PATTERNS OF COGNITIVE IMPAIRMENT IN ALZHEIMER'S DISEASE: ASSESSMENT AND DIFFERENTIAL DIAGNOSIS

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1. ABSTRACT

In routine clinical practice, the diagnosis of Alzheimer's disease (AD) is commonly made according to NINCDS-ADRDA criteria. As pathological verification is typically not available, such a diagnosis remains probable rather than definite. A diagnosis of probable AD is nevertheless fairly accurate (0.75-0.96), and may serve as a surrogate gold standard in clinical studies.

Probable AD is often considered a diagnosis of exclusion, but AD neuropathology characteristically

evolves in an ordered topographic sequence, which is mirrored in the pattern of evolution of neuropsychological deficits. Recognition of the resulting temporal profile of cognitive domain involvement allows positive rather than merely exclusionary diagnosis.

Certain other dementias may be difficult to distinguish from AD clinically: notably frontotemporal dementia (FTD), dementia with Lewy bodies (DLB), and various subtypes of vascular cognitive impairment. The distinction is made more difficult by the existence of variants of AD, presenting with predominant impairment of executive, visuoperceptual, or language domains, as well as by the common occurrence of mixed pathologies.

Against this background, the neuropsychological features of AD and its variant presentations, and its distinction from other dementias are reviewed. The properties of commonly-used cognitive assessment tools (MMSE, Mattis DRS, ADAS-Cog, CERAD and CAMDEX-R) are discussed, and the issue of diagnosing incipient AD on clinical grounds before the NINCDS-ADRDA criteria are fulfilled is addressed.

2. INTRODUCTION

The literature on the experimental neuropsychology of Alzheimer's disease (AD) is daunting in its extent. This review, however, will concentrate on the basis and utility of AD neuropsychological assessment, in its broadest sense, in routine clinical practice.

In the absence to date of a more reliable, readily available, and cost-efficient biomarker for AD, cognitive assessment of varying degrees of sophistication still plays a central role in clinical diagnosis. It serves several purposes: providing objective confirmation of a suggestive history of cognitive decline, refining the differential diagnosis in the light of the pattern of deficits found, furnishing a baseline against which the further deterioration expected in AD can be confirmed, highlighting the particular cognitive strengths and weaknesses of affected individuals to enable appropriate management strategies to be devised and, increasingly, enabling the effects of treatment to be gauged from serial assessments. It is axiomatic, however, that neuropsychological impairment cannot be detected in AD before significant neuronal dysfunction has occurred; truly preclinical detection will inevitably depend on the development of sensitive and specific biomarkers. It is also obvious that, while neuropsychological assessment may sensitively detect disruption of cognitive networks, it cannot directly indicate the pathological cause of that disruption. This must be inferred from the pattern of disruption across various cognitive domains, and from history, physical examination, and ancillary diagnostic studies.

Four aspects of the clinical neuropsychology of Alzheimer's disease are addressed below: i) the clinical diagnosis and neuropsychological features of typical AD, ii) some well-described variant patterns of cognitive impairment that can occur in AD, iii) the distinction of AD

from other common causes of dementia, and iv) the prediction of future development of dementia in aged patients with mild cognitive impairment.

3. THE RELATIONSHIP OF COGNITIVE DECLINE TO THE TOPOGRAPHICAL EVOLUTION OF AD NEUROPATHOLOGY

The neuropathological burden of AD is comprised of neuritic plaques, neurofibrillary tangles (NFT's), dystrophic neurites, and synaptic and neuronal loss (e.g. 1). Of these, the temporal evolution of the topographic distributions of plaques and NFT's has been studied in greatest detail. The distribution of NFT's correlates with the pattern of cognitive impairments in individual patients (2, 3), and, considered broadly, evolves in a characteristic pattern (4). The mesial temporal structures are typically amongst the first and most severely affected (4, 5), which is reflected in the early development of anterograde episodic memory impairment. Semantic memory impairment is often apparent next, manifested by impaired word list generation by category (semantic fluency) and confrontational naming deficits. It correlates with spread of NFT's to lateral temporal neocortex. Selective attention may also be disturbed at this stage (3), although the anatomicopathologic substrate for this is perhaps less certain. In the middle stages of the disease, involvement of the temporoparietal association cortex may manifest as impairment of comprehension, visuoperceptual dysfunction and apraxia. The prefrontal association cortex may also be affected, resulting in impairment of sequencing, planning and self-monitoring. Primary motor, sensory and (usually) visual cortices are relatively spared, correlating with a paucity of motor, somatic sensory and visual findings on neurological examination. In the later stages of the disease the patient is unable to cooperate meaningfully with standard neuropsychological assessment, although specialised cognitive batteries may still delineate residual capabilities (6). From the above it is evident that tests of anterograde episodic memory should display greatest sensitivity to early AD, and indeed might be expected to be the first cognitive domain affected in incipient AD (that is, AD pathology resulting in cognitive impairment, but not to the extent necessary to satisfy the NINCDS-ADRDA criteria). Most clinical studies of incipient AD have confirmed this expectation (see section 7.). However, episodic memory function is essentially unmeasurable on standard word list learning tasks in even moderately severely affected patients; that is, it displays an early "floor effect" (7). In contrast, tests of confrontational naming, semantic fluency, and visuoperceptual function show a steady decline throughout the course of the illness, parallelling increasing disease burden in association cortices, and are most useful in assessing dementia severity (7). Cognitive instruments claiming utility for disease detection *and* staging perforce employ tests of both episodic memory and of other domains.

4. THE NEUROPSYCHOLOGICAL PROFILE OF AD

4.1. Memory

Several separate memory systems exist, each with distinct networks of anatomical substrates (reviewed

by 8). Several different classifications have been propounded, but a simple one would include:

i) Explicit memory (for memories which can be stated). These memories include the current content of consciousness (sometimes termed "immediate memory" and exemplified by forwards digit span) as well as memories no longer in consciousness and therefore requiring retrieval (sometimes termed "long-term memory"). Long-term memory in turn is divided into (a) episodic memories, which are unique to the individual and are linked to a particular time and place (such as what one ate for dinner yesterday), and (b) semantic memories for non-personal information such as the meaning of words and the rules of grammar. Episodic memories in turn may be retrograde (laid down before apparent disease onset) or anterograde (laid down after onset of clinical disease), although the distinction may be debatable in a disease such as AD where accumulation of the pathological burden may begin decades before overt clinical involvement.

ii) Implicit memory (for memories which cannot be stated). This concept covers skills (e.g. reading mirror-writing, using a keyboard), conditioned reflexes, and priming (whereby exposure to a stimulus renders it unconsciously more likely to be selected later).

Another aspect of memory, "working memory", involves the manipulation of data in consciousness (e.g. backwards digit span), and the allocation of scarce cognitive resources amongst competing cognitive demands. It will not be discussed further in this section.

Given that these different memory systems employ different neuroanatomical substrates (8), it is reasonable to expect that they will be involved to different extents in AD, and this is indeed the case.

The consolidation of new episodic memories into long-term memory is dependent on the integrity of the hippocampus and other mesial temporal structures (8). In established AD, the direct and indirect entorhinal-hippocampal-amygdala connections are selectively and severely affected, resulting in severe amnesia (9). This is reflected at the macroscopic level by mesial temporal atrophy; a correlation exists between the extent of mesial temporal volume loss and the severity of episodic memory impairment (10). As already noted, these mesial structures are characteristically affected first in AD (4). It is therefore to be anticipated that the initial cognitive impairment will be of anterograde episodic memory, and indeed tests of new verbal memory (and often non-verbal memory as well) are indispensable components of instruments designed to detect mild and very mild AD.

4.1.1. Episodic memory

Episodic memory may be regarded as occurring in several stages. If a supraspan (i.e. longer than can be handled by immediate memory) word list is administered repeatedly, the number of spontaneously-recalled words increases. This "learning curve" reflects acquisition. The first and last few words in the list are more readily recalled: the primacy and recency effects. The acquired material must be encoded. Encoding may be aided by semantic (meaning-related) strategies, such as remembering "farmer; turkey" or "school; bell; parent" together from the Rey Auditory-Verbal Learning Test word list. Fragile encoding may manifest as reduced spontaneous recall of the main word list after one attempt at learning a second, distractor list (retroactive interference). The encoded memories must be retained over time - failure to do so is characterised as an abnormal forgetting rate. Lastly, words successfully encoded may not be able to be retrieved easily spontaneously; this can be distinguished from failure of encoding by incorporating a recognition memory task.

Episodic memory impairment in AD is typically manifest as a flattened learning curve (impaired acquisition) (11, 12). There also tends to be loss of primacy effect with increased recency effect (13 - 15), even in very mild disease (16). This preservation of recency effect may actually reflect preserved immediate memory in the face of acquisition failure. Encoding (or consolidation) has traditionally been regarded as "fragile" in AD, with an increase in the forgetting rate (13, 17, 18). However, Greene *et al.* (19) have argued that this apparently accelerated forgetting rate is an artefact, with immediate post-learning spontaneous recall being boosted by intact immediate memory. Whatever the cause, encoding is certainly disrupted, resulting in some loss of the usual advantage of delayed recognition over delayed free recall (12, 20). The impairment of delayed free recall is one of the most important diagnostic features of AD; such impairments have usually been found to discriminate most effectively between subjects with very mild AD (MMSE ≥24) and normal or depressed aged controls (7, 18, 21, 22). A potential explanation of AD patients' impaired encoding is their decreased ability to benefit from semantic (meaning-related) encoding strategies. A recent test designed to assess such benefits displayed high sensitivity and specificity (0.93; 0.99) in distinguishing between normal aged controls and subjects with mild AD (23). Lastly, certain qualitative abnormalities during episodic memory testing, such as perseverative (repetition) and intrusion errors, are suggestive of AD, although reports on their specificity vary (13, 24).

Patients' families often remark that autobiographical retrograde episodic ("long-term memory") function is better preserved than anterograde episodic ("short-term memory") function. There is actually a temporally graded (i.e. more severe for more recent decades) general retrograde memory impairment in AD (25, 26). Valid assessment of autobiographical memory is clearly difficult, but commercially available techniques do exist (27). These are not routinely employed in the clinical assessment of AD, however.

Damasio *et al.* (28) have postulated that (retrograde) memories have a multifocal cortical distribution, and are "bound" together through amodal "convergence" zones, which may help explain the relative preservation of memories from childhood and early adulthood in AD. More recent retrograde memories may

be affected by subtle, preclinical hippocampal dysfunction (e.g. see 29), or may remain more dependent on hippocampal "binding". The distinction between anterograde and retrograde deficits in a disease with a preclinical course probably extending over decades is therefore rather indefinite.

4.1.2. Semantic memory

Semantic memories may be conceptualised as networks of concepts with shared attributes (30). Studies in a few patients with highly focal lesions have supported the localisation of different classes of semantic knowledge (e.g. natural vs. man-made items) in separate but adjacent regions of the anterolateral temporal cortex (31). Functional imaging studies in normal subjects have supported this idea (32). As noted previously, temporal neocortex is involved relatively early in AD (4), so that tests of semantic memory are both sensitive and reasonably specific in mild AD (33, 34). Examples of such tests are object naming (see below), and word list generation by semantic category (e.g. naming as many types of animals as possible in 1 minute). Either or both are included in most cognitive assessment batteries. Patients with AD typically "dry up" when generating such word lists, producing most of their words in the first 15-30 seconds. While this feature is characteristic, and illuminates the pattern of disintegration of semantic memory in AD (reviewed by 35), it is usually only assessed qualitatively in the clinical setting. In contrast, verbal fluency by initial letter (e.g. F, A, S) tends to be better preserved in mild AD (34).

The ability to pronounce orthographically irregular (irregularly spelt) words, such as "ache", which also relies on an aspect of semantic memory, is commonly assessed in the National Adult Reading Test (NART; 36). NART scores correlate with full scale IQ in normals, and are widely used to estimate the level of premorbid intellectual function, as semantic memory is often considered to be relatively spared in neurologic disease (37). However, NART scores also decline in AD (38), which can cause underestimation of the degree of total decline.

Difficulty with object naming typically affects less commonly used words first (e.g. 39), and is frequently encountered in mild AD (40, 41). This naming difficulty, which is reflected in conversation by empty speech with circumlocutions, is a manifestation of impairment of semantic knowledge. Indeed, other language functions are usually preserved at this stage of the disease (42). AD patients frequently produce supracategory (e.g. "game" for "dominoes") or intracategory (e.g. "piano" for "harmonica") errors (41) which can easily be envisaged to result from dissolution of semantic memory structure. They also tend to produce circumlocutory errors, however (e.g. "thing you pour through" for "funnel") which might suggest a more specific naming deficit as well. Object naming tests may also detect visual agnosic deficits, where normal or subtly degraded object perception cannot be matched to the store of semantic information for that object. This can result in errors clearly based on visual

similarity (e.g. "snake" for "pretzel"). Visual agnosic errors are not a major contribution to object naming difficulties in the earliest stages of typical AD, however (39).

4.1.3. Implicit memory

Implicit memory functions have been extensively investigated in AD, but are not usually examined in routine clinical practice. Nevertheless, it is worth noting that motor skill learning is relatively normal in AD, in contrast to Huntington's disease (35). This presumably reflects the involvement of the basal ganglia in motor learning. The opposite pattern is seen with semantic and lexical priming (v.s.) which are preserved in Huntington's disease but impaired in AD (35), on the basis of involvement of association cortices in the latter.

In summary, memory impairments in AD evolve in a sequence reflecting the pattern of topographical involvement, with early impairment of anterograde episodic memory function followed by impairments in confrontational naming and word list generation by semantic category.

4.2. Language
4.2.1. Auditory comprehension, spontaneous speech, repetition and articulation

The subject of Alzheimer's original report was noted to display impaired naming and comprehension, and to produce paraphasic errors (43). Cummings and co-workers (44) described impaired auditory comprehension and fluent paraphasic spontaneous speech with relatively preserved repetition as characteristic of AD. This pattern of deficits is similar to transcortical sensory aphasia in the Boston classification. Cummings *et al.* (44) have suggested that inclusion of such impairment as a diagnostic criterion would improve the accuracy of diagnosis of AD. More recently, the typical pattern of language impairment in early AD has been considered as a consequence of dissolution of some aspects of semantic memory (see section 4.1.2.). Such dissolution underlies word-finding difficulties and impaired comprehension of complex written or aural material in early AD (e.g. 45). Syntax and phonology are usually considered to be spared initially (46), although a very recent and detailed analysis from the UK of single word production and conversation in 10 cases of AD demonstrated that articulation and phonology may indeed be impaired in early disease (47). Such impairment remains less common than the characteristic word-finding deficits, however (47). Language dysfunction progresses as the disease advances, until echolalia or mutism ensues in the terminal phases. Lastly, the comprehension deficits in early AD have been linked to impairment of aspects of working memory involving storage and ordering of propositions "online". Preliminary support for this model has emerged from recent studies (48), although the distinction between comprehension and working memory is not always clear (see 49 for discussion).

On routine clinical assessment, language impairment tends to be fairly subtle in mild AD, and is primarily manifested by word-finding difficulties and

naming impairments (50). As a result, persons with AD are reported to be impaired in making category membership judgements of both single words and pictures (51), and are also impaired in the knowledge of the meaning of words. Patients often resort to circumlocution as a compensatory strategy (e.g. "thing for picking things up" for "tongs"), with resultant loss of precision in conversational speech (52). At this stage of the disease, grammatical structure and syntax, and the musical aspects of speech (prosody) are typically still fairly well preserved, despite the decline in information content consequent on semantic impairment. As noted in section 4.1.2., patients with mild AD may perform more poorly on verbal fluency (word list generation) tasks based on semantic categories (e.g. animals, supermarket items) than on fluency tasks based on initial letter (e.g. F,A,S), due to relatively intact phonological processing despite semantic disruption (33).

As the disease advances to the moderate stage, impairment of comprehension becomes more obvious. In the first author's experience, this is often particularly evident when instructions for the neurological examination are given, even when there is no evidence of ideomotor dyspraxia on formal testing. Perhaps this is a reflection of the novelty and complexity of the instructions, from the patients' point of view. In keeping with this, patient's spontaneous speech loses complexity of grammatical structure, and content becomes increasingly devoid of meaning and paraphasic. With further disease progression, repetition begins to deteriorate, and intelligibility declines. This evolution of deficit to involve basic language function is thought to reflect increasing temporoparietal gyral atrophy (53). At this stage persons with AD will be increasingly isolated from, and confused by, social conversation. In severe AD, little or no verbal communication is possible, with verbal output reduced to meaningless repetition or mutism.

4.2.2. Reading and writing

Except in patients presenting with disproportionate visuoperceptual impairment (v.i.), reading and auditory comprehension decline in parallel. As explained above, these deficits may be attributed to a combination of semantic and working memory impairments (54). Although the ability to read aloud may be preserved in advanced AD (55, 56), patients have difficulty understanding longer, more complex sentences (51). Thus, a patient with moderately severe AD may be able to read a newspaper article aloud, but be unable to understand what they have read. Recent research suggests that this is an oversimplification, however. While orthographically regular words may be read correctly, illustrative of a well-learned and automatic skill, less common irregularly spelt words (e.g. "mauve" and "suite") are often mispronounced (regularised) in mild to moderate AD (57). As mentioned in section 4.1.2., pronunciation of orthographically irregular words is assessed by the National Adult Reading Test (NART; 36). Indeed, Patterson *et al.* (57) have shown that NART-estimated premorbid full-scale IQ has declined by about 1 standard deviation, or 15 IQ points, by the time AD has reached the moderate stage, while others have also demonstrated a decline in NART scores in AD patients

followed longitudinally (38). NART-estimated premorbid ability correlates reasonably well with years of education in non-demented subjects (37), and this demographic information may offer a reasonable substitute for the NART in moderate dementia.

Handwriting is incidentally sampled routinely in a number of cognitive instruments (e.g. the MMSE; see section 6.1.), but the presence or absence of dysgraphia is not assessed formally, and has rarely been investigated. However, one recent study has suggested that early AD does not consistently result in significant dysgraphia (58). When dysgraphia is present, it parallels dyslexia in that only irregularly spelt (orthographically irregular) words are misspelt, and in that this is probably also a manifestation of semantic memory decline (59). The authors have also observed significant spatial dysgraphia in rare patients with presumed AD presenting as a posterior cortical atrophy syndrome (see section 4.3.3.). This form of dysgraphia reflects the severe visuoperceptual impairment seen in these patients.

4.2.3. Variant presentation of AD with predominant language impairment

While language impairment is common in AD, it is rarely the presenting feature. Nevertheless, a few patients presenting with fluent or even non-fluent dysphasia have subsequently been shown pathologically to have AD (60 - 64). When aphasia is the presenting feature of AD, syntactic (use of grammar) and phonologic (intelligibility) deficits may predominate, contrary to their preservation in early cases of typical AD (62). As other cognitive deficits are probably always present to some degree at presentation, Green *et al.* (62) have argued that the label of *primary progressive aphasia* (PPA) (65), which requires the development of aphasia over at least two years without other deficits, cannot be applied. A case report from this group (61) described a patient who presented with a nonfluent aphasia (slow, effortful speech with verbal paraphasias), two months prior to death. At presentation, geometric figure copying was poor, although memory was intact. At post-mortem, AD pathologic features were found throughout the cortex. These findings illustrate the view that neuropsychological testing will typically identify asymptomatic impairments in other cognitive domains in AD patients with a PPA-like presentation.

What, then, is the relationship of such variant cases of AD to PPA? Mesulam and Weintraub (65) have provided the original diagnostic criteria for PPA: a progressive deterioration of language with preservation of activities of daily living for at least two years, and evidence of relatively normal nonlinguistic abilities on neuropsychological testing. While the aphasia can be nonfluent and agrammatic with relative preservation of comprehension, or fluent with semantic impairments resulting in impaired single-word comprehension and severe anomia, the latter syndrome is now usually classified separately as "semantic dementia" (66, 67). As with most focal cortical atrophy syndromes, the clinical features depend on the location of the pathology rather than its nature[a], and indeed a number of different pathologies

have been shown to underlie PPA. Dementia lacking specific histology (i.e. without inclusions), Pick's disease (*sensu strictori*), frontotemporal dementia with MND-like inclusions and even CJD have all been found to involve anterior language areas in non-fluent PPA (e.g. 65 - 69), whereas semantic dementia arises from involvement of the anterior temporal neocortex (70). Although AD may sometimes provide the pathologic substrate for PPA (60), and PPA itself often progresses to more widespread cognitive decline (60), presentation with PPA renders AD unlikely without completely excluding it.

4.3. Visuoperceptual functioning

Visual processing is complex, with different visual attributes being processed separately (71) before being bound into the unitary form perceived consciously. This separation may be regarded as commencing at the retinal ganglion cell level, where two separate pathways have their origins. These two pathways, the magnocellular and the parvocellular, are named after their respective relay cell layers in the lateral geniculate body. The magnocellular system has superior temporal resolution, resulting in motion sensitivity, but is not colour-sensitive (72). The parvocellular system carries information about colour, and has superior spatial sensitivity (resulting in superior visual acuity), but displays poorer temporal resolution (72). While visual processing at the cortical level is even more subdivided, with processing of colour, form, position and motion (amongst other attributes) being attributed to individual cortical regions, a broad classification of clinical utility recognises a dorsal (parietal) "where" pathway related to object location, and a ventral (inferotemporal) "what" pathway related to object recognition (72). The relationship between the two sets of pathways (magnocellular/ parvocellular; dorsal/ventral) is not clearcut, and it appears that both ventral and dorsal pathways receive some input from both the magnocellular and parvocellular pathways, although the dorsal pathway input is predominantly magnocellular (74). While this simple parcellation is useful to bear in mind, it glosses over the extensive reciprocal interactions between the various areas of visual association cortex.

Thorough assessment of cortical visual processing in AD necessitates testing of both dorsal and ventral processing streams, after exclusion of relevant coincidental anterior visual pathway pathology (e.g. senile macular degeneration). Visuoperceptual tests employed in routine clinical settings tend not to examine dorsal versus ventral processing in isolation, but may be more sensitive to impairment in one stream than the other. For example, the Benton Line Orientation Test (75) predominantly assesses the dorsal stream, whereas the Benton Facial Recognition Test (75) (really a test of facial *matching*) places more demands on the ventral stream. The Benton Visual Form Discrimination Test (75) might be regarded as tapping both processing streams, as each item requires matching of different shapes and of their positions relative to each other.

4.3.1. Anterior visual pathway (retinocalcarine) and early cortical visual processing defects in AD

While there have been some reports of impaired anterior visual pathway function in AD (76), routine neuro-ophthalmological examination is usually normal. Indeed, a careful clinical and electrophysiological investigation of the retinocalcarine pathways in AD by Rizzo *et al.* (77) failed to detect significant impairments. A more recent electrophysiological study confirmed that visual processing deficits in early AD are not attributable to neuroretinal dysfunction (78). In contrast, problems involving early stages of cortical visual processing are significantly more common in mild-moderate AD than in controls. Such impairments have been found in blue-yellow (tritan) colour discrimination (as assessed, for example, by the L'Anthony Album Tritan), and in contrast sensitivity (79, 80), although these functions are typically not assessed in the routine clinical setting. The spatial frequency of maximal contrast sensitivity impairment in AD remains in dispute, and the numerous tests developed for its measurement are not necessarily interchangeable. However, reduced contrast sensitivity in AD is important to assess, as it has been linked to impaired activities of daily living, falls, and visual hallucinations (81). Depth perception is multifactorial, and relies on several types of monocular clues including relative size, parallax, and obscuration. Stereopsis refers to depth perception based on binocular disparity, and may be divided into a local from dependent on whole object incongruity (e.g. stereo pictures) and a global form requiring "construction" of an object based on point by point disparities (e.g. Randot stereogram). All may be adversely affected in AD (79, 82 - 84), although findings have not always been consistent (80).

4.3.2. Dorsal and ventral visual pathway processing in AD

Analysis of spatial relationships (dorsal pathway processing) and object perception (ventral pathway processing) are typically preserved in the very early stages of AD (85, 86), although the Benton Visual Form Discrimination Test (75) may reveal deficits in visuoperceptual analysis at this stage (87). As the disease advances to the mild-moderate stages, deficits in both object recognition and spatial analysis are frequently found (88). Indeed, tests such as Gollin's Incomplete Figures and other fragmented figure tasks have disclosed deficits in 30-100% of patients at this stage (89, 90).

There has been some dispute as to whether AD patients with visual symptoms predominantly manifest disturbances in the dorsal or the ventral stream, but it emerges that both processing streams are disrupted (79, 80, 90 - 92), although to varying extents in different patients. In the light of this conclusion, and of the fact that the commonly-utilised clinical tests of visual processing are typically not pure tests of one pathway or the other, conceptual maintenance of a rigid dichotomy between dorsal and ventral processing streams may not be entirely appropriate when assessing patients with AD. Indeed, a recent functional imaging study of patients with mild-moderate AD showed that visuospatial deficits were related to bilateral parietal impairment, whereas object recognition deficits were related to right hemisphere temporo-parietal hypofunction (93). These findings are not entirely in accord with independent dorsal and ventral pathways, although concomitant spatial demands in the object

recognition tasks may account for the right parietal hypofunction observed.

Disorders of visuoperceptual processing may be markers of more widespread cognitive dysfunction (80, 94) and probably impact adversely on performance in other cognitive domains. The significance of such visual dysfunction for patient independence and safety, its frequency in mild-moderate AD, and its utility in differential diagnosis (see section 8.2.) combine to make its assessment an important part of neuropsychological examination of the AD patient. The cognitive assessment batteries reviewed in section 6, however, are largely inadequate in this area, necessitating the use of ancillary tests. Only the CAMDEX-R addresses this area directly, with an "unusual views" test for apperceptive visual agnosia (v.i.).

4.3.3. Visual agnosias

Visual agnosia represents a failure to match what is perceived with what is known of the perceived object. The term embraces two types of deficit: apperceptive visual agnosia, where the stimulus is insufficiently well perceived to enable it to be recognised when seen from an unusual viewpoint, or partly obscured, or otherwise degraded; and associative visual agnosia, where the object is correctly perceived, but is unable to be matched to (sufficiently) intact semantic information about that object. Apperceptive agnosia is often assessed in AD patients with tests such as overlapping figures (figure-ground discrimination), fragmented figures such as those of Gollin or Street (visual closure), or objects viewed from unusual angles (such as in the CAMDEX-R battery). Such tests can be administered rapidly, and our clinical practice is to employ all three types of task routinely. Apperceptive agnosia in AD has recently been correlated with tangle density in visual association cortex (95), again illustrating the relationship between the topography of AD neuropathology and the pattern of cognitive impairment observed.

4.3.4. Visual attention and neglect

Patients with very mild AD display problems associated with the ability to attend to relevant visual information whilst ignoring irrelevant distractors (visual selective attention). This is evident in their difficulties with response selection, inhibition of irrelevant responses, and speed of attentional switching (96). Alzheimer's disease may involve a specific deficit in the disengagement of visual selective attention from its current position (97), which is a prerequisite for shifting attention to engage the next relevant stimulus. On a visual search task where participants must locate a target (e.g. a red Q) that differs from the distractors around it (e.g. red Os and green Qs) by a conjunction of features (both colour and form), patients with AD are differentially impaired compared to healthy age-matched controls (98, 99), and display a highly localised attentional focus (100). The implications of such a focus for driving safety are immediately apparent!

Hemispatial neglect (an inattention to one side of space) has also been reported in AD (101, 102). Such neglect tends to be evident more commonly and more severely for left hemispace, in accordance with the well-known effects of unilateral right vs. left hemisphere strokes. On the line bisection task, for example, 25% of mild-moderate AD patients produced errors consistent with left spatial neglect (103). Indeed, this finding was considered to be more sensitive than SPECT in diagnosing early AD (103). A case study of one individual with AD reported the far less common right sided neglect correlating with left posterior atrophy and hypoperfusion (104).

4.3.5. Presentation with visuoperceptual dysfunction - Posterior Cortical Atrophy (PCA)

Some patients present with progressive visuoperceptual impairments, and develop posterior cortical atrophy evident neuroradiologically. It is now generally agreed that PCA usually represents a focal presentation of AD (60, 105, 106), although the number of detailed case reports with neuropathological confirmation is not large. NFT and to some extent neuritic plaque distribution correlates with these symptoms, with increased densities relative to typical AD in the occipital cortex (107 - 109). NFT density is also increased in the superior colliculus, which is involved in shifting visual attention (110), the posterior parietal cortex, involved in disengaging visual attention (110), and the posterior cingulate, involved in oculomotor control (111). One well-described patient with neuropathologically proven AD presented with prominent visual disturbance, showing impaired contrast sensitivity at low spatial frequencies, difficulty locating and identifying visual objects, visuospatial difficulty contributing to mathematical impairment, and an inability to perceive more than one letter at a time when reading, despite otherwise intact memory and intellect. The highest density of neurofibrillary tangles was in the occipito-parietal region, the posterior cingulate cortex, and in the hippocampus, with low density in the frontal cortex. Both dorsal and ventral pathways seemed to be equally affected, reflecting the impairments evident in both visuospatial skills and object identification, respectively (112). PCA can also be grossly asymmetric, as evidenced by another patient with predominantly right-sided atrophy and hypometabolism who displayed left-sided motor symptoms and left visual neglect as well as severe visuoperceptual impairment (113).

Specific deficits displayed in PCA include problems recognising objects and faces, spatial disorientation, visuoconstructional deficits, impairments in the focussing of visual attention, and even Riddoch's phenomenon (perception of moving but not static objects) on occasion. These problems result in a large discrepancy between verbal and performance (non-verbal) IQ (105). Patients with PCA particularly involving the parietal (dorsal) processing stream may present with one or more elements of Balint's syndrome, which encompasses the triad of ocular apraxia - an inability to direct gaze to peripheral stimuli, optic ataxia - an impairment in reaching accurately for a visual target, and simultanagnosia - a restriction of attention such that only one object can be perceived at a time (108, 114). One study of this subgroup of PCA patients with Balint's syndrome has demonstrated decreased contrast sensitivity for low spatial frequencies,

implicating the magnocellular visual system (114). Recently, two cases of PCA were reported who each developed a combination of Balint's and Gerstmann's syndromes (acalculia, finger agnosia, left-right disorientation and alexia/agraphia), as well as eventual frontal lobe involvement. Structural and functional imaging indicated bilateral parieto-occipital dysfunction (115).

As noted previously (see section 4.3.2.), typical AD may involve either the dorsal or the ventral processing pathways preferentially (although probably not selectively), causing various admixtures of visual deficits. Similarly, PET studies have indicated that PCA may involve dorsal more than ventral pathways (116), while one case study with neuropathological confirmation reported selective ventral pathway pathology in a patient with a specific deficit in object recognition (117). It has been suggested that PCA should be further divided into two or three subgroups depending on the primary site of pathology, which of course determines the pattern of deficit: biparietal cortices (dorsal visual pathway) versus occipito-temporal cortices (ventral visual pathway) (118), or both of these plus a third subgroup in which primary visual cortex is involved (60).

Patients with PCA typically evolve to develop the memory problems characteristic of AD, as well as deficits in other cognitive domains such as language and executive functioning (109, 112, 119).

4.4. Executive functioning and attention
4.4.1. Executive functioning
Executive functions refer to cognitive processes that are involved in planning, initiation and regulation of behaviour (120) and are critical to effective execution of goal-directed behaviour, such as cooking a meal or making a timely financial investment. Executive functioning is multi-faceted (121) and numerous models have been proposed. Examination of these is beyond the scope of this article, but one scheme would include planning of (output) monitoring, alternation and sequencing, set shifting and cognitive inhibition as important components (121). Executive dysfunction has sometimes been regarded as synonymous with the consequences of prefrontal lobe damage (122). However, executive skills probably rely on networks of interactive systems (123 - 125) involving both cortical and subcortical areas (e.g. cerebellum, basal ganglia) to achieve integration of information from multiple brain areas. Until fairly recently, executive dysfunction has not been considered to be an early feature of AD. In keeping with this, functional imaging studies have typically shown temporoparietal hypoperfusion/ hypometabolism, while changes in frontal cortex are less consistent and are seen in more advanced disease (126). Moreover, there is dispute as to whether significant prefrontal pathology is typically present in early AD (127).

Nevertheless, although there is debate about the sequence of cognitive deficits that follow or coexist with memory deficit during the progression of AD (128), there is increasing acceptance that executive deficits frequently appear early in the disease process (125, 129 - 132) and perhaps even in incipient AD (133). Indeed, many of the early problems that patients experience in the course of everyday activities may relate to disordered executive functioning (134). Family members often report that persons with AD experience difficulty adapting to change in their routine tasks (e.g. using an electric jug instead of the gas stove-top to boil water), or become befuddled by novel situations. Furthermore, these symptoms can be evident before basic cognitive abilities of language, praxis and visuospatial function are impaired sufficiently to account for the difficulties in their own right (132).

Impairments in executive functioning in early AD have been noted on several tasks that are considered as measures of executive control (130, 131). These tests are thought to assess either cognitive inhibition or coordination of cognitive resource allocation between multiple task demands. Although it is yet to be established whether all executive functions are equally affected, impairments in concurrent manipulation of information (set-shifting, self-monitoring, or sequencing) appear to be particularly sensitive to disruption in the early stages of AD (131). Collette *et al.* (130) and Perry and Hodges (132) have argued that executive functioning becomes increasingly impaired in AD as the disease progresses.

The neurobiological basis for the impairment of executive functioning observed in AD remains uncertain. While cognitive neuropsychological models suggest that executive deficits are related to primary prefrontal lobe impairment (135), it has been pointed out above that functional neuroimaging and pathologic findings are not always in accord with this idea (126, 127). Alternatively, it has been suggested that early executive and attentional impairments may result from basal forebrain cholinergic system disruption. This view, however, remains controversial (132). Finally, if the neural substrate for executive functioning consists of widespread neural networks rather than being confined to the frontal cortex, neurodegeneration affecting the corticocortical association fibres between association cortices would result in disruption of the efficient coordination of different cognitive processes, producing executive dysfunction (126). Divided attention (v.i.) would be expected to be particularly vulnerable to such dysfunction.

4.4.2. Attention
The term "attention" is broad and ill-defined, and is used loosely to cover a wide range of processes (136). Those aspects of attention relevant to this discussion are directed or focussed attention (which implies both selectivity and the screening out of distractions), sustained attention (over time), divided attention (between two or more concurrent tasks or sources of information, requiring both processing resources and an attention allocation strategy), and attentional switching (shifting attention from one task to another, requiring supervisory attentional control). The latter two varieties of attention obviously overlap, or are elements of, executive functioning, by virtue of their requirement for a supervisory attentional system, as well as for cognitive inhibition of inappropriate responses

(100, 132). Directed attention, via its requirement for cognitive inhibition to enable irrelevant distractions to be ignored, is also dependent on aspects of executive functioning. For these reasons, attentional problems in AD are often regarded as an aspect of executive dysfunction (132, 137). It should be noted that superficially simple attentional tests may in fact assess a number of aspects of attention simultaneously; for example Trails A (connecting numbers in order) makes demands on processing speed, and requires attentional shifting or even divided attention between visual search and drawing (136).

While capacity for sustained attention may not be significantly impaired in mild AD (132), accumulating evidence suggests that patients experience specific difficulty in speed of attentional switching (96) and in capacity for divided attention (123, 137), although the stage at which these problems emerge is debated (96). Clinically, impairment of divided attention and attentional switching results in behaviour that can be described as displaying both impaired cognitive flexibility and a tendency to be distracted by interference. One practical effect of these deficits has been illustrated in work by Alberoni *et al.* (138), in which patients with AD were impaired when trying to keep track of 'who said what' in a conversation amongst several people. Another study found that AD patient's walking speed slowed when they were required to perform a word generation task at the same time (139). An inability to handle more than one everyday task at a time can become extremely frustrating for family members, and may obviously impact adversely on driving safety (e.g. if driving while talking, or listening to the radio). Given that attentional impairment may be regarded as an aspect of executive dysfunction, it is perhaps not surprising that performance on Trails A predicted over 85% of variance in financial competency and competency for medical decision-making in patients with mild-moderate AD (140).

4.4.3. Presentation with executive dysfunction

There have been occasional reports of a variant of AD presenting with executive dysfunction (141). In these cases the term *frontal lobe variant* may be used to indicate the presence of early and prominent disturbances of executive functioning as the salient neuropsychological feature, overlaying an otherwise typical AD profile of cognitive impairment. Johnson *et al.* (142) described 3 cases of the frontal lobe variant of AD from a series of 63 clinically documented and pathologically confirmed AD cases. These patients had displayed severe impairments on tests of executive functioning, even during the mild stages of dementia. Concomitantly, they showed unusually high prefrontal NFT density at post-mortem. The same authors stated that 14% of patients with clinically diagnosed AD who presented to their memory clinic in the mild stages of dementia showed a similar pattern of neuropsychological deficits. This may seem a surprisingly high estimate for patients at presentation, but it is borne out by the findings of others. For example, Binetti *et al.* (143) reported that 7 of 25 mildly demented patients with AD, otherwise cognitively indistinguishable from patients with typical AD, had severe impairment on executive skills tests.

Another study of patients with very mild or mild AD disclosed three factors on factor analysis: mental control (which was related to prefrontal NFT density at follow-up post-mortem), memory-verbal (related to temporal NFT density), and visuospatial (parietal) (2). These figures are also in accord with the first author's own (as yet unpublished) data, where hierarchical cluster analysis of z scores of an object naming test, a visuoconstructional test and the error score on the Stroop test (of cognitive inhibition) was used to identify 8 of 36 patients with clinically diagnosed AD who displayed disproportionately severe impairments of cognitive inhibition.

Support for variability of the extent of prefrontal impairment in AD has also come from functional imaging studies. Haxby *et al.* (144) found disproportionate frontal hypometabolism in some patients, which was associated with greater attentional and word generation impairments. Other patients displayed disproportionately severe parietal hypometabolism, which was associated with more prominent comprehension and visuospatial problems (144). These different patterns of impairment were stable on repeated testing over time (144).

Patients with the frontal lobe variant of AD will show considerable similarity, both behaviourally and cognitively, to patients with other frontal dementia syndromes associated with non-AD pathology. However, the frontal lobe variant of AD can probably be distinguished from the frontal variants of frontotemporal dementia (fv-FTD) on the basis of the episodic memory dysfunction which is so typical of AD in its early stages. It is important to identify the frontal variant of AD, to enable potential problematic behavioural management issues and impairment of every day activities to be addressed appropriately.

4.5. Hemispheric asymmetry in AD

Some AD patients appear to have asymmetric hemispheric involvement on cognitive testing. In patients with moderate AD this may result, for example, in relatively impaired verbal semantic memory with relatively preserved visuospatial skills in those with predominantly left hemisphere disease, and the opposite pattern with disease mainly affecting the right hemisphere (145, 146). This presumptive localisation has been confirmed by PET scanning in one study (146).

5. STANDARD CLINICAL CRITERIA FOR THE DIAGNOSIS OF AD AND THEIR ACCURACY

AD is sometimes regarded merely as a diagnosis of exclusion in the demented patient. This is a misapprehension, which has probably arisen on the basis of the exclusionary clauses incorporated into the standard clinical diagnostic criteria (e.g. 147, 148). In conjunction with compatible results from physical examination, neuroimaging and a few basic laboratory tests, a typical pattern of cognitive deficits accumulating in a characteristic temporal sequence enables a positive provisional clinical diagnosis of AD to be made in typical cases. Indeed, it would be remarkable were this not so, given the disease's

Table 1. Three criteria used for the clinical diagnosis of Alzheimer's disease (paraphrased)

CONDITION	NINCDS-ADRDA	DSM-IV	ICD-10
Cognitive deficits	Memory decline and impairment in at least one other cognitive domain	Memory decline and at least one of aphasia, apraxia, agnosia, executive dysfunction	Memory decline and deterioration in judgement and thinking
Confirmation	MMSE or similar, and neuropsychological testing	-	-
Functional impairment	-	Impairment of social or occupational functioning	Impairment of activities of daily living
Course	Progressive worsening	Gradual onset and continuing decline	Gradual onset and slow deterioration
Exclusions	Age at onset <40 or >90*	Substance abuse or other major mental disorder	Sudden onset or focal neurological signs

*Sudden onset, focal neurological signs, and seizures or gait disturbances very early in the course make probable AD uncertain or unlikely, but do not exclude it. All three criteria require that clinical or laboratory evidence of another dementing disorder be absent, that the cognitive deficits represent a decline from the previous level of functioning, and that the deficits are not confined to a period of delirium.

characteristic and unique pattern of anatomical involvement and topographical spread.

5.1. Standard clinical criteria for AD

Neuropathological examination remains the gold standard for AD diagnosis in patients with cognitive decline[b], although the neuropathological criteria themselves continue to be refined (e.g. see 149). Of course, satisfaction of clinical criteria must substitute for neuropathological diagnosis in routine clinical practice. As such clinical criteria are often used as surrogate gold standards in clinical studies of AD, it is relevant to consider their characteristics, sensitivity, specificity, and shortcomings.

Two sets of standard criteria are commonly used for the clinical diagnosis of AD: NINCDS-ADRDA (148), and DSM-IV (147). The NINCDS-ADRDA criteria for definite AD require pathological confirmation of a clinical diagnosis of probable AD. To meet the criteria for probable AD, patients must first meet the criteria for dementia. These are satisfied by confirmation of a history of cognitive decline on clinical examination and psychometric testing. From this point on, the two criteria are similar (see Table 1). Both require a decline in cognition from previous levels, and demand the presence of memory impairment as well as impairment in at least one other unrelated cognitive domain. In addition, delirium and other causes of dementia must be excluded, and both criteria include some sort of reference to the gradual progression typical of AD. Although only DSM-IV requires the insidious onset characteristic of the disease, the NINCDS-ADRDA criteria note that a stroke-like (sudden) onset makes a diagnosis of otherwise probable AD uncertain or unlikely. DSM-IV requires impairment of functioning as well, but this is merely supportive in the NINCDS-ADRDA criteria. The ICD-10 criteria (150) are also included in Table 1 for interest, although they do not appear to be used frequently, at least in Australia.

The NINCDS-ADRDA criteria have been validated extensively against subsequent neuropathological diagnosis. The sensitivity of the "possible" and "probable"

categories combined is generally above 0.90 (e.g. 151 - 153), with one series as low as 0.83 (154). As would be expected, the specificity of the combined probable and possible categories is considerably lower in these studies, ranging from 0.61 - 0.73. When "probable AD" alone is considered, sensitivity decreases (to as low as 0.49 in one series), with the expected increase in reported specificity to as high as 1.0! (151). Rather than sensitivity and specificity, most studies have reported the proportion of patients diagnosed with AD in whom the disease is confirmed pathologically (accuracy); rates have ranged from 0.75 - 0.77 in community-based studies (155, 156), to 0.86 - 0.96 for "probable AD" in specialist clinics (e.g. 157 - 159).

The NINCDS-ADRDA, DSM-IV and ICD-10 criteria have not been compared directly, but the NINCDS-ADRDA criteria have been compared with the earlier DSM-III and DSM III-R criteria (151, 153). In these studies, the sensitivity and specificity of DSM-III and DSM III-R diagnoses of AD approximate those of NINCDS-ADRDA probable AD.

The three current sets of criteria share two major problems. First, none are fully operationalised; all require subjective judgement by clinicians. A partial exception is the NINCDS-ADRDA criteria, which specify the use of a screening test such as the MMSE (160) or the Blessed Dementia Scale to document dementia, with confirmation by neuropsychological testing. This subjectivity results in only moderate interrater agreement for NINCDS-ADRDA possible plus probable AD, with kappas of about 0.5 (154, 161), although agreement for the presence of dementia (of any type) is much higher. Second, the criteria require that other causes of dementia be excluded. Such exclusion is itself prone to error, as it is often based on imperfect clinical criteria for other conditions. Clinical criteria for vascular cognitive impairment, especially that associated with small vessel vascular disease, are notably imperfect (158, 162, 163, and see section 8.3.) and will probably remain so until further clinicopathological correlation studies result in adoption of a clinicopathologic or pathologic gold standard. Dementia with Lewy Bodies shows considerable clinical and pathologic overlap with

AD, with prospective validation studies of the Consensus Guidelines for DLB diagnosis (164) showing fair to good but still imperfect accuracy (164, 165; and see section 8.1.). The NINCDS-ADRDA criteria fail to distinguish frontotemporal dementia from AD accurately (166), and even a brief battery of cognitive tests may not suffice for this purpose (167, and see section 8.2.). The utility of the Consensus Criteria for FTD (67) in making this distinction has not been assessed, to our knowledge. The potential contribution of neuropsychological testing to the differential diagnosis of AD is discussed further in section 8.

Several AD clinicopathologic series have noted a high prevalence of non-AD neuropathology potentially related to cognitive impairment, principally vascular disease ("mixed dementia") and Lewy bodies. If only cases of neuropathologically "pure" AD without these additional pathologies are included, the accuracy of a clinical diagnosis of AD is considerably lower, varying between 0.33 and 0.51 (157, 168, 169). This inability to predict "pure" pathology is not confined to the NINCDS-ADRDA criteria; clinical diagnoses of Vascular Dementias and of Dementia with Lewy Bodies were similarly unable to separate pure from mixed pathologies in a recent prospective community study (170). Moreover, as Bowler *et al.* (168) have argued, the exclusion from neuropathologic series of subjects diagnosed clinically as having AD who do not subsequently die introduces a verification bias, which would lead to overestimation of diagnostic accuracy in published series.

In summary, subjects diagnosed with "probable AD" according to the NINCDS-ADRDA criteria are highly likely to have AD pathology, although the presence of other potentially relevant pathologies cannot be reliably excluded. A diagnosis of probable AD does constitute a reasonable surrogate gold standard against which to assess other diagnostic tools. However, such a diagnosis is insufficiently sensitive for routine clinical work, where possible plus probable AD may serve better, while accepting the inevitable loss of specificity.

6. SOME COMMONLY-EMPLOYED COGNITIVE ASSESSMENT INSTRUMENTS

Far too many cognitive batteries and screening tests exist to allow even their brief description here. This plethora of testing material is testament to the fact that no single battery is ideal for all purposes. Covering all cognitive domains thoroughly is obviously time-consuming and expensive, as well as potentially exhausting for the patient. This fatigue can easily impact adversely on performance in its own right. On the other hand, brief batteries may well miss important deficits. The purpose of the evaluation of the AD patient - early detection, staging, differential diagnosis , or delineating the pattern of impaired and preserved abilities to aid management, or a combination of these aims - must be considered when choosing an assessment instrument. Batteries designed to detect mild AD with high sensitivity will concentrate on cognitive functions lost early in the disease process, such as

episodic verbal anterograde memory (e.g. word list learning), and perhaps attention/executive functioning. A recent example is the Seven Minute Screen (171). Batteries used for assessing severity and progression of established AD must assess functions lost progressively throughout the disease, such as semantic memory, language and visuoperceptual function, rather than those subject to an early floor effect such as episodic memory. The Mini-Mental State examination (MMSE) (160) is most commonly employed for this purpose (v.i.), although it does display significant ceiling and floor effects. The Mattis Dementia Rating Scale (DRS) (172), the Severe Impairment Battery (173), and the Severe Cognitive Impairment Profile (6), unlike the MMSE, were deliberately designed to be sensitive to progression in AD throughout its later course. However, the first two each take about 30-40 minutes to administer. By selecting a combination of cognitive tasks on which performance is typically impaired early in AD with those on which performance becomes impaired later, a scale with reasonable sensitivity to mild AD that also clearly differentiates between mild, moderate and severe disease can be constructed. Examples include the Alzheimer's Disease Assessment Scale-Cognitive section (ADAS-Cog) (174, 175) and the DRS (172, 176). Lastly, by sampling across a wide range of domains, some batteries enable a cognitive profile to be constructed which can assist in the differential diagnosis of dementia. An example is the CAMCOG-R, which is part of a comprehensive structured assessment protocol (CAMDEX-R) (177; see below). No practicable battery can hope to cover all eventualities, however, and a flexible, hypothesis-driven exploratory approach by an experienced neuropsychologist will still be required for particular problems such as difficult differential diagnoses or unusual focal presentations of AD. The reader interested in details of individual batteries or tests will find Lezak's (120) monograph invaluable.

6.1. MMSE

A number of very brief mental status screening instruments exist, of which the best-known is the MMSE (160). It can be administered in about 5-10 minutes, is free, and does not require specific training or equipment, although precise administration and scoring criteria are necessary to maximise inter-rater reliability (178). Validated versions exist in many other languages, including Spanish and Chinese. While the MMSE has considerable utility in discriminating demented from normal elderly (v.i.), and is a standard measure used to stratify the severity and track the course of AD, important aspects of cognition such as non-verbal anterograde memory are not sampled at all, while others such as visuoperceptual functioning and semantic memory are sampled inadequately. Executive functioning is assessed inadequately in a simple working memory task in one version (spelling "world" backwards). Serial 7 subtraction from 100, an alternate task, is not equivalent (179). The language items are of widely varying difficulty, with the object naming, in particular, too easy to detect deficits often evident on other tests. Furthermore, the summed score can conceal important focal deficits. The MMSE is therefore unsuitable for elucidation of dementia type, or for the detection of frontotemporal

dementia or small vessel vascular cognitive improvement (see sections 8.2 and 8.3.).

The sensitivity and specificity of the MMSE for detecting AD depend on the cut-off score used; as the cut-off score is lowered and sensitivity improves, specificity declines. Several groups have derived receiver operating curves in an attempt to optimise its use. The usual cut-off applied is 23/24, with no normal 50-89 year-olds scoring below 24 in a study of 141 subjects (180). Kukull *et al.* (181) found a sensitivity of 0.63 with a specificity of 0.96 for dementia at this cut-off, whereas a cut-off score of 26 or 27 was preferable in symptomatic populations where the goal is to maximise detection of affected individuals. A similar conclusion was reached by Monsch *et al.* (182) who found that a cut-off of 26/27 resulted in sensitivity of 0.74 with a specificity of 1.0 in their AD-enriched study population, and by van Gorp *et al.* (183). Age and education also affect performance on the MMSE, and adjustment of the cut-off score for these factors is reported to improve diagnostic accuracy (184, and see discussion in 185). Despite its brevity, the MMSE may well be as accurate in differentiating demented from non-demented patients as longer screens (186, 187). A recent study addressed its utility in predicting the subsequent development of AD in a non-demented population with symptoms of memory impairment; a cut-off at $^{24}/_{25}$ was highly specific (0.98), but sensitivity was (not surprisingly) inadequate at 0.41 (188). Although an earlier study suggested some predictive efficacy (189) it is not recommended as a screening instrument for this application.

The MMSE is the commonest measure used to stratify the severity of dementia and follow its progression. A standard stratification is that of Haxby *et al.* (144): severe (MMSE ≤ 10), moderate (MMSE 11 - 21), mild (MMSE > 21). A "very mild" group is sometimes included for those with scores ≥ 24. The average rate of progression on the MMSE in AD has been assessed at about 3 points per year (190, 191, 192; and see Han *et al.* (193) for a recent meta-analysis), although there is considerable inter-individual variability, and the standard deviation of its measurement error, at 2.8 points, is close to the average annual decline (191). This last feature makes it unsuitable for following progression in individuals over short time intervals. A plateau-decline-plateau time course for the MMSE score is typically seen in AD, presumably due to ceiling and floor effects of the test (194). The psychometric properties of the MMSE have been reviewed by Tombaugh and McIntyre (179), and its limitations for dementia screening discussed by Anthony *et al.* (195).

6.2. ADAS-Cog

The ADAS-Cog (Alzheimer's Disease Assessment Scale-Cognitive section) (174) is now the major instrument used in drug trials in AD (e.g. 196 - 198), and as a result in Australia is the required instrument for confirming improvement in very mild AD to attract governmental subsidy for these medications. It was designed to sample many of the cognitive domains known to be affected in AD, rather than to illuminate its

differential diagnosis, and is fairly sensitive to even very mild and mild AD when compared with comprehensive neuropsychological testing (175). It takes about 30-40 minutes to administer. Although it does not require extensive neuropsychological education for its use, training is certainly necessary and standardisation improves reliability (199). Specialised stimulus materials are required. Validated versions exist in several languages, including Spanish, and more recently Chinese (200). The ADAS-Cog produces a global error score that *increases* (from an ideal score of zero) throughout the course of the disease (175, 201) to a maximum of 70. The ability of the ADAS-Cog to track AD throughout its course is conferred by the scale's assessment of a range of cognitive attributes. The ADAS-Cog does not, however, sample all of the cognitive domains known to be affected in AD adequately (e.g. visuoperceptual functioning), or even at all in the case of executive functions (202). The average yearly rate of decline in AD is about +9.5 points, although there is considerable inter-individual variation, and an apparently steeper decline is seen during the middle stages of the disease (203). The scale's ability to distinguish between different dementias has not been systematically examined, but in one study it was found to be incapable of discriminating reliably between mildly demented patients with AD or Huntington's disease (204).

6.3. Mattis DRS

The Mattis Dementia Rating Scale (DRS) (172), now commercially available in a revised form as the DRS-2, was designed to assess cognition in demented subjects throughout the course of their illness, avoiding floor effects in more advanced disease by the incorporation of sufficient simple items. The items themselves are similar to many used in qualitative neurological bedside testing, and the scale is suitable for bedside use by a non-neuropsychologist. It contains five sections, assessing constructs labelled memory, construction, initiation and perseveration, conceptualisation, and attention. As discussed by Spreen and Strauss (205), these labels may be somewhat misleading. Factor analysis suggests that the conceptualisation and memory sections do assess these domains, whereas the construction, attention, and initiation and perseveration sections seem to assess aspects of a single construct. The construction of the items is unusual, in that a "tripwire" approach is adopted. That is, the hardest level in each item is presented first, and easier levels presented only if this is failed[c]. This saves time with the cognitively intact elderly, but administration can take 30-45 minutes in the demented. The sections are totalled to provide a single summed score (maximum 144). This has, as expected, led to disagreement regarding the optimal cut-point (205) with suggestions ranging from ≤123 (Montgomery, 1982, cited in 205) to ≤134 (183). Monsch *et al.* (206), using receiver operating characteristic curves and a large community sample of AD patients and healthy elderly subjects found an optimal cut-off of ≤129, which yielded a sensitivity of 0.98 and a specificity of 0.97. Others have provided age and education-adjusted norms (see 205); scores do decline slightly with age, but there is some dispute as to whether education has an appreciable effect on cut-off scores (207 - 209, and see discussion in

205). The DRS is able to measure cognitive decline throughout the course of AD, even in the more advanced stages (192). Average decline in AD is about 11 points per year (192). The DRS may also be useful in the detection of incipient AD. Impaired scores on its memory subscale in subjects with "subclinical memory impairment" predicted development of AD with 93% accuracy over a 4-6 year follow-up (176). Given its sectional construction and three domain factor solution, the DRS might potentially be useful in the differential diagnosis of dementia. However, its reported success in discriminating Huntington's disease from AD (210, 211) has been disputed (204).

6.4. CERAD

The Consortium to Establish a Registry for Alzheimer's Disease (CERAD), have produced a semi-structured assessment originally designed for research data collection, but now often used for routine clinical assessment (212). It includes an informant interview, a clinician-administered physical examination, and a brief mental status assessment, including the Short Blessed Test. There is also a neuropsychological battery, which includes the MMSE, that the originators specify should be administered by a trained psychometrician (212). Norms have subsequently been published for the neuropsychological battery (213), and have recently been augmented by normative data for elderly Australians (214), African Caribbeans in the UK (215), and African Americans (216). The clinical utility of the CERAD protocol has also been demonstrated in a non-North American (Jamaican) population (217). While the protocol provides a useful basic structure for the assessment of typical AD, it does not detect some types of cognitive deficit important in the differential diagnosis of AD sufficiently well, or delineate the cognitive strengths and weaknesses of patients thoroughly. It is therefore our practice to supplement the neuropsychological battery with a number of other tests to improve detection of visuoperceptual abnormalities, executive dysfunction, and ideomotor apraxia. The battery does cover a range of dementia severities (218), and is acceptably sensitive to mild dementia (18, 212). The Word List Acquisition subscore alone had an accuracy of 0.92 in distinguishing subjects with mild dementia from controls (219). However, the neuropsychological battery's sensitivity in incipient or very mild AD has apparently not been addressed. In our hands the entire protocol takes about 90 minutes to administer, including the addictional components mentioned above.

6.5. CAMDEX-R

The Cambridge Examination for Mental Disorders of the Elderly (CAMDEX) (220), recently revised as the CAMDEX-R (177), consists of structured psychiatric and informant interviews, a brief physical examination and the Cambridge Cognitive Examination (CAMCOG), amongst other items. The entire schedule takes approximately 20 minutes for the informant interview and 60 minutes with the patient. The CAMCOG produces a summed score which is quite successful in distinguishing between very mild and mild dementia and normal ageing, (sensitivity 0.93; specificity 0.87) (221). Adjustment of the total cut-off score for demographic variables results in a sensitivity and specificity of 0.88 and 0.89 respectively for very mild dementia alone (222). Moreover, the CAMCOG also provides subscale scores for various cognitive domains, including those listed in DSM IV and ICD-10 criteria. These subscale scores allow the construction of a cognitive profile (177), which may well enable discrimination amongst the various dementias, although this proposition has apparently not been formally tested. Schmand *et al.* (223) divided the CAMCOG into a non-memory and a memory section, and found that the latter both detected established AD and predicted development of AD in a longitudinal study. Interestingly, a *higher* non-memory score was also predictive of AD development. In contrast, Nielsen *et al.* (224) constructed 14 composite measures from the CAMCOG items, and found that those who subsequently developed AD had lower scores on all 14 items at baseline. The CAMDEX-R comes with a detailed manual which allows an experienced non-psychometrician to administer it reliably. Indeed, inter-rater reliability amongst psychiatrists was shown to be high for the CAMCOG (220). In our opinion, either the CERAD protocol or the CAMDEX-R form a suitable basis for initial assessment in a memory clinic.

7. DIAGNOSIS OF INCIPIENT AD - PREDICTION OF PROGRESSION IN COGNITIVELY IMPAIRED BUT NON-DEMENTED ELDERLY

According to current (NINCDS-ADRDA) criteria, AD cannot be diagnosed clinically until memory decline and impairment in at least one other cognitive domain have been documented. Yet, AD has a preclinical course extending over decades (discussed in 225), and it is to be expected that subtle cognitive changes may well be observable before patients qualify as having NINCDS-ADRDA probable AD. In the absence of a reliable biomarker, the detection of incipient AD is likely to become a matter of considerable clinical importance as disease-modifying therapies reach routine clinical practice, because treatment is likely to have maximal functional impact if given prior to the onset of functional impairment (225, 226). It is also reasonable to suppose that such subtle cognitive changes are likely to occur in cognitive domains subserved by brain regions affected early in the disease, so it is unsurprising that episodic memory decline, correlating with mesial temporal dysfunction, has been most commonly reported as the initial cognitive change in incipient AD.

Four investigational strategies have been taken to identifying cognitive changes in incipient AD. First, any test sensitive to cognitive change in incipient AD should show robust differences between mild NINCDS-ADRDA probable AD and appropriately matched aged controls, indicating that the test indeed measures an ability which declines significantly in early AD. Second, non-demented individuals with cognitive symptoms who show abnormalities on such tests, should progress to probable AD if followed longitudinally. Third, individuals who show such abnormalities on screening of asymptomatic populations should also progress to probable AD. Fourth,

individuals carrying the rare causative mutations for early-onset familial disease should develop abnormalities on such tests as, or preferably before, they become symptomatic, and prior to the development of probable AD. The literature relating to each of these approaches is discussed in turn.

7.1. Tests showing robust abnormalities in mild AD

Tests of episodic memory (e.g. delayed free recall) are well established as the most effective neuropsychological discriminators in this situation. For example, performance on the CERAD battery recall test for a ten-word list after a delay of eight minutes allowed correct classification of 94% of healthy older adults and 86% of older adults with mild dementia (18). Identification of memory impairment in mild AD is in accord with neuropathologic data (see section 2.). It is also in agreement with a recent neuroimaging structural MRI study demonstrating that persons with mild AD appear to develop volume loss in the entorhinal cortex (a part of a memory-related neural system that receives projections from widespread limbic and association areas, and is intimately concerned with the functioning of the hippocampus), in the superior temporal sulcus region (a higher order multimodal association area of the cortex, necessary for immediate memory), and the anterior cingulate (an area strongly and reciprocally connected with the prefrontal cortex, which plays a role in executive functioning, and which is strongly and reciprocally connected with the prefrontal cortex) (227).

7.2. Tests predictive of progression to AD in symptomatic individuals

Although episodic memory is disturbed in mild AD, older adults often complain of memory failure. Clinicians must try to determine whether those presenting with a report of isolated memory impairment have incipient dementia or a more benign, age-related forgetfulness (128, 228). Even objective confirmation of the existence of mild memory problems beyond those seen in age-matched controls is not necessarily predictive of incipient dementia, but can be associated with a variety of medical and psychiatric conditions or with variability in normal aging. Therefore, longitudinal studies have been performed on older adults preselected for increased likelihood of progression to AD by the presence of objectively confirmed symptoms of memory impairment, in order to identify the diagnostic neuropsychological features of those who subsequently "convert" to AD. Overall, conversion rates of 6-12% per year have been noted (2, 129, 228 - 230). It is worth noting that even in the two series which reported 5 years of follow-up, over half of such subjects did *not* develop dementia (230, 231). Moreover, in the study of Visser *et al.* (230), 42% of subjects no longer evidenced memory impairment at the 5 year mark. No clear delineation of the neuropsychological profile at initial assessment of patients with incipient dementia emerges from the literature. However, Tierney *et al.* (229) reported that a logistic regression model, containing measures of delayed recall of information and of attention, was able to predict those patients with complaints of memory problems who would, or would not, later develop AD with an

accuracy of 0.89. Albert *et al.* (129) reported a 19% "conversion" rate to AD over 3 years of follow-up in patients with mild memory difficulty. A set of four baseline neuropsychological test performances related to memory and executive function discriminated converters from non-converters with an accuracy of 80%. Structural MRI studies of patients with mild memory difficulty (defined by a Clinical Dementia Rating score of 0.5 - "questionable"), in which 24% "converted" over 3 years, discriminated between the two groups with an accuracy of 0.75 (227). Such quantitative imaging studies therefore probably do not offer great advantages over more widely available and less expensive cognitive testing. However, as noted in section 7.1 above, this imaging study determined that volume loss in areas associated with executive functioning (anterior cingulate) and immediate memory/attention (superior temporal sulcus), as well as that concerned with episodic memory (entorhinal cortex) *together* offered the best discrimination between converters and non-converters. This is in accord with the study of Tierney *et al.* (229), and with recent work on attention and executive dysfunction in mild AD (see section 4.4.). (The study of Albert *et al.* (129) may have been performed on a subject group overlapping that of the imaging study, performed by the same group and with the same entry criteria (227)). These studies demonstrate that objectively confirmed isolated memory loss signals a significant rate of subsequent conversion to AD, albeit that the pre-dementia phase of isolated memory impairment may persist for many years. They also suggest that tests of attention and executive functioning may increase the accuracy of prediction in this population.

7.3. Tests predictive of progression to AD on screening of asymptomatic populations

A third approach is to perform a longitudinal study of individuals asymptomatic at entry and then follow them to determine the premonitory symptoms and signs of AD. Such community studies, whilst the ideal, are major undertakings, and few have been performed. The first wave of prospective community studies made two-point comparisons between baseline and long term follow-up. The Bronx Ageing Study (232) of non-dementing community residents aged between 75-85 years showed that, over a four-year follow-up period, a logistic regression model containing two episodic memory recall measures, a verbal fluency task, and a speed of processing task was moderately sensitive (0.50) and highly specific (0.94) at predicting progression to AD in a symptomatic population. A longitudinal 22-year follow-up of 1,000 non-demented older adults as part of the Framingham study suggested that a 'pre-clinical' phase of detectable cognitive deficits may precede "conversion" to AD by many years (233, 234). Low-normal scores on measures of new learning, recall, retention and abstract reasoning were associated with the later development of AD, while lowered scores on retention of information and abstract reasoning alone predicted conversion to AD after an extended dementia-free period of 10 years (233).

While episodic memory is widely agreed to merit assessment when attempting to identify individuals with incipient AD, consensus has not been reached as to which

aspect of episodic memory function is most reliably disrupted. The studies mentioned above have typically tested delayed spontaneous recall, or measured forgetting over a delay period. However, further studies have suggested that lowered performances in initial learning of information (acquisition) may be a better predictor of preclinical AD (235, 236). Notwithstanding such uncertainties, these studies all indicate that objective confirmation of mild cognitive impairment, particularly on tests of memory, and probably on tests of attention/executive function as well, has been shown to be a reasonable predictor of subsequent conversion to a diagnosis of AD in community dwelling older adults, while the absence of cognitive impairment seems to predict no further decline.

A later group of community follow-up studies has employed repeated testing over time, to delineate the evolution of cognitive changes during the preclinical phase of AD. In a recent prospective follow-up study (133) in which a non-demented cohort of 551 older adults were followed over a 3½ year surveillance period, it was found that episodic memory and executive functioning showed the greatest decline, relative to that attributable to normal ageing, in the years prior to the diagnosis of AD. As noted in the previous sections, the identification of executive dysfunction in incipient AD, in addition to episodic memory impairment, is concordant with the findings from several other recent studies (e.g. 129, 224, 227, 229, 233, 237). Another recent report describes a community sample of very old non-demented adults, assessed at baseline, and 3 and 6 years later (238, 239). When those who were diagnosed with probable AD at the last assessment were compared with those who were not, it was found that, as expected, there were group differences on specific measures of episodic memory at baseline. The magnitude of these deficits in the incipient AD group appeared relatively stable up to 3 years prior to diagnosis, however, with marked decline on almost all measures of functioning supervening in the three-year period before diagnosis.

7.4. Tests predicting progression to AD in individuals at high genetic risk

Early-onset AD, variously defined as having an onset before 60 or 65 years, is uncommon (<1% of all cases), but may be inherited as a dominant trait. In some of these early-onset AD pedigrees, causative mutations can be detected in one of three genes (encoding the anyloid precursor protein – APP, presenilin 1, or presenilin 2) (see 240 for a review). The advantage of studying at-risk individuals from such pedigrees is that each carries a 50% chance of developing the disease within a relatively defined age range, bias in case selection according to initial symptoms is avoided, the early onset limits the possibility of confounding by other brain pathology or normal ageing, and unaffected family members serve as well-matched controls. A potential disadvantage is that early-onset familial AD may not model the clinical features of late-onset sporadic AD faithfully. This issue is still unsettled (241). Fox *et al.* (242) reported the results of a longitudinal study of such at-risk asymptomatic individuals. Sixty-three asymptomatic participants aged between 31 and 63 years

underwent serial assessments over 6 years. Ten developed symptomatic impairment of episodic memory at 2.6 ± 1.4 years after initial assessment, and these participants subsequently progressed to possible or probable AD. There were no differences in demographic variables or MMSE scores between those who remained well and those who developed symptoms. However, the participants who developed AD had significantly lower verbal memory (p = 0.003) and performance IQ (p = 0.030) scores at their initial assessment than those who remained well, despite being overtly asymptomatic at that stage. Blinded qualitative assessment of serial MRI imaging also demonstrated diffuse cerebral and medial temporal lobe atrophy in 8 of 10 who progressed, but only at a stage when participants had developed possible or probable AD. This study suggests that in familial AD, measurable cognitive decline is present at least 2-3 years before symptoms are apparent, and 4-5 years before individuals fulfil criteria for probable AD. It further suggests that a decline in memory, especially verbal memory, is one of the earliest measurable cognitive deficits in AD.

7.5. Conclusion - the clinical detection of incipient AD

The neuropsychological studies reviewed in section 7 indicate the existence of a phase of detectable cognitive decline ("incipient AD") that can precede the NINCDS-ADRDA clinical diagnosis of probable AD by several years. Furthermore, the suggestion emerges that the degree of impairment may be relatively stable until a few years prior to diagnosis, when a marked decline in cognition begins which culminates in probable AD (243). In the absence of a sensitive and accurate biomarker, cognitive assessment remains the primary modality for identifying individuals with incipient AD. Such testing should include assessment of episodic memory, and probably of attention/executive functioning as well. The accuracy of such a diagnosis will need to be assessed in separate, prospective series, but is unlikely to be as high as that for probable AD. Nevertheless, it may be sufficient to target therapy efficiently. Neuroradiology may be a useful adjunct or even substitute if quantitative volumetry becomes widely and inexpensively available.

8. THE CLINICAL DISTINCTION OF AD FROM OTHER DEMENTIAS

AD has a wide differential diagnosis, but this discussion will be confined to three other common and frequently misdiagnosed conditions.

8.1. Dementia with Lewy bodies (DLB)

DLB may be the second commonest form of degenerative dementia: about 20% of patients who would once have been diagnosed as having probable AD have cortical Lewy bodies at post-mortem (244). Consensus Clinical Criteria for DLB were advanced in 1996 (164), and reviewed in 1999 (245). The three core features of DLB are parkinsonism, visual hallucinations, and a fluctuating cognitive state. Visual hallucinations (246) and signs of parkinsonism are thought to be more common in DLB than AD (247), however they are not always present in DLB (248), and both features *can* also occur in AD (249 - 257).

A study which investigated the diagnostic sensitivity of the Consensus Criteria for the clinical diagnosis of DLB (164) concluded that an important sign for the distinction of DLB from AD appears to be the presence of cognitive fluctuations, which are a frequent and specific indicator of DLB (248). These fluctuating attentional impairments are evident both clinically and on neuropsychological tasks (164, 258). Recently published clinician and informant-assessed fluctuation scales have been shown to correlate with neuropsychological and electroencephalographic measures of such fluctuation (259). Using the Consensus Criteria, DLB can be diagnosed with a sensitivity of 0.83 and a specificity of 0.91-0.92 (248, 260), although Hohl *et al.* (165) found a diagnostic accuracy of only 0.50 in another small prospective series.

Patients with DLB often satisfy inclusion criteria for NINCDS-ADRDA probable AD as well. The distinction of DLB from AD with significant visual symptoms is particularly difficult, as visuoperceptual problems are often early and prominent in DLB (164). DLB typically produces more visuoperceptual, visuo-constructive, and visuospatial dysfunction than AD, while AD in turn displays more prominent episodic memory impairment than DLB (261 - 263). Assessment of semantic memory is unhelpful, however, as deficits are similar in both disorders (262, 264). A recent comprehensive review of the literature concluded that impairment of spatial working memory in DLB was the most consistent difference between the cognitive profiles of DLB and AD (265). Patients with DLB performed significantly worse than patients with AD on visual tracking and attention switching (265), and visual matching to sample (266). Mori *et al.* (267) recently found that after matching for sex, age, and MMSE scores, patients with DLB were significantly more impaired than patients with AD on a number of visuoperceptual tasks, including size and form discrimination, overlapping figure identification, and visual counting (267). These differences are even apparent, at least at the group level, on a test as simple as interlocking pentagon copying from the MMSE (268). The prominent visuoperceptual abnormalities in DLB correlate with a reduction in occipital cortex metabolic rate compared with AD patients (269). It also appears that patients with DLB perform worse than those with AD on measures of executive functioning (244). This difference was robust enough to be detectable on the initiation/perseveration subscale of the Mattis DRS (270).

Only the minority of DLB patients have pure Lewy body pathology; most also have significant AD pathology, although tangles are often less frequent than in pure AD (271). This mixed group is sometimes referred to as having the Lewy body variant of AD (LBV). This group may overlap clinically with AD to a greater extent than "pure" DLB, especially in the milder stages (272). This is not surprising, given that both pathologies appear to contribute to the dementia in these patients (see discussion in 244). It has been shown that patients with LBV decline more rapidly than those with "pure" AD (5.6 vs. 3.9 MMSE points/year), so the distinction is nevertheless of prognostic importance (273). It is interesting that patients

with AD who develop extrapyramidal signs tend to follow a similar time course to those with LBV (272, 274).

A recent retrospective clinicopathological study suggests that patients with pure DLB are distinguishable from patients with LBV by the presence of two or more of acute/subacute onset, early parkinsonism, early hallucinations and early incontinence, whereas LBV was best separated from AD by the presence of cognitive fluctuations (275). This remains to be confirmed, however.

8.2. Frontotemporal dementias

The frontotemporal dementias (FTDs) are associated with focal degeneration of the frontal and/or temporal lobes. The clinical syndromes which ensue reflect the distribution rather than the nature of the underlying pathology. Pathologic entities which may give rise to these syndromes include dementia without distinctive histopathology, Pick's disease (*sensu strictori*), dementia with motor neuron disease-like inclusions, and corticobasal degeneration (274). Consensus clinical criteria for the diagnosis of the FTD's were published in 1998 (67). The distinctive feature of FTD is a marked alteration in social behaviour and personality (277). At the extreme, AD and FTD can be strikingly different in their behavioural presentation. An interesting meta-analysis of effect sizes seen in a range of cognitive domains in studies comparing FTD with controls and AD with controls shows that cognitive flexibility/abstraction and performance skills are more impaired in FTD, whereas memory acquisition, memory recall and verbal skill are far more affected in AD (278). However, attempts to differentiate FTD from AD directly using standard neuropsychological tests and diagnostic criteria have often proved disappointing. In a series of pathologically proven cases of AD and FTD, Varma *et al.* (166) found that although the NINCDS-ADRDA criteria for probable AD were highly sensitive in detecting patients with pathologically verified AD (0.93), specificity was very low at only 0.23. Indeed, most patients with FTD also fulfilled NINCDS-ADRDA criteria for AD. Deficits in problem solving significantly favoured FTD, while impairments of orientation and praxis significantly increased the odds of AD (166).

In a large recent study with incomplete pathological verification, Binetti *et al.* (279) noted that caregivers reported personality change and language impairment significantly more commonly in FTD than AD. Symptoms of memory impairment were common in both, but more prevalent in AD. On neuropsychological testing at presentation, visuospatial dysfunction was only evident in the AD group. Explicit memory was better in FTD than in AD, although still worse than that in controls. During the course of the illness, reasoning ability, explicit memory, and visuospatial functioning worsened equally in both patient groups (279). It was concluded that although FTD presents a characteristic cognitive profile and course, neuropsychological testing does not clearly distinguish FTD from AD. A further study by this group (280) confirmed the overlap in neuropsychological profile between FTD and AD, including on traditional "frontal lobe" tests. Only Rey Complex Figure recall and a

visuoperceptual test (worse in AD), and phonemic verbal fluency (i.e. word list generation by initial letter) and oral apraxia (both worse in FTD) distinguished between the two groups. In a further study attempting to discern the distinguishing features of FTD (right and left hemisphere predominant) and AD (281), patients with asymmetric FTD predominantly affecting the left prefrontal region were consistently identified as more impaired on language measures (word retrieval, verbal semantic memory) and verbal executive ability (phonemic fluency). Right FTD patients were found to display more perseverative behaviour than AD patients. In keeping with other results, there were no significant differences between FTD groups and AD on memory scores (verbal and non-verbal). However, another recent study by Lindau *et al.* (282) compared the earliest symptoms in patients with FTD (right, left and bilateral subgroupings) and AD. They reported that disinhibition, social awkwardness, passivity and loss of executive function were more common in FTD, while memory loss was more common in AD. Disinhibition was greatest in the asymmetric right subgroup, language dysfunction was commonest in the asymmetric left subgroup and loss of executive function was most frequent in the bilateral group. The authors argued that the anatomic site of FTD predicted the nature of first symptoms.

Perry and Hodges (283) argue that at least part of the difficulty in differential diagnosis relates to the inclusion of patients with atrophy predominantly involving either frontal or temporal lobes within the category of FTD, creating confusion in the neuropsychological profiles. Using a wide-ranging neuropsychological battery, they compared patients with the frontal variant of FTD (fv-FTD) and patients with the temporal variant of FTD (tv-FTD) to patients with mild AD. Fv-FTD, known previously as dementia of frontal type or frontal lobe degeneration, is characterised by impairments in behaviour and personality. Tv-FTD however, typically presents with a progressive fluent aphasia, and is sometimes referred to as semantic dementia. Distinct neuropsychological profiles emerged for these three groups of patients, reflecting the topographical distribution of disease in each group. The cardinal feature of mild AD was impairment of episodic memory, compounded by dysfunction of semantic memory, attention and executive functions (283), while visuospatial function was preserved. Patients with fv-FTD demonstrated severe deficits in attention and executive functions. Although impaired relative to controls, the fv-FTD patients performed significantly better than patients with AD on episodic memory tests, and significantly better than both patients with AD and patients with tv-FTD on tests of semantic memory. Perry and Hodges (283) note that it is the finding of significantly greater involvement of selective attention and executive function (concept shifting) in fv-FTD that provides the best evidence for the differentiation of this group from the other two. Patients with tv-FTD, in contrast, showed severe deficits in semantic memory with preservation of episodic memory, attention and executive function. These preserved abilities differentiated the patients with tv-FTD from patients with AD. Rahman *et al.* (284) similarly confirmed the specificity of the neuropsychological impairments found in fv-FTD by identifying more marked impairments in attentional set-shifting and in risk-taking behaviour in patients with fvFTD.

One further complication in the diagnosis of FTD lies in the heterogeneity of the fv-FTD group. Those with predominant dorsolateral frontal involvement may well show abnormalities on traditional tests of executive functioning, but those with predominant orbitofrontal involvement may perform perfectly on such tests, despite a clear history of behavioural dysregulation (285). In light of the above, perhaps the most interesting approach to the diagnosis of FTD patients has been the use of standardised behavioural rather than cognitive scales. On the Frontal Behavioural Inventory, FTD patients displayed significantly more perseveration, indifference, inappropriateness and loss of insight than patients with other dementias (286). A different behavioural questionnaire, partly derived from the Neuropsychiatric Inventory (287), showed that stereotypic behaviour, changes in eating preference, disinhibition and poor social awareness reliably indicated a diagnosis of FTD rather than AD, whereas executive dysfunction and poor self-care were dependent on dementia severity rather than type (288). The characteristic lack of social awareness in orbitofrontal FTD may be amenable to formal assessment; the "faux pas test" is promising in this regard (289). Of course, the patients in these series had already been assigned to AD or FTD groups on clinical grounds, and the true utility of this promising approach in early disease remains to be tested in prospective series, with longitudinal clinical, or, preferably, pathological verification.

8.3. Vascular dementias

The term "vascular dementias", rather than "vascular dementia", is used deliberately to emphasise that several different processes are subsumed under this heading (290).

Multi-infarct dementia is usually, but not always, straightforward to recognise, through a history of strokes and/or stepwise cognitive decline, and the presence of focal neurological signs and neuroimaging changes. The exact clinical features depend on the locations and extents of the infarcts. However, the various current diagnostic criteria can produce quite different results in the same patient group (291 - 293). The NINDS-AIREN criteria (294) are usually used in research studies; they appear to have low sensitivity but high specificity (170, 291, 295). One of the main problems with the standard criteria apart from those of the ADDTC (296), is their insistence on a definition of dementia in which memory impairment is obligatory. This is unnecessarily restrictive and potentially misleading for causes of acquired cognitive impairment other than AD, and amnesia may not feature prominently in patients with multiple cognitive impairments resulting from vascular disease (162). For this reason, the term "vascular cognitive impairment" may be preferable (162) (v.i.). The separation of AD with multiple infarcts (a form of "mixed dementia") from multi-infarct dementia alone is potentially difficult. The Hachinski Ischaemic Score (297) has been used in this

context, but despite its good sensitivity (0.93) it has very poor specificity (0.17) for mixed dementia when compared with pathological diagnosis (298). Another approach is to rely on clinical judgement that some of the deficits are progressive, and are not accounted for by the known strokes. A biological marker for AD would presumably improve diagnostic accuracy in this situation (163).

Critical infarct dementia, or strategic infarction, occurs when a single (often small) ischaemic lesion, by virtue of its placement, disrupts a number of cognitive networks. Examples would include infarcts of the anterior or medial thalamus, caudate, or dominant angular gyrus. The dramatic cognitive effects of such relatively small lesions can surprise the clinician unaware of these syndromes. Hodges & Graham (299) have provided a useful brief review.

Progressive deep white matter ischaemia causing *small vessel vascular dementia* (SVVD), sometimes called subcortical ischemic dementia, presents the greatest diagnostic problem. It is the commonest form of vascular dementia (300), but despite the work of Esiri (301) and Englund (302), there is no universally accepted pathological gold standard for its diagnosis. Unlike the stepwise decline typically seen with multi-infarct dementia, small vessel vascular dementia, especially the non-lacunar form(s), can be steadily progressive, making separation from AD even more difficult. The use of neuroimaging as a surrogate gold standard is also problematic; MRI is very sensitive but not very specific, and deep white matter T2 hyperintense "lesions" may be due to several different processes, including ischemic demyelination, lacunar infarction, oedema and dilated perivascular spaces (303). These different causes of abnormal T2 signal are likely to be of varying significance for cognition. To complicate matters further, these abnormalities are more common in subjects meeting criteria for probable AD (and DLB) than in aged controls (e.g. 107). Vascular risk factors such as diabetes and hypertension have also emerged as important risk factors in community studies of AD (see 304, for review). It is as yet unclear whether deep white matter ischemia is irrelevant to cognition in AD (305) or whether it summates with AD pathology, reducing the threshold at which AD becomes clinically evident by reducing brain reserve (308, 309). These differing views may be reconciliable if there is a threshold of ischemic burden which must be exceeded for cognitive impairment to occur (308, 309).

It might be thought from the above that SVVD would be an elusive clinical diagnosis, and that the extent of the contribution of deep white matter ischemia to the cognitive decline of AD would be difficult to judge pathologically. Despite the lack of agreed criteria, however, a recognisable syndrome of SVVD does appear to exist (e.g. see 299, 310). Features such as frontal gait disorder ("gait apraxia"), upper motor neuron dysfunction giving rise to pseudobulbar palsy and extensor plantars, and urinary incontinence may be evident on history and neurological examination (311). Despite the uncertainties outlined above, MRI imaging is useful if available, as there appears to be a threshold of about 10 cm^2 above which typical neuropsychological deficits (v.i.) consistently emerge (308, 309). Furthermore, analysis of the distribution of T2 hyperintensities may yield useful information; while a hyperintense diffuse periventricular halo is often non-specific, irregular, more extensive lesions, or those away from the ventricles are more likely to be ischemic (312, 313). Visual ratings of vascular lesion burden by trained observers are sufficiently reliable for most clinical and research settings; computerised volumetry is not required (314).

Most studies comparing neuropsychological findings in AD and vascular dementias have failed to distinguish between the various forms of the latter (315). Such pooling might be expected to blur the neuropsychological distinction of SVVD from AD, by including subjects with infarcts resulting in one or more of the "four A's" of "cortical" dementia: aphasia, apraxia, agnosia, and amnesia. While there is therefore inevitably some overlap with the findings in AD in many cognitive domains, a recent review of 27 adequate studies demonstrated that executive functioning is relatively more impaired and verbal episodic anterograde memory relatively better preserved in vascular dementias compared with AD of similar overall severity (315). A similar picture emerges when SVVD is studied specifically (305, 316): deficits in executive functioning are prominent. These include difficulties with phonemic as *well* as semantic fluency, and impairments of attention, abstraction, and set shifting (317, 318). Slowing of cognition, which may be quantified on tasks such as the trail making test, is also commonly evident (299). Visuoperceptual functioning is typically preserved, and, while information retrieval is often poor, clinical experience suggests that recognition is better preserved than in AD (299). The neuropsychology of vascular dementia has recently been reviewed (316, 319).

As the commonly-used criteria for the diagnosis of dementia (DSM-IV, NINCDS-ADRDA, ICD10) all require memory impairment, it is apparent that some patients with small vessel vascular disease may fail to fulfil these criteria, while nevertheless displaying executive dysfunction. It has been cogently argued that the term "vascular dementia" should be replaced by "vascular cognitive impairment", to direct attention to those at the earliest symptomatic stage of small vessel vascular disease (e.g. 162). This appears sensible, although if testing of recognition memory is undertaken, it is unlikely that non-demented (non-amnesic) patients with vascular cognitive impairment will be confused with AD, where episodic memory impairment is a primary requirement and the earliest neuropsychological feature.

9. SUMMARY

Cognitive assessment remains a cornerstone of the diagnosis and differential diagnosis of dementia. While it can detect neuronal dysfunction satisfactorily, determination of the *cause* of that dysfunction relies on comparison of the pattern of cognitive impairment with the topographical patterns of involvement characteristic of

different causes of dementia. That is, the *presence* of cognitive impairment can be detected directly, but the *cause* must be inferred. Despite this, a positive clinical diagnosis of Alzheimer's disease can be made with reasonable accuracy, relying both on the typical temporal pattern of involvement of cognitive domains and the exclusion of other causes of dementia. The typical evolution of deficits from episodic memory impairment through disruption of semantic memory to involvement of visuoperceptual and executive domains reflects the characteristic spread of neuropathological disease burden from mesial temporal structures through temporal neocortex to temporoparietal and prefrontal association areas. One of the pitfalls of such assessment is the existence of patients with variant presentations of AD. These, too, reflect the topographical distribution of neuronal dysfunction in these patients. At least in patients presenting with language or executive dysfunction, separation from focal cortical atrophy syndromes at presentation can be attempted by detection of impairment in other domains typically involved in AD, such as episodic memory and visuoperceptual functioning. On the basis of the few well-described cases that have come to post-mortem, presentation with progressive visuoperceptual impairment (posterior cortical atrophy) is typically due to Alzheimer's disease. The distinction of AD from two other primary dementias, FTD and DLB, can be difficult on the basis of cognitive testing alone, but recent studies emphasising the structured assessment of cognitive fluctuations (in DLB) and behavioural alterations (in FTD) hold promise.

The concept of vascular dementia is currently in evolution, not least because of the recognition that significant cognitive impairment may exist in the absence of episodic memory disturbance (and therefore dementia, as currently defined). There is also recognition that different types and distributions of vascular damage give rise to different clinical profiles. Perhaps most intriguing is the relationship of deep white matter vascular damage to AD - incidental, additive or an aetiologic factor in its own right. Further detailed clinicopathological study of SVVD is required, although a recognisable clinical presentation does appear to exist.

One of the greatest challenges facing those practising in this field is the detection of incipient AD: that is, AD prior to the development of dementia. This will assume great clinical importance with the advent of disease-altering treatments for AD. There is accumulating evidence that episodic memory impairment, particularly if progressive, presages the development of dementia by up to several years. However, neuropsychological assessment suffers from the inherent limitation that it cannot detect the presence of neuropathology until significant neuronal dysfunction has ensued. Given the decades-long preclinical course of AD neuropathology, a diagnostic test sensitive to and specific for AD neuropathological burden before the advent of widespread neuronal dysfunction is highly desirable. Such a test would also enable refinement of cognitive testing for early symptomatic disease detection.

Once AD has been diagnosed clinically, judgement of disease progression and response to therapy can be achieved efficiently using existing assessment instruments. These roles for neuropsychological assessment, as well as the recognition of individual patterns of cognitive impairment and preservation to underpin design of individualised intervention programs, are likely to remain of importance even if the role of cognitive assessment in disease diagnosis is overtaken by other diagnostic modalities.

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Footnotes: [a] Posterior cortical atrophy may be an exception, with AD typically providing its pathologic substrate (see section 4.3.3.). [b] An exception might be made for those rare patients with an established genetic basis for early-onset familial AD. [c] The Cognistat (Neurobehavioral Cognitive Status Examination), not reviewed further here, has adopted a similar "tripwire" approach.

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