# 5

# Neuropsychological assessment of dementia

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The concept of dementia as a 'progressive global cognitive decline in clear consciousness' has been refined gradually over the past two decades. It is increasingly apparent that each form of dementia has a distinct cognitive profile, at least in the mild stages of the disease, and that this reflects the pattern of underlying neuropathological change (Fray *et al.*, 1996; Hodges, 1998; Rahman and Sahakian, 1999). For example, NINCDS-ADRDA (National Institute of Neurological and Communicative Disorders and Stroke/Alzheimer's Disease and Related Disorders Association) criteria for a diagnosis of probable Alzheimer's disease requires 'deterioration in two or more areas of cognition, including memory, sufficient to interfere with work or social function' (McKhann *et al.*, 1984).

Advances in the understanding of the neuropsychology of the dementias has led to a greater role for neuropsychological assessment in the diagnosis and treatment of the various neurodegenerative diseases. In this chapter a brief outline of the rationale for neuropsychological assessment is given, together with a description of what a detailed neuropsychological assessment can offer a clinician over and above simple rating scales such as the Mini-Mental State Examination (MMSE) (Folstein *et al.*, 1975) and ADAS-cog (Rosen *et al.*, 1984). In addition, some commonly used neuropsychological tests are described. The article focuses on Alzheimer's disease (AD), since this is the most prevalent and probably the best understood dementia from a neuropsychological perspective, but also refers to other related conditions in the section on differential diagnosis.

## 5.1 NEUROPSYCHOLOGICAL ASSESSMENT: GENERAL CONSIDERATIONS

Cognitive processes are often broken down or grouped into meaningful functional units such as memory, attention, orientation, language, spatial cognition, perception, visuomotor and constructional ability and executive functioning. Many of these groupings can be further subdivided; for example, memory can be broken down into declarative (explicit or 'conscious') and non-declarative (implicit or 'unconscious') components. These divisions are based on functional dissociations (e.g. different patient groups perform differentially), anatomical dissociations (lesions to different cortical regions produce distinct patterns of cognitive deficit, implying that different underlying neural networks are involved – e.g. Owen *et al.*, 1990, 1995, 1996d; Owen, 1998), or a combination of the two. A neuropsychological assessment can provide a clinician with a profile of the patient's performance, demonstrating specific areas of cognitive impairment and intellectual sparing. Moreover, some conclusions may be drawn with respect to the neuroanatomical and/or neurochemical substrates likely to be involved. Hence, neuropsychological assessment pro-

vides a powerful investigative tool which may be crucial for the diagnosis and management of many patient groups (see McCarthy and Warrington, 1990).

The quality of a neuropsychological test is measured by how well its psychometric properties conform to theoretical notions of reliability and validity (Kline, 1986). Good validity means that the test actually measures what it is purported to measure. Good reliability means the test's measurements are accurate and consistent across different clinicians, locations, and times. In order to be used reliably for diagnosis at a single case level, the key qualities required of a test are specificity (any deficit found on a test is unique to one patient group and not a range of conditions) and sensitivity (the test should be sensitive to the earliest stages of a neurodegenerative disease and even subtle changes in a patient's condition).

Extensive validation procedures should always be employed in order to measure how well a test meets these psychometric criteria. For example, if a test is assumed to be sensitive to frontal lobe function, deficits should be observed in patients with frontal lobe lesions (Owen *et al.*, 1990, 1995, 1996d); further, where available, neuroimaging data should demonstrate some frontal lobe activation in healthy controls performing the same task (e.g. Owen *et al.*, 1996b).

## 5.2 IMPORTANCE OF A COMPREHENSIVE NEUROPSYCHOLOGICAL ASSESSMENT

Why should clinicians carry out a comprehensive neuropsychological assessment when brief screening measures are available? The answer is that short mental status tests are suitable for some aspects of performance assessment (e.g. screening, gross staging of severity), but neglect others. For example, the Mini-Mental State Examination (Folstein *et al.*, 1975) is one of the most widely used brief measures of global cognitive function. Its strengths are that it is inexpensive, rapid, highly portable, and can be interpreted and administered with little training. It is standardized and has been successfully applied in cross-national studies. However, the MMSE has poor sensitivity to very mild dementia, generates false-negative diagnoses in highly educated people and false-positive diagnoses in poorly educated people, and demonstrates ethnicity biases (Tombaugh *et al.*, 1992; Nadler *et al.*, 1994; Wilder *et al.*, 1995). It's major limitation, however, is that it provides only a global index of cognitive performance. A full neuropsychological battery produces a much wider range of scores and taps more cognitive domains, making early detection possible and providing differential diagnosis within the dementias. In addition, a comprehensive assessment can provide information from which to measure change as a result of the progression of the disease or the administration of a new treatment, and, in some cases, aid in the management decisions regarding individual patients. In all cases, however, neuropsychology should be viewed as contributing to a diagnosis along with other forms of assessment (e.g. structured clinical interview, neuroimaging, etc.). The most accurate diagnosis and treatment recommendations will always be made by combining clinical, neuropsychological and neuroimaging expertise (Perry and Hodges, 1996).

## 5.3 EARLY DETECTION OF DEMENTIA

Until relatively recently, the early detection of dementia has been neglected, in part because of the absence of effective treatments and also because sufficiently sensitive neuropsychological tests were not available. The emergence of new drugs to treat the symptoms of AD (e.g. rivastigmine, donepezil) is a sign that the therapeutic nihilism seen in the dementias is coming to an end. It is widely believed that if neuroprotective agents that modify the disease process are to be effective, then it is vital that clinicians are able to detect a dementia early and accurately, before the emergence of global cognitive impairment (Lawrence and Sahakian, 1996; Hodges, 1998). Further, early detection of dementias can give patients and their families more time to come to terms with the diagnosis of dementia, to make the necessary personal and financial arrangements, and to reduce the anxiety patients may feel when they are unsure of their diagnosis (Morgan and Baade, 1997).

Neuropsychological testing has a clear role in the early detection of dementia. It is non-invasive, well tolerated by patients, relatively inexpensive and, most importantly, it may be sensitive to the prodromal phase often seen in dementia (see Fowler *et al.*, 1997). For example, it is believed that there is an insidious onset of symptoms in AD which precedes diagnosis by 2–3 years (Jost and Grossberg, 1995), and a range of evidence suggests this may first manifest as problems in learning and episodic memory (Lawrence and Sahakian, 2000).

The episodic memory deficit in AD was first demonstrated by showing that memory tests could differentiate a group of clear-cut Alzheimer's patients from a group of healthy elderly control subjects. For example, the main difference between patients with AD and healthy controls is difficulty in acquiring and retaining new information, even over a period as short as 10 minutes (Kasznaik, 1986; Albert *et al.*, 1989; Butters *et al.*, 1995). Recent memories are more difficult to recall than older memories, referred to as a temporal gradient for recall. However, a more stringent test of how well a paradigm can detect AD is to see if it can predict which patients will go on to develop dementia. A number of longitudinal studies have taken this approach. Fox *et al.* (1998) followed 63 asymptomatic individuals at risk of autosomal dominant AD over a 6-year period. The 10

subjects who developed dementia during this time could be identified at first assessment (when they were ostensibly unaffected) by significantly lower verbal memory and performance IQ on cognitive testing. These subjects were initially no different in terms of age, family history and initial MMSE scores. First assessment was typically 2–3 years before symptoms were manifest and 4–5 years before a diagnosis of probable AD was made, a result that clearly illustrates the potential sensitivity of cognitive testing. Blinded assessment of serial MRI imaging showed that diffuse cerebral and medial temporal lobe atrophy was found in subjects only after they were clinically affected, suggesting that a patient's neuropsychological profile may be a more sensitive early indicator than imaging data. These results support the notion that the earliest cognitive deficits seen in AD include episodic memory impairment.

Other longitudinal studies in elderly subjects generally concur with these results. In the Framingham study, 'preclinical' deficits in verbal recall (as indexed by the percentage retained in the Logical Memory Test and Paired Associate Learning Test) preceded clinical diagnosis of AD in some cases by more than 6 years (Linn *et al.*, 1995). Similarly, in the Bronx ageing study, two tests of verbal memory, the Fuld Object Memory Evaluation and the Bushke Selective Reminding Test, predicted many subjects who would go on to develop AD (Masur *et al.*, 1995).

In a more recent study, the Cambridge Neuropsychology Test Automated Battery (CANTAB), was used to ascertain whether early AD could be detected in a group of 'questionable' dementia subjects recruited from a memory clinic setting (Fowler *et al.*, 1997). These are people who present with subjective memory complaints, may or may not show some degree of impairment on standard neuropsychological tests, but do not fulfil NINCDS-ADRDA criteria for dementia (Rosen *et al.*, 1984). Fowler *et al.* (1997) demonstrated that the paired associate learning task (PAL) from CANTAB (Robbins *et al.*, 1998) could split the questionable dementia group between those who had a poor prognosis and went on to develop AD (between 6 and 24 months later) and those who had a good prognosis and remained unimpaired (see Figure 5.1).

The CANTAB PAL requires subjects to learn and remember abstract visual patterns associated with various locations on a touch-sensitive computer screen. Patterns are presented in one of six or eight boxes around the edge of the screen (Figure 5.2). After a brief delay, the same patterns are presented in the middle of the screen and the subject is required to touch the box in which they saw that pattern appear. If this is not completed correctly the subject is reminded where each pattern belonged and tested again. This process continues until the task is satisfactorily completed or ten trials have been attempted. The CANTAB PAL was able to detect those people in the questionable dementia group who

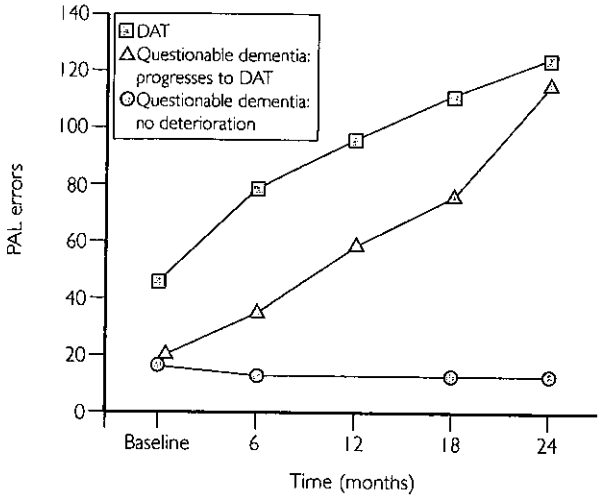


**Figure 5.1** *The performance of patients with questionable dementia (who subsequently go on to develop dementia between 6 and 24 months), questionable dementia (who do not go on to develop dementia), and Alzheimer's disease (AD) on the CANTAB visuospatial paired associates learning task over time (adapted from Fowler* et al., *1995, 1997).*

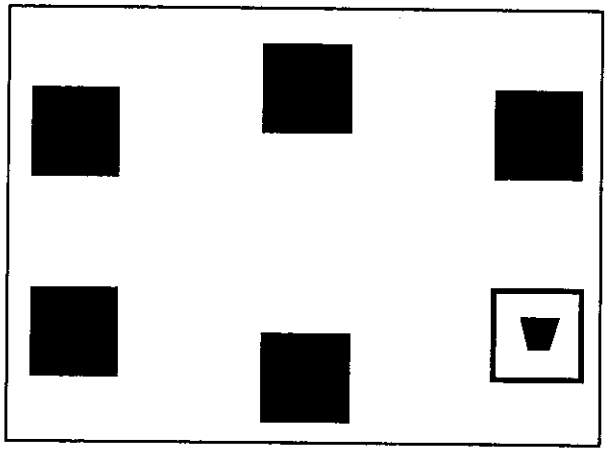

**Figure 5.2** *The CANTAB visuospatial paired associates learning task. The subjects are required to memorize the locations of six to eight patterns that appear one at a time in different boxes around the computer screen.*

went on to dement about 18 months earlier than traditional neuropsychological tests (Fowler *et al.*, 1997).

The neuropsychological picture of preclinical episodic memory deficit in AD is complemented by reasonably consistent patterns of neuropathology. Thus posterior regions of association cortex are especially impaired in AD, particularly medial temporal regions (parahippocampal and entorhinal cortex). The neurodegeneration in AD is progressive, both within an affected area and extending to other previously unaffected regions. This conclusion is consistent with evidence from *in vivo* neuroimaging including positron

emission tomography (PET; Grady *et al.*, 1988; Haxby *et al.*, 1990; see also reviews by Smith and Jobst, 1996 and Goodwin, 1996), as well as post-mortem neuropathology (Braak and Braak, 1991). The particular clusters of deficits seen in AD progress in a predominantly posterior-to-anterior axis across the cerebral cortex and can be understood by reference to classical syndromes seen in the neuropsychological literature, both in terms of underlying cognitive processes and their associated neural substrates. The main difference from studies, for example, of patients with neurosurgical excisions or strokes is the relatively continuous, progressive deterioration in AD. The occurrence of focal degenerative disorders also indicates a more restricted form of progressive neurodegeneration, limited to a particular part of the cerebral cortex, as may be the case for semantic dementia and the temporal lobe (Hodges *et al.*, 1992), or lobar atrophy which affects regions of the anterior neocortex (Neary *et al.*, 1994).

## 5.4 DIFFERENTIAL DIAGNOSIS OF DEMENTIA

Neuropsychological testing can help a clinician to make a differential diagnosis between a dementia and other non-neurodegenerative disorders, such as depression. It can also help to differentiate between different neurodegenerative disorders, including AD, frontotemporal dementia (FTD), Parkinson's disease (PD), and Huntington's disease (HD). In this regard, it is increasingly apparent that each disorder, at least in its early stages, has a unique cognitive hallmark that can be used to aid differential diagnosis.

Perry and Hodges (1996) have outlined the memory profile most commonly encountered in a number of different disorders. In short, three broad domains in memory have been studied in detail: working memory, episodic and semantic (declarative) memory and implicit (non-declarative) memory.

Working memory refers to a system assumed to be necessary for holding information 'on line', usually over short periods of time. Baddeley (1992) argues this system comprises an 'articulatory loop' for rehearsing verbal material, a 'visuospatial scratch pad' for rehearsing visual information, and a 'central executive' which is assumed to regulate these two slave systems. Recent neuropsychological and neuroimaging studies using PET implicate regions of the lateral prefrontal cortex in working memory (e.g. Owen *et al.*, 1996b, 1996d; for review see Owen, 1997).

Episodic memory can be defined as personally experienced events that are specific to a time and context. This can be tested by recall of recently presented verbal material in story or word list form or visual material such as recall of faces or abstract figures, for example, the CANTAB delayed matching to sample test (e.g. Sahakian *et al.*, 1988). Semantic memory, on the other hand, refers to memory for facts, concepts and knowledge. It is not specific to a time or context and is culturally shared. It may be tested by picture naming, category fluency, word-picture matching and vocabulary tests. Episodic and semantic memory both rely on various regions within the medial temporal lobe and the diencephalon (Squire, 1992).

Finally, whereas episodic and semantic memory are components of 'explicit' or 'declarative' ('conscious') memory, conditioning and priming effects, skill learning, and habits are all examples of implicit (or 'non-conscious') memory.

### 5.4.1 Alzheimer's disease

Different neurodegenerative diseases may be associated with distinct profiles of impairment across these memory domains. AD is characterized by a profound deficit in episodic memory, usually with both verbal and non-verbal material lost (Squire, 1992; Welch *et al.*, 1992). It is generally accepted that encoding of new memories is impaired in dementia of Alzheimer type (DAT), but it is unclear if this is accompanied by 'faster forgetting' or loss from memory stores (Kopelman, 1985; Sahakian *et al.*, 1988; Pillon *et al.*, 1994; Greene *et al.*, 1996). A well-replicated finding is that delayed recall is much more impaired than immediate recall, which may support a faster forgetting hypothesis (Pillon *et al.*, 1994). However, Greene *et al.* (1996) demonstrate that intact immediate recall seen in AD may reflect the preservation of working memory found in the early stages of the disease. Related research suggests that the slave systems of working memory (the 'articulatory loop' and the 'visuospatial scratch pad') are intact in early AD (Baddeley, 1986), although the central executive may be compromised (Paulesu *et al.*, 1993). Although AD does lead to semantic memory loss, this may not be an early change (Hodges and Patterson, 1995). It is unclear if any loss of semantic memory reflects damage to memory 'stores' or impaired retrieval (Nebes, 1989; Chertkow and Bub, 1990; Bayles *et al.*, 1991; Chan *et al.*, 1995). Remote memory (e.g. autobiographical memory for famous persons and events) is also impaired in AD, with evidence of a temporally graded loss (Sagar *et al.*, 1988; Kopelman, 1989; Greene *et al.*, 1995).

### 5.4.2 Semantic dementia

In semantic dementia there is a selective impairment of semantic memory, which causes severe anomia, single word comprehension, reduced exemplar production in category fluency tests, and an impaired general knowledge. Other components of speech production, perceptual and non-verbal problem-solving abilities, and

episodic memory are relatively spared (Snowden *et al.*, 1989; Hodges *et al.*, 1992; Breddin *et al.*, 1994; Saffran and Schwartz, 1994).

### 5.4.3 Frontal variant frontotemporal dementia

Frontal variant frontotemporal dementia (fvFTD), is usually associated with failure on frontal lobe tests in the absence of severe amnesia, aphasia, perceptual or spatial disorders. However, there are frequently marked behavioural changes including lack of insight, disinhibition, loss of personal and social awareness, mental rigidity and inflexibility, perseverative behaviour and emotional lability (Gregory and Hodges, 1996). Recent studies by Rahman, Sahakian and colleagues (Rahman and Sahakian, 2000; Rahman *et al.*, 1999), indicate that neuropsychological tests sensitive to the orbitofrontal/ventromedial cortex are able to detect impairment even in very mild fvFTD patients.

### 5.4.4 Huntington's disease and Parkinson's disease

Huntington's disease (HD) is associated with working memory decline and impaired retrieval from both episodic and semantic memory. Hodges *et al.* (1990) compared the performance of patients with AD and Huntington's disease on the Boston Naming Test, a measure of visual semantic memory. HD patients made significantly more visual errors, where they produced answers visually similar to the correct solution but from a different semantic category; for example, they would mistake a pen for asparagus. By contrast, AD patients made significantly more semantic super-ordinate errors, where they gave an answer denoting the general category of the correct answer rather than the exact exemplar; for example, a car would be described as a vehicle. In a more recent study, Rosser and Hodges (1994) compared AD, HD and PD patients matched using the dementia rating scale (DRS) on verbal fluency tasks. In letter fluency tasks subjects are asked to name as many words as possible that start with a certain letter in 60 seconds. In category fluency tasks the subject has 60 seconds in which to generate as many examples that fit a certain semantic category as possible. All groups were impaired relative to controls on both measures. Interestingly, subjects in the AD group were less impaired on the letter fluency but equally impaired on category fluency as those in the other two patient groups. On this basis, it was suggested that AD involves a selective degradation of the semantic memory store whereas in HD and PD the central impairment is in the retrieval of that information.

One of the difficulties with comparing patient groups is that very rarely are the same tests employed for assessment. Lawrence and Sahakian (1996) have recently compared the profile of impairment found in AD with that observed in patients with PD, HD and progressive supranuclear palsy using the Cambridge Neuropsychological Test Automated Battery (CANTAB; Robbins *et al.*, 1994a, 1996, 1998). Patients in the early stages of AD were impaired on tests of learning and memory sensitive to parietal and temporal lobe damage, particularly paired associate learning, pattern recognition memory and delayed matching to sample paradigms (see Figure 5.3).

They were relatively unimpaired on tests of central executive function, such as attentional set shifting. Patients in the early stages of the frontostriatal dementias showed the opposite pattern, being impaired on central executive tasks but relatively intact on memory tasks sensitive to temporal and parietal lobe damage. Indeed, the task most sensitive to genetically confirmed, but preclinical HD is the CANTAB attentional shift task (Lawrence and Sahakian, 1996, 1998). Cognitive flexibility is a requirement for this task, since patients must perform an extradimensional shift similar to a category shift in the Wisconsin Card Sorting Test.

### 5.4.5 Depression

It is now known that significant cognitive impairments often accompany the onset of depression (see Murphy *et al.*, 1999). For this reason, in old age psychiatry, the differential diagnosis between depression and dementia remains an important problem. For example, it has been suggested that around 10% of cases initially diagnosed as dementia are later reclassified as depression (DesRosiers, 1992). Since there are effective treatments for depression, accurate diagnosis is important. Historically, reversibility has been considered a hallmark of the cognitive impair-

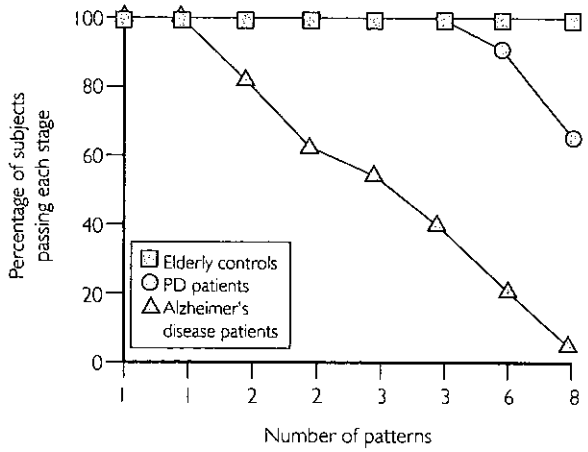


**Figure 5.3** *Performance of patients with AD, PD and elderly control subjects on the CANTAB visuospatial paired associates learning task. Compared to controls, only the AD patients are profoundly impaired, even at the most basic levels of task difficulty (adapted from Sahakian* et al., *1988).*

ment seen in depression and is implicit in the use of the term 'pseudodementia'. However, Abas *et al.* (1990) suggest that significant cognitive impairment may persist in many patients following recovery of depressed mood and that the term 'pseudodementia' appears unclear and misleading. In fact, most attempts to differentiate these two disorders using traditional tests have failed. For example, O'Carroll *et al.* (1994) showed that the Wechsler memory scale could not reliably differentiate between depression and DAT, with up to 25% of the depressed patients being misclassified. O'Carroll *et al.* (1997) showed that the delayed word recall test led to 44% of depressives being misclassified as suffering from AD.

In summary, it is clear that traditional neuropsychological tests cannot yet unambiguously differentiate between depression and dementia. However, Murphy *et al.* (1999) have suggested that divided attention tasks and tests of prospective memory may be useful for this purpose and, in particular, examining the way in which patients fail may be important for the differential diagnosis of depression. For example, Beats *et al.* (1996) reported that elderly depressed patients showed a 'catastrophic' response to perceived failure. Following on from this, recent work by Elliott, Sahakian and colleagues (Elliott *et al.*, 1996, 1997b) indicted that depressed patients show an abnormal response to feedback and that this appears to be diagnosis specific. The efficacy of this measure is currently being tested to see if it can reliably differentiate AD from depression.

## 5.5 MONITORING PROGRESSION IN DEMENTIA

Another role for neuropsychological testing is to measure the rate of progression of disease, achieved by giving an identical assessment at a number of different time intervals. This is important because it can help the clinician assess the efficacy of any pharmacological or other therapeutic intervention. At the moment the ADAS-cog (Rosen *et al.*, 1984) is a test commonly used to measure the efficacy of agents acting on memory. However, recent advancements in the understanding of the taxonomy of memory and the cognitive profile of dementia makes it likely that a more advanced neuropsychological test will be needed. For example, the ADAS-cog lacks an attentional subscale, an important cognitive domain for AD and one which responds to cholinergic therapies such as tacrine and nicotine (see Sahakian *et al.*, 1990; Jones *et al.*, 1992). It is good practice to look for change on neuropsychological measures applied in a memory clinic setting to determine whether an individual patient is benefiting from medication at a cognitive level. Obviously for this purpose, measures which are sensitive to change must be used (e.g. CANTAB Rapid Visual Information Processing task, CANTAB Simple and Choice Reaction Time task). It is also important to determine how gains in cognitive function impact on the patient's daily living and quality of life, as well as the quality of life of the patient's carer.

## 5.6 FURTHER CONSIDERATIONS IN NEUROPSYCHOLOGICAL ASSESSMENT

The neuropsychological assessment has to be tailored to the individual needs of the patient and the reason for the referral. Nevertheless, it is important to retain 'benchmark' tests that remain the same in order that the neuropsychologist can compare between patients within the same group, across patient groups and for use for longitudinal follow-up. On a very general level, the assessment of a patient should involve an evaluation of their cognitive function in the major domains afflicted by the dementia, an estimate of premorbid functioning to compare results to, and a measure of how much this affects the patient's functioning in everyday life. The test battery chosen should ideally be sensitive to even subtle deficits in patients, have demonstrated psychometric reliability and validity, be relatively easy to administer and not excessively long, have been validated longitudinally, have equivalent forms, and have its practice effects understood (Ferris and Kluger, 1997).

Exactly which test to use depends on the precise hypothesis being tested. For example, different tests are sensitive to different severities of dementia. A test like the CANTAB paired associate learning task (Fowler *et al.*, 1997) is excellent for the early detection of AD (see Figure 5.1), but due to its sensitivity may not be ideal for measuring disease progression. Other CANTAB tests, such as the Delayed Matching To Sample Test, the Attentional Shift Test and the Visual Search Test, may be more suitable for assessing staging and severity of dementia (see Sahakian *et al.*, 1988, 1990; Sahgal *et al.*, 1992a, 1992b). Further, a lengthy battery may be useful for the detailed assessment of cognitive function in the mild stages of dementia but may not be appropriate or feasible in more moderately/severely demented patients with major attentional difficulties. The CANTAB nonverbal tests may be combined with tests of verbal function, together with measures of premorbid or current intelligence level (e.g. NART, WAIS-R, respectively). For those without access to computerized assessment, an example of a 'pencil and paper' battery may include measures of premorbid and current intellectual function (e.g. National Adult Reading Test, Wechsler Adult Intelligence Scale – Revised, respectively), episodic memory (e.g. Wechsler Logical Memory, Kendrick Object Learning Task, Warrington Recognition Memory for words and faces), working memory (e.g. Corsi block tapping task, forward and backwards digit span), semantic memory (e.g. Graded Naming Test, category fluency,

Boston Naming Test), attention (e.g. the Stroop test, symbol digit substitution), visuospatial construction (e.g. drawing a clock face, Ray–Oesterreich figure), and executive functions (e.g. Wisconsin Card Sorting Test). It is important to include verbal and non-verbal stimuli, to examine both recognition and recall, and to assess performance at both immediate and delayed memory. An alternative to combining individual tests is to use an already constructed battery. Some of the more commonly used ones are described briefly below.

- The Consortium To Establish A Registry For Dementia of the Alzheimer's Type (CERAD; Morris, 1997) battery includes the Boston Naming Test, verbal fluency, the MMSE and two other subtests, covering memory, language, constructional praxis, and intellectual status.
- The Wechsler Memory Scale – Revised (WMS-R; Kaplan *et al.*, 1991) is made up of 13 subtests that take about 45 minutes to administer. The areas tested include orientation, attention, verbal memory, visual memory and delayed recall.
- The Halstead–Reitan battery (Reitan and Wolfson, 1993) consists of 10 tests that tap sensory, perceptual, motor, attention, language and problem-solving abilities.
- The Cambridge Neuropsychological Test Automated Battery (CANTAB; Robbins and Sahakian, 1994) is a set of computerized neuropsychological tests that tap visual memory, attention, and working memory and planning. Computerized batteries have a number of distinct advantages over more traditional 'paper and pencil' tests (see Figure 5.4), and this has been discussed in detail elsewhere (see Robbins *et al.*, 1994b, 1996, 1998).

In brief, each CANTAB battery employs a touch-sensitive screen and has a preliminary test of sensorimotor function, which enables subjects with marked visual or motor deficits to be screened out. The range of tests utilized allows a component analysis of cognitive function, offering the clinician a profile of a patient's strengths and weaknesses. Moreover, the various tests have been validated on neurosurgical cases with well-defined cortical excisions (e.g. Owen *et al.*, 1990, 1991, 1995, 1996d). In addition, neural validation has been provided by a growing set of neuroimaging data, some conducted in elderly depressed patients (e.g. Owen *et al.*, 1996a, 1996b, 1999; Baker *et al.*, 1996; Elliott *et al.*, 1997a). The main elements of the battery have already been tested in probable (subsequently confirmed) cases of DAT in a memory clinic setting (Sahakian *et al.*, 1988, 1990; Sahgal *et al.*, 1991, 1992a, 1992b), in longitudinal follow-up of some patients (Robbins *et al.*, 1996) and in a double-blind, placebo-controlled trial of the acetylcholinesterase inhibitor tacrine (Eagger *et al.*, 1991; Sahakian *et al.*, 1993). The pattern of cognitive deficits shown on this battery fits quite well with the generally accepted neural

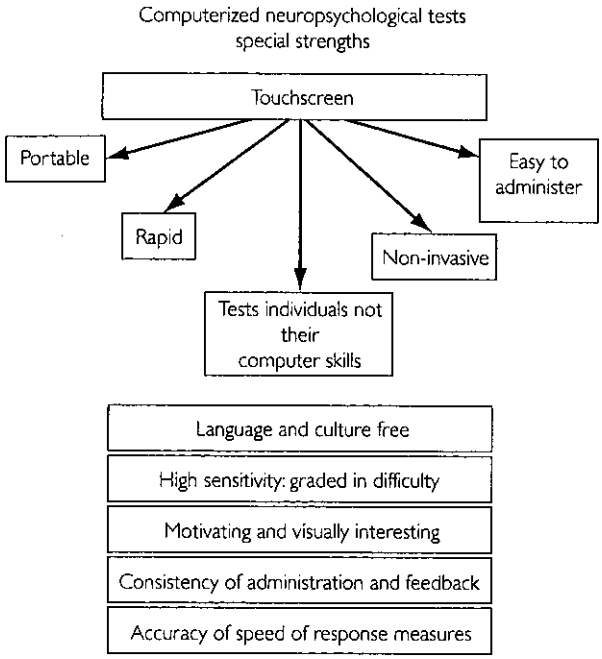


**Figure 5.4** *The advantages of computerized testing.*

progression for the disease proposed above. Thus, for example, tests that are particularly sensitive to temporal lobe (including hippocampal) damage are more sensitive to impairments in DAT patients than tests shown to be sensitive to frontal lobe dysfunction (Sahakian *et al.*, 1990). The CANTAB tests have also been given to elderly patients with depression, who exhibit some gross similarities to AD in the nature of the deficits, but where cognitive improvement on many, though not all, cognitive measures, may occur on remission from clinical depression. Recently, norms have been published for many of the CANTAB tests on a large ($n$ = approximately 800) sample of normal community-dwelling elderly volunteers (Robbins *et al.*, 1994b, 1997), and a high degree of test-retest reliability has been confirmed using the same subjects. Moreover, the existence of graded difficulty levels within each test reduces the common problem of floor and ceiling effects on neuropsychological tests for AD. It should be emphasized that computerized testing with non-verbal tests offers some advantages over conventional testing in terms of multinational trials and objective standardization of the administration (e.g. timing of stimuli and nature of feedback) and of the measures that include latencies. However, it is important for such testing to be conducted in the presence of a trained clinical psychologist and in conjunction with conventional tests.

Whilst the CANTAB battery shows some promise in the detection and evaluation of dementia, it has only recently been compared against more traditional methods in a memory clinic setting. As discussed above, Fowler *et al.* (1995, 1997) have shown recently that the CANTAB test of visuospatial paired associates learning

effectively differentiated cases of questionable dementia compared with tests from the Wechsler Memory Scale including delayed recall. In 21 cases, there was an advantage of 6–12 months in the differentiation afforded by these tests over their conventional counterparts. Moreover, there are both neuropsychological (Owen *et al.*, 1995) and neuroimaging (Owen *et al.*, 1996c) data which suggest that this test may be sensitive to damage to regions including the parahippocampal gyrus and entorhinal cortex, areas thought to be at risk in early AD.

In summary, the CANTAB tests are objective and standardized, have a high patient compliance, store and log data accurately and efficiently, are well normed and cover a wide range of cognitive functions.

## 5.7 CONCLUSION

In an age where no means of preventing devastating neurodegenerative diseases such as AD exists, neuropsychological assessment will continue to have a useful role in the early detection of dementia, in differentiating between the various forms of dementia, in monitoring the progression of the disease, in assessing the efficacy of any new treatments, and in managing individual patients. Recent neuropsychological research has developed our understanding of these, and related, conditions and should continue to do so in the future. The key challenges for neuropsychologists over the next decade are to translate their experimental knowledge into clinically useful tests that reliably detect and differentially diagnose depression and dementia at a single case, rather than a group level, to compare patient groups on the same tests (i.e. 'benchmark' tests), and to more fully understand the neural networks underlying task performance. Theoretically driven neuropsychological testing will have a key role in the early detection, differential diagnosis and development of rational treatment strategies for the dementias well into the new millennium.

## REFERENCES


Abas, M.A., Sahakian, B.J. and Levy, R. (1990) Neuropsychological deficits and CT scan changes in elderly depressives. *Psychological Medicine* **20**, 507–20.

Albert, M.S., Moss, M.B. and Milberg, W. (1989) Memory testing to improve the differential diagnosis of Alzheimer's disease. In Iqbal, K., Wisniewski, H.M. and Winblad B. (eds), *Alzheimer's Disease and Related Disorders: Proceedings of the First International Conference*. New York: Alan R. Liss, 55–69.

Baddeley, A.D. (1986) *Working Memory*. Oxford: OUP.

Baddeley, A.D. (1992) Working memory. *Science* **255**, 556–9.

Baker, S.C., Rogers, R.D., Owen, A.M. *et al.* (1996) Neural systems engaged by planning: a PET study of the tower of London task. *Neuropsychologia* **34**, 515–26.

Bayles, K.A., Tomoeda, C.K., Kasaniak, A.W. and Trosset, M.W. (1991) Alzheimer's disease effects on semantic memory: loss of structure or impaired processing. *Journal of Cognitive Neuroscience* **3**, 166–82.

Beats, B.C., Sahakian, B.J. and Levy, R. (1996) Cognitive performance in tests sensitive to frontal lobe dysfunction in the elderly depressed. *Psychological Medicine* **26**, 591–603.

Braak, H. and Braak, E. (1991) Neuropathological staging of Alzheimer-related changes. *Acta Neuropathologica* **82**, 239–59.

Breddin, S.D., Saffran, F.M. and Coslett, H.B. (1994) Reversal of the concreteness effect in a patient with semantic dementia. *Cognitive Neuropsychology* **2**, 617–61.

Butters, N., Delis, D.C. and Lucas, J.A. (1995) Clinical assessment of memory disorders in amnesia and dementia. *Annual Review of Psychology* **46**, 493–523.

Chan, A.S., Butters, N., Salmon, D.P., Johnson, S.A., Paulsen, J.S. and Swenson M.R (1995) Comparison of the semantic networks in patients with dementia and amnesia. *Neuropsychology* **9**, 177–86.

Chertkow, H. and Bub, D. (1990) Semantic memory loss in dementia of the Alzheimer type. What do various measures measure? *Brain* **113**, 397–417.

DesRosiers, G. (1992) Primary or depressive dementia: psychometric assessment. *Clinical Psychology Review* **12**, 307–43.

Eagger, S.A., Levy, R. and Sahakian, B.J. (1991) Tacrine in Alzheimer's disease. *Lancet* **337**, 989–92.

Elliott, R., Sahakian, B.J., McKay, A.P., Herod, J.J., Robbins, T.W. and Paykel, E.S. (1996) Neuropsychological impairments in depression: the influence of perceived failure on subsequent performance. *Psychological Medicine* **26**, 975–89.

Elliott, R., Baker, S.C., Rogers, R.D. *et al.* (1997a) Prefrontal dysfunction in depressed patients performing a complex planning task: a study using positron emission tomography. *Psychological Medicine* **27**, 931–42.

Elliott, R., Sahakian, B.J., Herod, J.J., Robbins, T.W. and Paykel, E.S. (1997b) Abnormal response to negative feedback in depression: evidence for a diagnosis specific impairment. *Journal of Neurology, Neurosurgery and Psychiatry* **63**, 74–82.

Ferris, S.H. and Kluger, A. (1997) Assessing cognition in Alzheimer disease research. *Alzheimer Disease and Associated Disorders* **11(Suppl. 6)**, 45–9.

Folstein, M.F. (1997) Differential diagnosis of dementia: the clinical process. Geriatric psychiatry. *Psychiatric Clinics of North America* **20**, 44–57.

Folstein, M.F., Folstein S.E. and McHugh, P.R. (1975) Mini-mental state: a practical method for grading the cognitive state of patient for clinician. *Journal of Psychiatric Research* **12**, 189–98.

Fowler, K.S., Saling, M.M., Conway, E.L., Semple, J.S. and Louis, W.J. (1995) Computerised delayed matching-to-

sample and paired associate performance in the early detection of dementia. *Applied Neuropsychology* **2**, 72–8.

Fowler, K.S., Saling, M.M., Conway, E.L., Semple, J.M. and Louis, W.J. (1997) Computerised neuropsychological tests in the early detection of dementia: prospective findings. *Journal of the International Neuropsychological Society* **3**, 139–46.

Fox, N.C., Warrington, E.K., Seiffer, A.L., Agnew, S.K. and Rossor, M.N. (1998) Presymptomatic cognitive deficits in individuals at risk of familial Alzheimer's disease: a longitudinal prospective study. *Brain* **121**, 1631–9.

Fray, P.J., Robbins, T.W. and Sahakian, B.J. (1996) Neuropsychiatric applications of CANTAB. *International Journal of Geriatric Psychiatry* **11**, 329–36.

Goodwin, G.M. (1996) Functional Imaging, affective disorder and dementia. *British Medical Bulletin* **52**, 495–512.

Grady, C.L., Haxby, J.V., Horwitz, B. *et al.* (1988) Longitudinal study of the early neuropsychological and cerebral metabolic changes in dementia of the Alzheimer type. *Journal of Clinical and Experimental Neuropsychology* **10**, 576–96.

Greene, J.D.W., Hodges, J.R. and Baddeley, A. (1995) Autobiographical memory and executive function in early dementia of the Alzheimer type. *Neuropsychologia* **33**, 1647–70.

Greene, J.D.W, Baddeley, A.D. and Hodges, J.R. (1996) Recall and recognition of verbal and non-verbal material in early Alzheimer's disease: evidence from the Doors and People Test. *Neuropsychologia* **34**, 537–51.

Gregory, C.A. and Hodges, J.R. (1996) Clinical features of frontal lobe dementia in comparison to Alzheimer's disease. *Journal of Neural Transmission (Supplement)* **47**, 103–23.

Haxby, J.V., Grady, C.L., Koss, E. *et al.* (1990) Longitudinal study of cerebral metabolic asymmetries and associated neuropsychological patterns in early dementia of the Alzheimer type. *Archives of Neurology* **47**, 753–60.

Hodges, J.R. (1998). The amnestic prodrome of Alzhiemer's disease. *Brain* **121**, 1601–2.

Hodges, J.R. and Patterson, K. (1995) Is semantic memory consistently impaired early in the course of Alzheimer's disease: neuroanatomical and diagnostic implications. *Neuropsychologia* **33**, 441–59.

Hodges, J.R., Salmon, D.P. and Butters, N. (1990) Differential impact of semantic and episodic memory in Alzheimer's disease and Huntington's disease: a controlled prospective study. *Journal of Neurology, Neurosurgery and Psychiatry* **53**, 1089–95.

Hodges, J.R., Patterson, K., Oxbury, S. and Funnell, E. (1992) Semantic dementia: progressive fluent aphasia with temporal lobe atrophy. *Brain* **115**, 1783–806.

Jones, G.M.M., Sahakian, B.J., Levy, R., Warburton, D.M. and Gray, J.A.(1992) The effects of acute sub-cutaneous nicotine on attention, information processing and short-term memory in Alzheimer's disease. *Psychopharmacology* **108**, 485–94.

Jost, B.C. and Grossberg, G.T. (1995) The natural history of Alzheimer's disease: a brain bank study. *Journal of the American Geriatrics Society* **43**, 1314–15.

Kaplan, E., Fein, D., Morris, R. *et al.* (1991) *WAIS-R as a Neuropsychological Instrument.* San Antonio: Psychological Corporation.

Kaszniak, A.W. (1986) The neuropsychology of dementia. In Grant, I. and Adams, K.M. (eds) *Neuropsychological Assessment of Neuropsychiatric Disorders.* New York: Oxford University Press, 172–200.

Kline, P. (1986) *A Handbook of Test Construction.* London: Methuen.

Kopelman, M.D. (1985) Rates of forgetting in Alzheimer's type dementia and Korsakoff's syndrome. *Neuropsychologia* **23**, 623–38.

Kopelman, M.D (1989) Remote and autobiographical memory, temporal context memory and frontal atrophy in Korsakoff and Alzheimer patients. *Neuropsychologia* **27**, 437–60.

Lawrence, A.D. and Sahakian, B.J. (1996) The neuropsychology of fronto-striatal dementias. In Woods, R.T. (eds), *Handbook of the Clinical Psychology of Ageing.* Chichester: John Wiley & Sons Ltd.

Lawrence, A.D. and Sahakian, B.J (2000) Outcome variables in dementia trials: conceptual and practical issues. In Guiloff, R.J. (ed.), *Clinical Trials in Neurology.* Berlin: Springer-Verlag.

Linn, R.T., Wolf, P.A., Bachman, D.L. *et al.* (1995) The 'preclinical phase' of probable Alzheimer's disease: a 13 year prospective study of the Framingham cohort. *Archives of Neurology* **52**, 485–90.

Masur, D.M., Sliwinski, M., Lipton, R.B., Blau, A.D. and Crystal, H.A. (1995) Neuropsychological prediction of dementia and the absence of dementia in healthy elderly persons. *Neurology* **45**, 2112–13.

McCarthy, R.A. and Warrington, E.K. (1990) *Cognitive Neuropsychology: a Clinical Introduction.* London: Academic Press.

McKhann, G., Drachman, D., Folstein, M., Katzman, R., Price, D. and Stadlan, E.M. (1984) Clinical diagnosis of Alzheimer's disease: report of the NINCDS-ADRDA Work Group under the auspices of the Department of Health and Human Services Task Force on Alzheimer's Disease. *Neurology* **34**, 939–44.

Morgan, C.D. and Baade, L.E. (1997) Neuropsychological testing and assessment scales for dementia of the Alzheimer's type. Geriatric psychiatry. *Psychiatric Clinics of North America* **20**, 25–43.

Morris, J.C. (1997) Clinical assessment of DAT. *Neurology* **49(Suppl.)** 1–6.

Murphy, F.C., Sahakian, B.J. and O'Carroll, R.E. (1999) Cognitive impairment in depression: psychological models and clinical issues. In Ebmeier, K. (ed.), *Advances in Biological Psychiatry: New Models for Depression*, Vol. 19. Basel: Karger.

Nadler, J.D., Richardson, E.D. and Malloy, P.F. (1994) Detection of impairment with the Mini-Mental State Examination.

*Neuropsychiatry, Neuropsychology and Behavioural Neurology* **7**, 109–113.

Neary, D., Snowden, J.S. and Mann, D.M.A. (1994) Dementia of frontal lobe type. In Burns, A. and Levy, R. (eds), *Dementia*. London: Chapman and Hall, 815–22.

Nebes, R.B. (1989) Semantic memory in Alzheimer's disease. *Psychological Bulletin* **106**, 377–94.

O'Carroll, R.E., Curran, S.M., Ross, M. *et al.* (1994) The differentiation of major depression from dementia of the Alzheimer type using within-subject neuropsychological discrepancy analysis. *British Journal of Clinical Psychology* **33**, 23–32.

O' Carroll, R.E., Prentice, N., Conway, S. and Ryman, A. (1997) Performance on the delayed word recall test (DWL) fails to clearly differentiate between depression and Alzheimer's disease in the elderly. *Psychological Medicine* **27**, 967–71.

Owen, A.M. (1997) The functional organization of working memory processes within human lateral frontal cortex: the contribution of functional neuroimaging. *European Journal of Neuroscience* **9**, 1329–39.

Owen, A.M. (1998) Memory: dissociating multiple memory processes. *Current Biology* **8(23)**, R850–2.

Owen, A.M., Downes, J.D., Sahakian, B.J., Polkey, C.E. and Robbins T.W. (1990) Planning and spatial working memory following frontal lobe lesions in man. *Neuropsychologia* **28**, 1021–34.

Owen, A.M., Roberts, A.C., Polkey, C.E., Sahakian, B.J. and Robbins T.W. (1991) Extra-dimensional versus intra-dimensional set shifting performance following frontal lobe excisions, temporal lobe excisions or amygdalo-hippocampectomy in man. *Neuropsychologia* **29**, 993–1006.

Owen, A.M., Sahakian, B.J., Semple, J., Polkey, C.E. and Robbins, T.W. (1995) Visuo-spatial short term recognition memory and learning after temporal lobe excisions, frontal lobe excisions or amygdalo-hippocampectomy in man. *Neuropsychologia* **33(1)**, 1–24.

Owen, A.M., Doyon, J., Petrides, M. and Evans, A.C. (1996a) Planning and spatial working memory examined with positron emission tomography (PET). *European Journal of Neuroscience* **8**, 353–64.

Owen, A.M., Evans, A.C. and Petrides, M. (1996b) Evidence for a two-stage model of spatial working memory processing within the lateral frontal cortex: a positron emission tomography study. *Cerebral Cortex* **6**, 31–8.

Owen, A.M. Milner, B., Petrides, M. and Evans, A. (1996c) A specific role for the right parahippocampal region in the retrieval of object-location: a positron emission tomography study. *Journal of Cognitive Neuroscience* **8**, 588–602.

Owen, A.M., Morris, R.G., Sahakian, B.J., Polkey, C.E. and Robbins, T.W. (1996d) Double dissociations of memory and executive functions in working memory tasks following frontal lobe excisions, temporal lobe excisions or amygdalo-hippocampectomy in man. *Brain* **119**, 1597–615.

Owen, A.M., Herrod, N.J., Menon, D.K. *et al.* (1999) Redefining the functional organisation of working memory processes within human lateral prefrontal cortex. *European Journal of Neuroscience* **11**, 567–74.

Paulesu, E., Frith, C.D. and Frackowiak, R.S.J. (1993) The neural correlates of the verbal components of working memory. *Nature* **362**, 342–5.

Perry R.J. and Hodges, J.R. (1996). Spectrum of memory dysfunction in degenerative disease. *Current Opinion in Neurology* **9**, 281–5.

Pillon, B., Deweer, B., Michon, A., Malapini, C., Agid, Y. and Dubois, B. (1994) Are explicit memory disorders of PSP related to damage to frontostriatal circuits? Comparison with AD, PD, and HD. *Neurology* **44**, 1264–9.

Rahman, S. and Sahakian, B.J. (2000) Dementia. In Sirtori, C. (ed.) *European Textbook of Clinical Pharmacology*. McGraw-Hill Clinical Medicine series. New York: McGraw-Hill, Chapter 12.

Rahman, S., Sahakian, B.J., Hodges, J.R., Rogers, R.D. and Robbins, T.W. (1999) Specific cognitive deficits in frontal variant frontotemporal dementia. *Brain* **122(Pt 8)**, 1469–93.

Reitan, R.M. and Wolfson, D. (1993) *The Halstead–Reitan Neuropsychological Test Battery: Theory and Clinical Interpretation*, 2nd edn. Tuscon: Neuropsychology Press.

Robbins, T.W., James, M., Lange, K., Owen, A.M., Quinn, N. and Marsden, C.D. (1992) Cognitive performance in patients with multiple system atrophy. *Brain* **115**, 271–91.

Robbins, T.W., James, M., Owen, A.M. *et al.* (1994a) Cognitive deficits in progressive supranuclear palsy, Parkinson's disease and multiple system atrophy in tests sensitive to frontal lobe dysfunction. *Journal of Neurology, Neurosurgery and Psychiatry* **57**, 79–88.

Robbins, T.W. and Sahakian, B.J (1994) Computer methods of assessment of cognitive function. In Copeland, J.R.M, Abou-Selah, M.T. and Blazer, D.G. (eds), *Principles and Practice of Geriatric Psychiatry*. Chichester: John Wiley & Sons, 205–9.

Robbins, T.W., James, M., Owen, A., Sahakian, B.J., McInnes, L. and Rabbit, P.M. (1994b) Cambridge Neuropsychological Test Automated Battery (CANTAB): a factor analytic study of a large sample of normal elderly volunteers. *Dementia* **5**, 266–81.

Robbins, T.W., Elliott, R. and Sahakian, B.J. (1996) Neuropsychology – dementia and affective disorders. *British Medical Bulletin* **52**, 627–43.

Robbins, T.W., Semple, J., Kumar, R. *et al.* (1997) Effects of scopolamine on delayed-matching-to-sample and paired associates tests of visual memory and learning in human subjects: comparison with diazepam and implications for dementia. *Psychopharmacology* **134**, 95–106.

Robbins, T.W., James, M., Owen, A.M., Sahakian, B.J., McInnes, L. and Rabbitt, P. (1998) A study of performance on tests from the CANTAB battery sensitive to frontal lobe dysfunction in a large sample of normal volunteers: implications for theories of executive function and cognitive ageing. *Journal of the International Neuropsychological Society* **4**, 474–90.

Rosen, W.G., Mohs, R.C. and Davis, K.L. (1984) A new rating scale for Alzheimer's disease. *American Journal of Psychiatry* **141**, 1356–64.

Rosser, A. and Hodges, J.R. (1994) Initial letter and semantic category fluency in Alzheimer's disease, Huntington's disease, and progressive supranuclear palsy. *Journal of Neurology, Neurosurgery and Neuropsychiatry* **57**, 1389–94.

Saffran, E.M. and Schwartz, M.F. (1994) Of cabbages and things: semantic memory from a neuropsychological perspective – a tutorial review. In Umita, C. and Moscovitch, M. (eds), *Attention and Performance*, Vol. 15. Cambridge, MA: MIT Press, 507–35.

Sagar, H.J., Cohen, N.J., Sullivan, E.V., Corkin, S. and Growden, J.H. (1988) Remote memory function in Alzheimer's disease and Parkinson's disease. *Brain* **111**, 185–206.

Sahakian, B.J., Morris, R.G., Evenden, J.L. *et al.* (1988) A comparative study of the visuospatial memory and learning in Alzheimer-type dementia and Parkinson's disease. *Brain* **111**, 695–718.

Sahakian, B.J., Downes, J.J., Eagger, S. *et al.* (1990) Sparing of attentional relative to mnemonic function in a subgroup of patients with dementia of the Alzheimer type. *Neuropsychologia* **28**, 1197–213.

Sahakian, B.J., Owen, A.M., Morant, N.J. *et al.* (1993) Further analysis of the cognitive effects of tetrahydroaminoacridine (THA) in Alzheimer's disease: assessment of attentional and mnemonic function using CANTAB. *Psychopharmacology* **110**, 395–401.

Sahgal, A., Sahakian, B.J., Robbins, T.W. *et al.* (1991) Detection of visual memory and learning deficits in Alzheimer's disease using the Cambridge Neuropsychological Test Automated Battery. *Dementia* **2**, 150–8.

Sahgal, A., Galloway, P.H., McKeith, I.G. *et al.* (1992a) Matching to sample deficits in patients with senile dementias of the Alzheimer and Lewy body types. *Archives of Neurology* **49**, 1043–6.

Sahgal, A., Lloyd, S., Wray, C.J. *et al.* (1992b) Does visuospatial memory in senile dementia of the Alzheimer type depend on the severity of the disorder? *International Journal of Geriatric Psychiatry* **7**, 427–36.

Smith, A.D. and Jobst, K.A. (1996) Use of structural imaging to study the progression of Alzheimer's Disease. *British Medical Bulletin* **52**, 575–86.

Snowden, J.S., Goulding, P.J. and Neary, D. (1989) Semantic dementia: a form of circumscribed cerebral atrophy. *Behavioural Neurology* **2**, 167–82.

Squire, L.R. (1992) Memory and the hippocampus: a synthesis from findings with rats, monkeys, and humans. *Psychological Review* **99**, 195–231.

Tombaugh, T.M. and McIntyre N.J. (1992) The Mini-Mental State Examination: a comprehensive review. *Journal of American Geriatric Society* **40**, 922–35.

Welch, K., Butters, N., Hughes, J.P., Mohs, R.C. and Heyman, A. (1992) Detection and staging of dementia in Alzheimer's disease: use of the neuropsychological measures developed for the Consortium to Establish a Register For Alzheimer's Disease (CERAD). *Archives of Neurology* **49**, 448–52.

Wilder, D., Cross, P., Chen, J. *et al.* (1995) Operating characteristics of brief screens for dementia in a multicultural population. *American Journal of Geriatric Psychiatry* **3**, 96–107.