the cost-effectiveness of these benefits has been questioned (AD 2000 Collaborative Group 2004; Kaduszkiewicz et al. 2005). CFC has been involved in ChEI trials (Wilcock et al. 2003).

ChEI trial dropouts who received active medication showed less cognitive decline at follow-up than patients who received placebo (Farlow et al. 2003).

Naturalistic studies suggest that AD patients taking drugs licensed for dementia have a significantly lower risk of deterioration than those not taking these drugs (Lopez et al. 2005; Ellul et al. 2007), and their progression to nursing home placement is delayed (Lopez et al. 2002, 2005). These findings have prompted the suggestion that ChEIs may alter the natural history of AD, and may therefore have "disease-modifying" effects over and above their symptomatic action. However, there is no evidence that any one of the ChEIs prevent the progression from mild cognitive impairment (MCI) to AD in the long term (Salloway et al. 2004; Petersen et al. 2005; Feldman et al. 2007; Winblad et al. 2008), a finding confirmed by systematic reviews (Russ and Morling 2012; Masoodi 2013).

With the publication of guidance by the National Institute for Clinical Excellence (NICE) in 2001, ChEIs became widely available for the symptomatic treatment of mild-to-moderate AD in the UK (National Institute for Clinical Excellence 2001 [NICE was later rebranded as the National Institute for Health and Care Excellence]). Subsequent NICE guidance was more stringent in its recommendations, based on cost effectiveness analyses, thereby restricting ChEI use to moderate AD as defined by a Mini-Mental State Examination (MMSE) score of 10–20 (National Institute for Health and Clinical Excellence 2006). The most recent (and "final") pronouncement from NICE (2011) returns to the recommendation of ChEI use in mild disease.

An audit of practice in CFC (2001–2003 inclusive), at a time when ChEI prescription was permitted in the clinic (see Sect. 1.1, Fig. 1.1), suggested compliance with the then current NICE (2001) guidance for ChEIs, as well as drug efficacy in terms of MMSE scores in the short term (up to 16 months of treatment) (Larner 2004a). The majority of AD patients remained on medication beyond 6 months, contrary to the assumption of the NICE guidance that perhaps only half to two-thirds of patients would show sufficient response, with the unresponsive remainder stopping treatment (National Institute for Clinical Excellence 2001). Long term retention time has been used previously as a surrogate global measure of drug efficacy, as well as of tolerability (e.g. Marson et al. 2007). The possibility that this observation of high retention rate might have been related to the fact that patients in this cohort were younger than those examined in the pivotal clinical trials was considered, but in fact younger patients (<65 years of age) appeared to respond no differently to ChEIs than older patients (Larner 2004a), contrary to the findings in a prior report (Evans et al. 2000).

In the aforementioned audit, and in subsequent clinical experience, ChEIs have generally been extremely well tolerated (Larner 2004a), with less than 5% of patients developing gastrointestinal adverse effects. These findings are commensurate with those of systematic reviews. Headache has sometimes been mentioned as an adverse effect of ChEIs (e.g. Whitehead et al. 2004), but in a cohort of 143 patients treated with ChEIs in CFC only two developed headache, and in one of these patients the symptoms were transient and did not recur on rechallenge (Larner 2006c). Use of transdermal formulations may potentially reduce adverse effects of ChEIs by lowering the maximum plasma concentration (C_{max}) and time to reach C_{max} but with comparable drug exposure (area under the curve) (Winblad et al. 2007; Larner 2010a).

Monitoring the treatment effect of ChEIs by means of MMSE scores (see Sect. 4.1.1), as recommended by NICE (National Institute for Clinical Excellence 2001; National Institute for Health and Clinical Excellence 2006), is difficult to justify for a variety of reasons, including the variable natural history of AD as judged by MMSE scores (Holmes and Lovestone 2003), inter-rater errors in scoring the attention/calculation section of the MMSE (Davey and Jamieson 2004), and the inadequacy of the MMSE for detecting the small changes in cognition which ChEIs might produce (Bowie et al. 1999). This latter problem, measuring change in a manner relevant to the clinical problem of progressive dementia, was foreseen some years earlier when trials of anti-dementia drugs were in their infancy (Swash et al. 1991). Another issue which may require consideration is patient anxiety in the face of cognitive testing which, despite their forgetfulness, they know might lead to cessation of drug therapy, which might be termed an example of the "Godot syndrome" (Larner and Doran 2002).

ChEIs have also been examined in a number of other conditions which cause cognitive impairment (Box 10.1) (Larner 2010b; Li et al. 2015), some in clinical trials, but in many off-licence. For example, they have been reported to have clinical effects in dementia with Lewy bodies (McKeith et al. 2000), Parkinson's disease dementia (PDD; Emre et al. 2004; Dubois et al. 2012), vascular cognitive impairment (Erkinjuntti et al. 2004), and multiple sclerosis (Krupp et al. 2004). However, only in PDD has the evidence been sufficient (e.g. Rolinski et al. 2012) for ChEIs to be licensed for this indication.

Box 10.1: Conditions in which use of ChEIs has been reported (* = licensed; adapted from Larner 2010b)

Alzheimer's disease (mild*/moderate*/severe)
Mild cognitive impairment (prodromal AD)
Down syndrome
Dementia with Lewy bodies
Parkinson's disease dementia*
Progressive supranuclear palsy
Vascular dementia
CADASIL
Frontotemporal lobar degeneration
Huntington's disease
Multiple sclerosis
Cognitive impairments in epilepsy
Delirium (treatment and prevention)
Traumatic brain injury
Sleep-related disorders: obstructive sleep apnoea syndrome, narcolepsy
Psychiatric disorders: schizophrenia, bipolar disorder
Cognitive disorder in brain tumour patients
Wernicke-Korsakoff syndrome, alcohol-related dementia
Subarachnoid haemorrhage
Cerebral amyloid angiopathy

A trend of efficacy of galantamine in aphasic variant FTLD was reported by Kertesz et al. (2008) but the trial was brief and the numbers treated small. Others have also noted successful use of ChEIs in "language variants" of FTD (Lipton and Marshall 2013:87). It is perhaps possible that some of these patients may in fact harbour AD pathology as the substrate of the logopenic progressive aphasia phenotype (see Sect. 8.1.2.1). In CFC, inadvertent experience of ChEI use in FTLD misdiagnosed as AD has been uniformly negative (Davies and Larner 2009). Off licence experience with ChEIs in two multiple sclerosis patients with severe cognitive impairment has suggested limited efficacy (Larner 2010b).

The existing evidence base supports the use of the glutamate receptor antagonist memantine in AD (McShane et al. 2006; Raina et al. 2008) although NICE (2011) have ruled against its use outwith clinical trials. Combination therapy with both ChEI and memantine has been advocated, with trials suggesting both synergy (Tariot et al. 2004) and no benefit over and above ChEI use alone (Howard et al. 2012). Local funding issues have ensured that almost no experience has been gained in CFC with the use of memantine.

10.2.2 Novel Therapies

Novel dementia therapies, particularly for AD, have been developed in the hope of addressing the deficiencies of existing treatments. Some of these have reached clinical trials (Larner 2002, 2004b, 2010c; Mangialasche et al. 2010; Rafii and Aisen 2015). CFC has been involved in trials of some of these compounds through the agency of the WCNN Clinical Trials Unit (e.g. tarenflurbil: Wilcock et al. 2008; rosiglitazone; tideglusib). However, none have gained licensing approval and reached the clinical arena. Secretase inhibitors seemed to have a sound theoretical basis, designed to interrupt the biosynthetic pathway for amyloid peptides which are thought to be central to disease pathogenesis (Larner 2004b). However, the first such trialled drug (LY450139, also known as semagacestat) was withdrawn because of lack of efficacy and safety concerns (Larner 2010c; Doody et al. 2013 and http://www.nejm.org/doi/suppl/10.1056/NEJMoa1210951/suppl_file/nejmoa1210951_appendix.pdf). The increasing focus on intravenously delivered monoclonal antibody therapies for AD has not impacted on CFC practice for both economic and logistical reasons.

Treatment for other dementing conditions has lagged behind that of AD, although prion disease has evoked much research (Larner and Doran 2003; Trevitt and Collinge 2006), befitting its high public profile.

Academic interest in dementia, perhaps at least in part stimulated by increased research funding, has continued to escalate with the ultimate hope of discovering treatments to address the clinical and societal burdens of dementia. There also appears to be a political will to support this undertaking, as exemplified by a G8 summit meeting in London in December 2013 which made a bold commitment to develop a cure or treatment for dementia by 2025 (https://www.gov.uk/government/uploads/system/uploads/attachment_data/file/265868/2901669_G8_DementiaSummitCommunique_acc.pdf).

10.3 Other, Non-Pharmacological, Therapies

The struggle to find meaningful therapeutics for dementia has shifted the focus more towards strategies of disease prevention. Some analyses suggest a third of dementia cases may be preventable, by means of tackling issues such as smoking, depression, hearing loss, education, hypertension, diabetes, obesity, social isolation and lack of exercise (Livingston et al. 2017). However, a recent long term (ca. 30 years) follow up study found no evidence for a neuroprotective effect from physical activity (Sabia et al. 2017). The (comforting) belief that moderate alcohol consumption might be protective for brain health has also been challenged by a recent longitudinal cohort study (Topiwala et al. 2017). A definitive dementia preventative strategy has yet to evolve.

10.3.1 Complementary and Alternative Therapies (CAT)

ChEIs and memantine are far from a complete therapeutic solution to the clinical phenomenology of AD. In the absence of other licensed treatments, it is unsurprising that patients and their carers may seek complementary and alternative therapies (CAT), including "natural health products", available on a non-prescription basis. Various CAT are claimed to help memory disorders and dementia, although the evidence base supporting this conclusion is weak (Diamond et al. 2003). Nonetheless many patients use these agents.

A study of patients with probable AD ($n = 84$; time from diagnosis 3–60 months) seen for follow-up visits in CFC over a 6-month period (January–June 2006) (Larner 2007a) found that 21 (= 25%) had at one time or another used CAT for memory problems (range 1–3 medications, median 1). The most commonly used agents were ginkgo biloba (14) and vitamin E (10). Five patients mentioned that they had used omega oils (Table 10.1). Both ginkgo biloba and vitamin E have some modest evidence favouring their use in dementia (Sano et al. 1997; Oken et al. 1998; Birks and Grimley Evans 2009), although there are more recent studies suggesting that ginkgo does not reduce progression from subjective memory complaints to AD

Table 10.1 Awareness and use of CAT (adapted from Alzheimer's Disease Society (ADS) website devoted to CAT, www.alzheimer's.org.uk/After_diagnosis/Treatments/info_complementary.htm) in CFC AD population ($n = 84$) (Larner 2007a)

	Heard of?	Used?
Ginkgo (*Ginkgo biloba*)	53	14
Silymarin	3	0
Chotosan	2	0
Kami-umtan-to	0	0
Yizhi capsule	2	0
Huperazine	6	1
Lemon balm (*Melissa officinalis*)	37	0
Acupuncture	75	2
Vitamin E	72	10
Melatonin	26	0

(Vellas et al. 2012) nor that it helps cognitive impairment in multiple sclerosis (Lovera et al. 2012). Vitamin E may slow functional decline in mild-to-moderate AD (Dysken et al. 2014).

The CFC data may be compared with those from a Canadian dementia clinic study which found that about 10% of the clinic population had used complementary treatments for their cognitive problems (Hogan and Ebly 1996) and a US study of caregivers which reported that 55% had tried at least one medication to try to improve the patient's memory, most usually vitamins (Coleman et al. 1995). Just over 50% of mildly cognitively impaired patients and their caregivers attending a memory clinic were reported to be current users of natural health products, with vitamin E, ginkgo and glucosamine being the most commonly used (Sharma et al. 2006). An Australian community-based survey found that 2.8% of 60–64 year-olds reported using medications to try to enhance memory (Jorm et al. 2004).

10.3.2 Gardening

Gardening activities are sometimes used as an occupational therapy for patients with dementia (Heath 2004). Since physical and intellectual activities in midlife may protect against the development of AD (Friedland et al. 2001), it has been suggested that gardening may be one component of a healthy ageing programme to prevent dementia, through stimulation of the mind (Dowd and Davidhizar 2003).

A study of 100 consecutive community-dwelling patients with a diagnosis of dementia (F:M = 54:46, 54% female; mean age ± SD = 65.6 ± 8.3 years; age range 44–82 years), most of whom had AD (n = 87), found that of the 38 who professed a premorbid interest in gardening, 27 (= 71%) were still undertaking some gardening activity, perhaps just "pottering", weeding, cutting the grass, or attending to indoor plants. Cessation of gardening activity was due in some cases to loss of interest (sometimes rekindled after commencement of ChEI therapy), physical infirmity, loss of concentration, visual agnosia, forgetting the names of plants, not knowing when to plant things, and difficulty handling plants or garden implements, probably as a consequence of clinically apparent apraxia. An individualised approach tailored to cognitive abilities and deficits may therefore be required if gardening is contemplated as a component of occupational therapy for dementia patients (Larner 2005a).

10.4 Nursing Home Placement

Studies of the natural history of AD have indicated the limited value of rate of change of MMSE scores in assessing therapeutic responses (Holmes and Lovestone 2003). Hence the use of traditional milestones as end-points, such as nursing home placement, may be more meaningful in assessing drug efficacy, although this does require longer term follow-up than in studies using cognitive, behavioural, or functional rating scales.

Nursing home placement may itself be taken to reflect a measure of global patient function. Such an endpoint also has significant economic implications, since costs escalate greatly with nursing home placement. Interestingly, nursing home placement was the end-point in one ChEI trial, such that all costs accruing after this time point were censored, a policy which may have influenced the trialists' conclusion that ChEI are not cost effective (AD2000 Collaborative Group 2004). In long term conditions such as dementia, long term studies are required in order to answer definitively such contentious issues.

An observational study by Lopez et al. (2002) came to the conclusion that ChEIs may influence the natural history of AD, over and above their recognised symptomatic effects. In this study, the frequency of permanent nursing home placement was much lower in patients receiving ChEI (5.9%, 95% confidence interval [CI] = 1.9%–9.9%) than in untreated patients (41.5%, 95% CI = 33.2%–49.7%), suggesting a long-term beneficial effect from ChEIs. However, the possibility that these findings might represent a cohort effect cannot be entirely excluded, since it would seem likely that the patients not receiving ChEIs dated from earlier in the studied epoch (1983–1999). Moreover, it is possible that earlier referral, diagnosis, support and counselling, may have contributed to the delayed institutionalization through reduced caregiver burden (e.g. Brodaty et al. 2003). Nevertheless, the figures for nursing home placement in the untreated patients were similar to those reported in a prospective study which found 35% and 62% of "mild" and "advanced" AD cases in nursing homes after 2 years (Knopman et al. 1988). Reduced frequency of nursing home placement was also found in a study of AD patients previously commenced on donepezil as part of randomised clinical trials (Geldmacher et al. 2003). Lower risk of nursing home placement, as well as lower likelihood of disease progression, was confirmed in a further study from the Pittsburgh group examining the effects of ChEIs over 24–36 month follow up periods (Lopez et al. 2005). Long-term treatment with galantamine or other ChEIs appeared to be associated with a significant delay in the time to nursing home placement in patients with AD and AD with cerebrovascular disease (Feldman et al. 2008). Any such delay in nursing home placement may have health care cost-saving implications (Provenzano et al. 2001).

A retrospective case note audit of patients prescribed ChEIs at CFC (2001–2005 inclusive) identified 98 patients who had received ChEI for >9 months (F:M: = 54:44, 55% female; mean age at onset of treatment = 63.9 ± 7.7 years, age range 49–84 years). Of these 98 patients, 93 had AD, 60 of whom (= 65%) had early-onset AD. Other diagnoses were DLB/PDD (3) and FTLD (2). Total follow-up in this group was over 217 patient years of ChEI treatment, with mean treatment duration of 26.6 (± 13.3) months (range 9–60 months). Eight of the 98 patients had permanently entered nursing homes during the study period (= 8.2%, 95% CI = 2.7%–13.6%). Of these eight (F:M = 6:2), six had AD and two had PDD. Behavioural and psychological problems were the proximate reason for nursing home placement in all cases. Eight of the 98 patients, all with AD, had died during the study period (= 8.2%; 95% CI = 2.7%–13.6%) Of these eight (F:M = 4:4), six died from causes judged AD-related (inanition, infection), two from non-AD-related causes (one from a bowel carcinoma, one from a myocardial infarction). Only one of these eight deaths was in a nursing home resident (Larner 2007b). Hence the figures for

permanent nursing home placement in this cohort were comparable to those of Lopez et al. (2002) study (8.2% vs. 5.9%), albeit that this cohort was younger (mean age 63.9 ± 7.7 years vs. 72.7 ± 7.2 years) and that follow-up was shorter (26.6 ± 13.3 months vs. 34.6 ± 21.3 months). The lower death rate (8.2% vs. 12.6%) may be a reflection of the age disparities (Larner 2007b).

A reduced risk of nursing home placement has been noted in patients treated with the combination of ChEIs and memantine (Atri et al. 2008; Lopez et al. 2009), which might reflect a synergistic effect between these medications (Tariot et al. 2004) although this was not observed in another study (Howard et al. 2012).

10.5 Policy Consequences

The days when hospital clinicians were relatively autonomous practitioners who could decide, based on their experience and expertise, what was best for their patient are now, for good or ill, long past (a slightly different dispensation persists in UK primary care, where general practitioners are deemed to know what is best for their patients, and are therefore able to pick and choose which services they wish to use, and indeed in some locations to act as commissioners for them). Various documents, labelled as guidelines or guidance, yet adherence to which is mandatory rather than optional (sometimes with adverse financial consequences for non-adherence), have emerged from UK government sponsored bodies, ostensibly to render practice uniform, but in implementation to constrain doctors. The effects of these policies, easy enough to formulate, are seldom if ever examined, the hallmark of ideology, not science. In any arena or forum where facts are few and comment is free, evaluations of (health policy) reforms are likely to be either absent or piecemeal. Moreover a gap between policy intent and what happens in practice is well-recognised (in the bureaucratic metastory, representation is inevitably distortion). For example, use of referral guidelines for the identification of brain or central nervous system cancers ("2-week wait referrals") usually result in the referral of patients without such cancers (Abernethy Holland and Larner 2008; Panicker and Larner 2012).

All such policies or "reforms" should rightly be regarded as experiments (Campbell 1969; McKee et al. 2012) and hence should be administered (with informed consent of the target population, rather than enforced implementation) and evaluated as such. Although clinicians may feel undermined by political interference, and that they are being obligated (if not financially coerced) to make failed policies work, nevertheless there is opportunity to collect data to try to measure the outcomes of these experiments, in preparation for the hoped-for (mythical?) advent of evidence-based policy making. Some attempts have been made to do this within CFC practice.

10.5.1 NICE/SCIE (2006) Guidelines

The National Institute for Health and Clinical Excellence/Social Care Institute for Excellence (NICE/SCIE) guidelines recommended that psychiatrists, particularly old age psychiatrists, should manage the entire dementia care pathway from

Table 10.2 CFC referral numbers and sources before and after NICE/SCIE guidelines of 2006 (Larner 2009b)

	Before NICE/SCIE (2005–2006)	After NICE/SCIE (2007–2008)
New referrals seen	213	382
New referrals from psychiatrists (% of total)	49 (23)	80 (21)

diagnosis to end-of-life care, acting as a "single point of referral" for all cases (National Institute for Health and Clinical Excellence/Social Care Institute for Excellence 2006). Neurologists were mentioned only once in the document, prompting the suggestion that the specialist dementia interests of some neurologists had been (perhaps inadvertently, perhaps wilfully) overlooked (Doran and Larner 2008). Compliance with the NICE/SCIE guidelines might have been anticipated to erode the number of general referrals to neurology-led memory clinics, and referrals to these clinics from psychiatrists in particular.

The impact of NICE/SCIE guidelines in a neurology-led memory service was examined in CFC by comparing referral numbers and source in the 2-year periods immediately before (January 2005–December 2006) and after (January 2007–December 2008) publication of the NICE/SCIE document (Larner 2009b). These data (Table 10.2) indicated a similar percentage of referrals from psychiatrists in both time periods (23% and 21% respectively). The null hypothesis tested was that the proportion of referrals from psychiatrists (see Sect. 1.2.2) was the same in cohorts referred before and after publication of the NICE/SCIE guidelines (equivalence hypothesis). The result of the χ^2 test did not permit rejection of the null hypothesis ($\chi^2 = 0.39$, df = 1, $p > 0.5$), a finding corroborated by the Z test ($Z = 0.56$, $p > 0.05$).

Whilst the NICE/SCIE guidelines might possibly have been instrumental in increasing the total number of referrals (see Sect. 1.1), by raising public and professional awareness of dementia, the evidence from this survey did not suggest that referral practice from psychiatry to neurology had changed in light of NICE/SCIE. The data suggested that psychiatrists continued to value access to a neurology-led dementia service and that, *pace* NICE/SCIE, neurologists still have a *de facto* role in the dementia care pathway (Larner 2007c, 2009b).

10.5.2 QOF Depression Indicators (2006)

The Quality and Outcomes Framework (QOF) of the general practitioner General Medical Services contract in the United Kingdom (UK), introduced in April 2006, included amongst its provisions Depression Indicator 2, viz.:

> "In those patients with a new diagnosis of depression, recorded between the preceeding 1 April to 31 March, the percentage of patients who have had an assessment of severity at the outset of treatment using an assessment tool validated for use in primary care."

Three depression severity measures were suggested: the Patient Health Questionnaire depression module, PHQ-9 (see Sect. 5.2.2); the Hospital Anxiety and Depression Scale (HADS); and the Beck Depression Inventory, Second Edition (BDI-II) (British Medical Association 2006).

Prior studies of non-overlapping cohorts of patients seen at CFC showed that the percentage of patients referred to the clinic from primary care who received a diagnosis of dementia was between 37 and 40% (relative risk of dementia in primary care referrals = 0.55 to 0.69) (Larner 2005b; Fisher and Larner 2007). Some of these non-demented patients referred from primary care may have had depression, rather than dementia, as a cause for their symptoms, and hence improvements in the diagnosis of depression in primary care, perhaps as a consequence of QOF implementation, might have been anticipated to reduce these non-dementia referrals to CFC from primary care.

To test this hypothesis, a study was undertaken to examine whether any change occurred in the frequency of non-dementia diagnoses in patients referred from primary care before and after QOF introduction (Fearn and Larner 2009). All referrals from primary care seen in the 18 month periods immediately preceding (November 2004–April 2006) and following (May 2006–October 2007) introduction of the QOF in April 2006 were examined.

The percentage of all referrals to CFC which originated from primary care was about half (Table 10.3) in both time periods ($\chi^2 = 0.88$, df = 1, $p > 0.1$; Z = 0.77, $p > 0.05$). Of the primary care referrals, about one third had dementia. The relative risk of diagnosis of dementia in a primary care referral pre- and post-QOF was 0.55 (95% confidence interval [CI] 0.40–0.74) and 0.66 (95% CI 0.49–0.89), respectively (Fearn and Larner 2009). All these findings were similar to those in previously reported cohorts from CFC (Larner 2005b; Fisher and Larner 2007).

The null hypothesis tested was that the proportion of patients referred from primary care with dementia was the same in cohorts seen both before and after introduction of the QOF Depression Indicator (equivalence hypothesis). The result of the χ^2 test did not permit rejection of the null hypothesis ($\chi^2 = 0.54$, df = 1, $p > 0.05$), a finding corroborated by the Z test (Z = 0.60, $p > 0.05$) (Fearn and Larner 2009).

This observational survey found no change in the frequency of non-demented patients referred to a dedicated dementia clinic from primary care following introduction of the QOF Depression Indicator which recommended use of validated scales to measure the severity of depression. Clearly this finding is subject to the caveats applicable to any single-centre study with relatively small patient cohorts, but if true may have various explanations, including lack of uptake of Indicator use

Table 10.3 CFC practice before and after introduction of QOF Depression Indicator of 2006 (Fearn and Larner 2009)

	Pre-QOF (Nov 2004-April 2006)	Post-QOF (May 2006–October 2007)
N	186	186
GP referrals (%)	96 (51.6)	105 (56.5)
GP referrals with dementia (%)	34 (35.4)	32 (30.5)

in primary care in this region (very few referrals letters mentioned use of either depression or cognitive scales: Fisher and Larner 2007; Menon and Larner 2011), or inefficacy of the recommended depression severity scales to differentiate depression from dementia. For example, PHQ-9 was found to be of only moderate diagnostic utility for the differentiation of depression and dementia in a clinic-based cohort (see Sect. 5.2.2; Hancock and Larner 2009). Alternatively, methodological variables, such as sample size or the use of a surrogate measure of test efficacy (referrals to a dementia clinic as a measure for change in practice) may have caused a failure to find an effect that did in fact exist (i.e. type II error).

10.5.3 National Dementia Strategy (2009)

The National Dementia Strategy (NDS) for England was officially launched on 3rd February 2009 (Department of Health 2009). It proposed three key themes to address the problem of dementia: improved awareness of the condition; early diagnosis and intervention; and higher quality of care. A pathway for NDS implementation, anticipated to roll-out over a 5-year period, was also proposed. One year on, a report into progress on NDS delivery was published (National Audit Office 2010) but this omitted frontline services since they were not anticipated to have changed, as local implementation plans were still being developed. Following a change of political regime, the *Prime Minister's Challenge on Dementia* of 2012 and 2015 sought to build on the NDS, sharing the key NDS commitment to increase dementia diagnosis rates, a necessity in view of the recognised dementia diagnosis gap (Department of Health 2012a, 2015).

The possible impact of NDS in CFC was examined by comparing referral numbers, sources, and diagnoses in the 12-month periods immediately before (February 2008–February 2009) and after (February 2009–February 2010) the NDS launch (Table 10.4; see also Table 1.2, right hand columns) (Larner 2010d). These data showed a 12% increase in new referrals seen in the second time period, with a marked increase in the percentage of referrals coming from primary care (70.2% vs. 58.2%). The null hypothesis that the proportion of new referrals from primary care was the same in the cohorts referred before and after NDS launch (equivalence hypothesis) was rejected ($\chi^2 = 6.18$, df = 1, $p < 0.01$).

A small decrease in the percentage of patients receiving a diagnosis of dementia (DSM-IV-TR criteria) was noted in the patient cohort from the second time period

Table 10.4 Referral numbers, sources and diagnoses before and after NDS launch (Larner 2010d)

	Before NDS launch (Feb 2008–Feb 2009)	After NDS launch (Feb 2009–Feb 2010)
New referrals seen	225	252
New referrals from primary care (% of total new referrals)	131 (58.2)	175 (70.2)
New diagnoses of dementia (% of total new referrals)	74 (32.9)	75 (29.8)

(29.8% vs. 32.9%). The null hypothesis that the proportion of new referrals receiving a diagnosis of dementia was the same in the two cohorts was not rejected ($\chi^2 = 0.63$, df = 1, $p > 0.1$) (Larner 2010d).

Extending this analysis to encompass the 5-year period 2009–2013 showed that referral numbers were found to have increased, most particularly those from primary care (Table 1.3). The null hypothesis that the proportion of patients referred from primary care over this period did not differ significantly was rejected ($\chi^2 = 22.1$, df = 4, $p < 0.001$). Considering patient diagnoses, the null hypothesis that the proportion of all referred patients who were diagnosed with dementia over this period did not differ significantly was not rejected ($\chi^2 = 4.03$, df = 4, $p > 0.1$), and likewise for a diagnosis of any cognitive impairment (= dementia + MCI; $\chi^2 = 3.85$, df = 4, $p > 0.1$) (Larner 2014).

These findings suggested that the NDS may have increased the total number of referrals to CFC, perhaps by raising awareness of dementia, although the initial increase was not as marked as that seen following the publication of the NICE/SCIE guidelines (see Sect. 10.5.1; Table 10.2). The post-NDS increase in referrals came mostly from primary care, supporting the contention that GPs were becoming more positive about diagnosing dementia early (National Audit Office 2010). However, there was no accompanying increase in the number of new diagnoses of dementia, and hence no evidence for closure of the dementia "diagnosis gap" (i.e. too few people being diagnosed with dementia or diagnosed early enough; it is reported that only a third to a half of people in England with AD receive a formal diagnosis: National Audit Office 2007; Alzheimer's Society 2011; 2013). The impression was that more "worried well" individuals were being referred, rather than those with previously undiagnosed dementia (see Sect. 8.3).

10.5.4 NICE Guidance (2011): Anti-Dementia Drugs

The most recent (and "final") guidance on the use of the anti-dementia drugs published by the National Institute for Health and Clinical Excellence (2011) made these drugs available as per licence, effective from 1st June 2011, and hence more easily accessible than had previously been the case following previous NICE guidance (2006). One anticipation of this liberalization of drug availability was that more people who might be candidates for licensed use of these medications (i.e. mild to moderate AD and Parkinson's disease dementia) would be referred to dementia/memory clinics, with a possible diminution in the recognised dementia "diagnosis gap" resulting from too few people being diagnosed with dementia or diagnosed early enough (Alzheimer's Society 2011, 2013).

The possible impact of the NICE 2011 guidance in a neurology-led memory service was examined by comparing referral numbers, sources, patient diagnoses and candidacy for treatment with cholinesterase inhibitors in the 12-month periods immediately before (1st June 2010–31st May 2011) and after (1st June 2011–31st May 2012) publication of the guidance (Larner 2012a). These data showed no change in numbers of new referrals between the two time periods (Table 10.5), but

Table 10.5 Referral numbers, sources, patient diagnoses and candidacy for ChEI/memantine treatment before and after NICE 2011 guidance (NICE217) effective (adapted from Larner 2012a)

	Before NICE217 effective (1 June 2010–31 May 2011)	After NICE217 effective (1 June 2011–31 May 2012)
New referrals seen	230	225
F:M (% female)	108:122 (47.0)	126:99 (56.0)
Age range (median), years	19–88 (61.5)	18–93 (61)
New referrals from primary care (% of total new referrals)	169 (73.5)	186 (82.7)
New diagnoses of dementia (% of total new referrals)	68 (29.6)	62 (27.6)
Candidacy for treatment with ChEI/memantine (% of total new referrals; % with dementia)	44 (19.1; 64.7)	44 (19.6; 71.0)

with an increase in the percentage of referrals coming from primary care in the second time period (82.7% vs. 73.5%). The null hypothesis that the proportion of new referrals from primary care was the same in the cohorts referred before and after NICE 2011 guidance (equivalence hypothesis) was rejected ($\chi^2 = 5.12$, df = 1, $p < 0.05$). However, there was no change in the percentage of patients receiving a diagnosis of dementia (DSM-IV-TR criteria; $\chi^2 = 0.17$, df = 1, $p > 0.5$).

The proportion of patients deemed candidates for treatment with ChEI/memantine was examined. Exclusions included patients with frontotemporal lobar degenerations, vascular dementia/subcortical ischaemic vascular dementia, dementia with Lewy bodies, Huntington's disease, Down syndrome, alcohol-related dementia, and prion disease, since these conditions fall outwith drug licence, although ChEI have sometimes been used in these conditions (Box 10.1; Larner 2010b). This analysis showed no change in the proportion of patients suitable for these medications, examining either the whole cohort ($\chi^2 = 0$) or those patients with dementia only ($\chi^2 = 0.56$, df = 1, $p > 0.5$).

Unlike the situation with NICE/SCIE (Sect. 10.5.1; Larner 2009b) and the National Dementia Strategy (Sect. 10.5.3; Larner 2010d, 2014), there was no increase observed in referrals to CFC following the NICE 2011 guidance on anti-dementia drugs. Of perhaps greater concern, no increase in the number of referrals deemed candidates for treatment with these drugs was observed, and hence no evidence for closure of the dementia diagnosis gap.

10.5.5 Dementia CQUIN (2012)

The Dementia Commissioning for Quality and Innovation (Dementia CQUIN) document published under the auspices of the UK Government in April 2012 (Department of Health 2012b) sought to implement a proactive approach to identify people with dementia, in part to address the dementia diagnosis gap (Alzheimer's Society 2011, 2013). Dementia CQUIN required all individuals aged 75 years or over presenting to secondary care for whatever reason to be asked a screening

question ("Have you been more forgetful in the past 12 months to the extent that it has significantly affected your life?"), which if answered in the affirmative was to trigger a "Dementia Risk Assessment". Compliance with the Dementia CQUIN was incentivised with cash payments according to level of performance. The principles of the Dementia CQUIN were also proposed for use in primary care, despite a lack of evidence for such screening (Brunet et al. 2012). Evidence for the utility of the single screening question was not presented (probably because this had not been examined); post hoc data is scant, and not compelling (see Sects. 3.1.1.1 and 3.1.1.3; Larner 2018b).

Details of the Dementia CQUIN "Dementia Risk Assessment" were unspecified, but it would seem likely that administration of some form of cognitive screening instrument (CSI) would form an integral part of any such assessment. One such CSI, the Six-Item Cognitive Impairment Test (6CIT; Sect. 4.1.6; Brooke and Bullock 1999; Gale and Larner 2017), was accepted as a Dementia CQUIN target by two NHS Trusts within the CFC catchment area (Liverpool Community Health and Bridgewater Community Healthcare).

In a prospective study, referral letters of consecutive patients seen in CFC over a 6-month period (July–December 2012) following publication of the Dementia CQUIN (April 2012) were examined for any mention of use of the 6CIT prior to referral (Cagliarini et al. 2013), a methodology used in previous studies (Fisher and Larner 2007; Menon and Larner 2011). The study found that of 132 consecutive referrals to CFC (F:M = 58:74, 44% female; age range 20–88 years, median 58 years) very few had been assessed with 6CIT prior to referral (7/132 = 5.3%), although this was an increase on previous cohorts (1/123 = 0.81%, October 2004–September 2006; Fisher and Larner 2007; and 2/175 = 1.14%, February 2009–February 2010; Menon and Larner 2011) and was maintained in later studies (8/140 = 5.7%; Ghadiri-Sani and Larner 2014; 38/246 = 15.4%; Cannon and Larner 2016; Table 1.5). Concerns over possible 6CIT overuse or misuse, which had been expressed locally, thus seemed to be without foundation. Indeed, more widespread use of 6CIT or other suitable CSI may be required to facilitate the aims of the Dementia CQUIN in closing the dementia diagnosis gap.

10.5.6 NICE Guidelines (2015): To Delay or Prevent Dementia Onset

NICE guidelines on delaying or preventing dementia—a worthy goal in light of the ongoing absence of disease-modifying therapy—were published in October 2015 (National Institute for Health and Care Excellence 2015). There were in all 15 recommendations delivered in two subsections: promoting healthy lifestyles (8) and service organisation and delivery (7). The headline recommendations were summarised as: stop smoking; be more physically active; reduce alcohol consumption; adopt a healthy diet; and achieve and/or maintain a healthy weight. Most controversial was the suggestion that no level of alcohol consumption was protective, as previously thought.

The guideline reads as a series of prescriptions and proscriptions for behaviour modification, an approach which has been described (Larner 2015a) as managerial or "Skinnerian", since it seems largely uninterested in the cognitive processes which cause people to fail to adopt, or indeed to do the opposite of, what promotes health. There seemed to be no expectation or plan to measure any impact of the guidelines.

10.6 Integrated Care Pathways (ICPs)

This book began by asking what contribution(s) to the diagnosis and care of people with cognitive disorders a neurology-led dementia clinic could make (see Introduction). The intervening sections have hopefully given some examples of potential contributions such a clinic can make. But services do not exist in isolation, so it is pertinent to ask where neurology-led dementia clinics might fit in with other services for patients with cognitive dysfunction.

A short answer might be "nowhere", this being an almost inescapable implication of the NICE/SCIE (2006) guidelines wherein neurologists were mentioned only once, a propos the initiation of cholinesterase inhibitor therapy (National Institute for Health and Clinical Excellence/Social Care Institute for Excellence 2006:30). Of possible significance to this conclusion, however, was the fact that there was no input from a neurologist in the preparation of this document (Doran and Larner 2008). The National Dementia Strategy said a little more about neurologists (Larner 2009a), including the possibility that memory clinic services could be provided by neurologists (Department of Health 2008:77). Previously, a report on services for younger people with dementia published jointly by the Royal College of Psychiatrists and the Alzheimer's Society (2006) suggested that dedicated clinics may be required for the diagnosis of early-onset dementia and that such clinics might have a neurological lead.

Dementia is a multi-dimensional construct (American Psychiatric Association 2000) and a syndrome with variable age at onset and many possible causes (Larner 2008a, 2013a). Patient diagnosis may involve a wide array of professional groups in both primary and secondary care (e.g. Sect. 1.2). Hence it may be envisaged as a "boundary" condition which transcends traditional professional categories. The division between neurology and psychiatry is, after all, arbitrary (both deal with brain disorders) and hence it is not surprising that both neurological and psychiatric symptoms may occur in the same patient suffering from a single brain disease, although regrettably some diagnostic criteria for dementia disorders may neglect the psychiatric features (e.g. motor neurone disease: Sathasivam et al. 2008; prion disease: Zerr et al. 2009; Ali et al. 2013).

This interface between neurology and psychiatry has been a major focus of interest in the CFC (e.g. Larner and Doran 2002; Larner 2003b, 2006b, 2007d, 2008b, 2010e, 2013b; Doran and Larner 2004; Doran et al. 2006; Hancock and Larner 2008, 2009, 2015; Sathasivam et al. 2008; Abernethy Holland and Larner 2009; Fearn and Larner 2009; Wong et al. 2010; Ali et al. 2013; Bonello et al. 2014; Ziso et al. 2014; Randall et al. 2015; Williamson and Larner 2016). A "single point of

referral" (NICE/SCIE) or a "simple single focus of referrals from primary care" (NDS) may not therefore be entirely desirable. Diversity rather than uniformity may best serve patient needs in such a heterogeneous syndrome. The ideal model of service has not, to this author's knowledge, yet been defined.

If it be acknowledged that individuals with different generic skills may be involved in the assessment of patients with cognitive impairment and suspected dementia, the development of an integrated care pathway (ICP) may be an appropriate management strategy (Larner 2007e). ICPs aim to outline key diagnostic and therapeutic tasks and their timing for a condition or procedure, defined by specific inclusion and exclusion criteria (Kitchiner and Bundred 1996; Campbell et al. 1998) and facilitate the evaluation of process. Prior experience of developing an ICP for a "boundary" condition which transcends professional categories and involves more than one professional group in diagnosis and management (viz. idiopathic intracranial hypertension; Larner 2007f) was used to inform the development of a dementia ICP.

Most cases of dementia are of long duration, sometimes lasting for decades, with evolving symptomatology (neurological, psychiatric, functional, neurovegetative) and hence changing care needs. All these factors suggest that developing a meaningful ICP for dementia may be very difficult, let alone a test-treatment pathway (Ferrante di Ruffano et al. 2012; also known as phase IV diagnostic test accuracy studies: Larner 2015b:9,132–3), although some attempts have previously been made (e.g. Naidoo and Bullock 2001; Department of Health 2009:22). Any dementia ICP should accommodate the various interested disciplines, including old age psychiatry, psychiatry, geriatric medicine, and possibly clinical genetics and palliative care, as well as neurology (Box 10.2; Larner 2007e).

Patients who might reasonably be referred to a neurologist with specialist interest in dementia/cognitive disorders include those:

- ≤65 years of age.
- With neurological signs in addition to cognitive impairment, not deemed simply age-related (Sect. 3.2; Larner 2006d, 2012b, 2016:6–7), e.g.:

  Parkinsonism (raising the possibility of dementia with Lewy bodies, Parkinson's disease dementia, progressive supranuclear palsy, corticobasal degeneration, as well as AD).
  Myoclonus (prion disease, AD)
  Chorea (Huntington's disease)
  Muscle wasting +/− fasciculation (FTD/MND)
  Sensory complaints (prion disease, multiple sclerosis)

  In other words where there may be a suspicion of "secondary" dementia (Kurlan 2006).

- >65 years with family history of dementia suggesting autosomal dominant disease transmission (e.g. ≥3 affected family members in two generations with one person being a first-degree relative of the other two; Cruts et al. 1998; Goldman et al. 2005): for consideration of neurogenetic testing.

Box 10.2: Proposed integrated care pathway for dementia diagnosis (adapted from Larner 2007e)

Inclusion criteria:

- All patients presenting in primary care with complaint of memory impairment, preferably with informant corroboration.

Exclusion criteria:

- Patients with established aetiological diagnosis of dementia; generally should be referred directly to old age psychiatrists to access dementia care pathway, as per United Kingdom NICE/SCIE guidance, although there may be exceptions where specialised dedicated services exist (e.g. HIV dementia, Huntington's disease, prion disease, alcohol-related cognitive problems).

REFERRAL PATHWAY OPTIONS:
(A) Referral to old age psychiatrist:

- Elderly patients (>65 years)
- Monosymptomatic progressive impairment of episodic memory
- Absence of neurological signs, other than those appropriate to normal ageing
- ± behavioural and psychiatric symptoms of dementia (apathy, aggression)
- ± Impaired activities of daily living such that social and/or pastoral care in the community is required (as per NICE/SCIE).

(B) Referral to geriatrician, preferably with an interest in dementia:

- Elderly patients (>65 years)
- Comorbid pathology which may impact on cognitive function and requiring specific management

Once diagnosis of dementia is established, option to refer to old age psychiatry to access social care services as per NICE/SCIE.

(C) Referral to neurologist with specialist interest in dementia/cognitive disorders:

- Patients ≤65 years of age
- Patients of any age with family history of dementia suggesting autosomal dominant disease transmission
- Patients with neurological signs in addition to cognitive impairment and not appropriate to age, e.g. parkinsonism, myoclonus, chorea, muscle wasting ± fasciculation, sensory complaints, i.e. suspicion of secondary dementia

- Cognitive screening instrument administered, e.g. MACE, MoCA
- Informant collateral history plus assessment, e.g. AD8, IQCODE
- Morphological brain imaging (CT ± MRI)
- ± behavioural assessment (e.g. NPI, Cambridge Behavioural Inventory), functional assessment (e.g. IADL, DAD)
- ± Formal neuropsychological assessment by neuropsychologist (if diagnosis remains in doubt)
- ± functional brain imaging: SPECT, MR spectroscopy, amyloid PET
- ± diagnostic neurogenetic testing (may require input from clinical geneticist—see D)
- ± CSF analysis (Aβ42, total tau, phospho-tau)
- ± Brain biopsy
- ± other tissue biopsy (bone marrow, skin, rectum)

Once diagnosis of dementia is established, refer to young-onset dementia services where available, or old age psychiatry to access social care services as per NICE/SCIE.

(D) Referral to clinical geneticist:

- Any patient with a clinical phenotype and/or family history suggestive of a monogenic Mendelian disease (e.g. Huntington's disease) in whom diagnostic genetic testing is contemplated, for appropriate genetic counselling (see Sect. 7.3).
- Any patient with a family history of dementia suggesting autosomal dominant disease transmission (i.e. ≥3 affected family members in two generations with one person being a first-degree relative of the other two).
- Asymptomatic individuals ≤65 years of age with family history of dementia suggestive of autosomal dominant disease transmission (i.e. ≥3 affected family members in two generations with one person being a first-degree relative of the other two), or with a defined dementia-causing genetic mutation (e.g. presenilin-1, Huntington's disease) in immediate family member(s), who are contemplating or requesting predictive genetic testing, for appropriate genetic counselling.

(E) Referral to psychiatrist:

- Memory complaints associated with evidence or history of primary psychiatric disorder (depression, anxiety, schizophrenia) in the absence of other neurological symptoms and signs.

Developing ICPs for specific dementia diagnoses, such as the frontotemporal lobar degenerations (FTLDs), may be even more problematic than developing an ICP for dementia per se, in part because of the variable phenotype, encompassing either behavioural change or linguistic impairment (language fluency or comprehension) depending on whether the brunt of pathology falls within the frontal or temporal lobes, respectively. Although prototypical forms of FTLDs are relatively easily recognised by clinicians with experience of these conditions, diagnosis may often be challenging because of overlap of symptoms with the far more common condition of AD, with occasional misdiagnosis occurring (Davies and Larner 2009). The overlap between FTLDs and AD was reflected in older clinical diagnostic criteria (Varma et al. 1999). Delayed diagnosis of FTLD, even following contact with medical services, is common, with an average delay of nearly 3 years in a Scandinavian series, in which nearly three-quarters of patients initially received a non-dementia diagnosis (Rosness et al. 2008).

Neuropsychiatric symptoms are common in FTLDs (Mendez et al. 2008a; Box 10.3); symptoms which are incorporated in recent diagnostic criteria for behavioural variant FTD (Rascovsky et al. 2011). A sizeable proportion of FTLD referrals to CFC have come from psychiatry clinics (see Sect. 1.2.2). Psychosis is rare in FTLDs (Mendez et al. 2008b), with the possible exception of FTD/MND (Larner 2008b, 2013b), such that many of these patients are referred initially to psychiatry services, thereafter to neurology-led dementia clinics when features atypical for primary psychiatric disorders emerge (Larner 2007c, 2009b; Sathasivam et al. 2008; Ziso et al. 2014).

An ICP for FTLDs taking into account these problems has been proposed, based on empirical data from patients and their carers (Box 10.4; Davies and Larner 2010).

Once a diagnosis of dementia, and hopefully dementia subtype, has been established, patients may be referred on from neurology to young-onset dementia services where these are available or to old age psychiatry services to access appropriate pharmacotherapy and social care, as per NICE/SCIE (2006) recommendations. However, it is clear that for early diagnosis of dementia, neurologists with a special interest in the field should continue to have a role in the diagnostic phase of the dementia care pathway (Larner 2007c).

Box 10.3: Neurobehavioural features of FTLDs (after Mendez et al. 2008a)

Apathy-abulia
Disinhibition-impulsivity
Loss of insight
Decreased emotion, empathy
Violation of social/moral norms
Changes in dietary or eating behaviour
Repetitive behaviours

Box 10.4: Proposed integrated care pathway for frontotemporal dementia diagnosis (adapted from Davies and Larner 2010)

Inclusion criteria:

- All patients presenting in primary care and/or to psychiatry/old age psychiatry services with new, prominent neurobehavioural features (Box 10.3), based on history from a knowledgeable informant and corroborated by appropriate test instruments.

Exclusion criteria:

- Patients with an established alternative aetiological diagnosis of dementia, and/or monosymptomatic episodic memory impairment; such patients should be referred directly to old age psychiatrists to access dementia care pathway, as per United Kingdom NICE/SCIE guidance.

Referral to neurologist with specialist interest in dementia/cognitive disorders

1. Referral criteria:

- Patients ≤65 years of age.
- Patients with family history of dementia suggestive of autosomal dominant disease transmission (i.e. ≥3 affected family members in two generations with one person being a first-degree relative of the other two) since positive family history of dementia is more common in FTLD than AD.
- Patients with neurological signs suggestive of either frontal dysfunction ("frontal release signs", "primitive reflexes", e.g. pout, snout, grasp, palmomental reflexes) and/or anterior horn cell disease (cramps, muscle wasting especially around shoulder girdle, fasciculation).

2. Clinical diagnostic assessment:

- Cognitive assessment (e.g. MACE, MoCA).
- Behavioural assessment (e.g. Frontal Assessment Battery, Frontal Behavioural Inventory, Middelheim Frontality Index, FRONTIER Executive Screen).
- Functional assessment (Instrumental Activities of Daily Living Scale, Disability Assessment for Dementia).
- Collateral (caregiver) history: FLOPS, Iowa, IQCODE, CBI, AD8.

3. Investigation:

- Brain imaging: structural (CT, MRI), functional (SPECT, MRS, PET).

- EMG (even in absence of clinical fasciculation, to look for subclinical evidence of anterior horn cell disorder).
- ± EEG (typically normal in FTLDs, cf. AD).
- ± Neurogenetic testing if positive family history suggestive of autosomal dominant disease transmission, initially for tau, progranulin and C9orf72 gene mutations, or designated FTD panel.

4. Management:

- Provision of information to patient and carers about FTLDs.
- Referral to voluntary services (e.g. Alzheimer's Society, Pick's Disease Society).
- ± Referral to psychiatric services to manage neuropsychiatric symptoms.
- ± Randomisation to clinical trials.

10.7 Summary and Recommendations

Management of dementia is much more than simply pharmacotherapy although this is inevitably the sphere in which neurologists will be most involved. The liberalisation of guidance with respect to use of ChEIs and memantine (National Institute for Health and Clinical Excellence 2011) may have made these drugs more widely available (cf. Larner 2012a), and there seems no reason not to give all AD patients a trial of these medications unless there are compelling contraindications.

Addressing the information needs of patients and their carers is also of great and increasing relevance, a need which may be facilitated by contact with patient care organisations such as the Alzheimer's Society and signposting to selected information, for example materials accessible online. Use of integrated care pathways may facilitate diagnosis of dementia and integration of all appropriate service providers within the health care system, hopefully in a seamless manner. Implementation of national policies (the "top down" approach) may have outcomes unanticipated by their instigators, despite which clinicians will go about their work irrespective, guided by the training and expertise that they have acquired (the "bottom up" approach).

10.8 Concluding Thoughts

The foregoing chapters have hopefully demonstrated that neurologists are not redundant in the diagnosis and management of people with cognitive disorders, indeed have a valuable if circumscribed role to play. This clinical role may also facilitate research studies. However, it is not, and never was, the purpose of this book to be a merely factional account, a case of special pleading for the retention of neurology-led dementia clinics.

Whatever misgivings a neurologist may have about the National Dementia Strategy (NDS) for England as originally presented (Department of Health 2008, 2009; Larner 2009a), not least the anticipated changes in quality of life based on data from a single, 6-month, uncontrolled study (Banerjee et al. 2007), nevertheless the NDS authors were entirely correct to characterise their publications with the indefinite article ("a National Dementia Strategy"; Department of Health 2008, 2009) rather than the definite article (although it became *de facto* "the National Dementia Strategy"). Wittingly or not, this original appelation indicated that many other National Dementia Strategies were and are possible.

For example, one "National Dementia Strategy" might take the form of a campaign of vigorous primary and secondary prevention of dementia, by screening the whole adult population for recognised risk factors for dementia (e.g. vascular risk factors, especially hypertension; Patterson et al. 2008). Predicting dementia risk in 20 years time, based on factors such as age, education, blood pressure, cholesterol, and obesity (Kivipelto et al. 2006), might be an appropriate public health strategy, emphasizing a life-long, lifestyle approach to cognitive well-being ("brain health"; Lincoln et al. 2014). There is some preliminary evidence of falling overall prevalence and incidence of dementia in the UK but whether these reductions are a consequence of improved prevention and treatment of vascular risk factors, or due to other factors (e.g. better education, living conditions) is currently unknown (Matthews et al. 2016; Wu et al. 2016). Certainly a multidomain intervention targeting diet, exercise, and cognitive training as well as monitoring vascular risk factors has been reported to prevent cognitive decline in elderly at-risk people (Ngandu et al. 2015).

Another "National Dementia Strategy" might be based on genetic epidemiology, constructing "polygenic hazard scores" for the development of AD (Desikan et al. 2017; Larner and Bracewell 2017). Such "bioprediction" (Baum 2016), estimating individual differences in AD risk across a patient's lifetime, might be used at the individual level for the purpose of targeted screening or administration of preventative measures, as well as for future planning.

With predictions of dramatic increases in the number of dementia sufferers in the coming decades (e.g. Ferri et al. 2005; Alzheimer's Society 2007, 2014; Prince et al. 2015), prevalence continuing to increase even if incidence is falling because of the ageing of the population (Ahmadi-Abhari et al. 2017), another "National Dementia Strategy" or component thereof, might be to develop a dementia specialty *per se*, transcending current professional boundaries between neurology, psychiatry, geriatrics, etc. The skills required to diagnose and manage the dementia syndrome effectively require elements from all these disciplines, and potentially others as well (e.g. clinical genetics, palliative care). If management of the dementia care pathway from diagnosis to end-of-life care via a "single point of referral" for all cases (National Institute for Health and Clinical Excellence/Social Care Institute for Excellence 2006) is a legitimate goal, then specific training in dementia would seem to be legitimate, with all the implications of developing a faculty, training programmes, and certification to assure specific standards are met. The admixture of skills required for such a dementia specialist would perhaps make this a potentially attractive discipline to trainees.

Such an approach would perhaps return us to Alzheimer himself, neither a neurologist nor a psychiatrist, but a neuropsychiatrist of the German tradition (Larner 2006e). Ultimately the label is unimportant: what patients with dementia and their caregivers need are clinicians with the appropriate knowledge base, and supported by the appropriate resources, to ensure their concerns are appropriately addressed.

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