REVIEW ARTICLE

Alzheimer's centennial legacy: origins, landmarks and the current status of knowledge concerning cognitive aspects

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This review commemorates 100 years of research into Alzheimer's disease and, by happy coincidence, the publication of 100 papers in *Brain* on the topic. The first part of the review traces the evolution of concepts and landmarks in the modern history of Alzheimer's disease. It highlights the continuing role of careful clinico-pathological studies which have set the stage for each major leap forwards, such as the emergence of the cholinergic hypothesis, and the realisation that subjects pass through an amnestic prodrome which is thought to reflect dysfunction of the hippocampal formation before the onset of full blown dementia. The contribution of structural and functional imaging is briefly described. The important contribution of publications in *Brain* is illustrated throughout the first section. The second part attempts to review the current status of our knowledge concerning behavioural, neuropsychological and neuropsychiatric aspects of the disease, emphasizing areas of continuing controversy.

Introduction

This review celebrates the 100th Anniversary of Alzheimer's presentation at the Tübingen meeting and also, by coincidence, the publication of 100 papers in *Brain* on the topic of Alzheimer's disease, over a half of which appeared in the last decade. This pattern parallels the phenomenal growth of the global Alzheimer research enterprise since the 1980s which makes it impossible to cover comprehensively any aspect (*see* Table 1). The scope of this review is more limited. The first section traces the evolution of concepts and landmarks in the modern history of Alzheimer's disease. It is the story of Cinderella who was transformed from a poor neglected orphan to a princess after the discovery of a series of glass slippers or, in this case perhaps, glass slides given the central role that neuropathology played in the revival of interest after World War II. I make no apologies for the contribution of publications in *Brain* over the past 50 years to the overall

story. The second part of the review focuses on an area of particular interest: cognitive and behavioural aspects of Alzheimer's disease. Again I attempt to cover the main developments and highlight areas of continuing controversy. Genetics and molecular biology, two giants of the story, are covered in a parallel review (Masters and Beyreuther, 2006).

Historical survey
Alzheimer's case: Auguste D

The story begins at the beginning of the 20th century, a time of tremendous changes in the classification of neurological and mental illness. As always, fortune favoured the well-prepared mind and Alois Alzheimer was well positioned to capitalize on his observations. On November 25, 1901, a 51-year-old woman, Auguste D, was admitted to the

Frankfurt State Asylum where she was examined by this up-and-coming young psychiatrist (*see* Fig. 1). Auguste D had a striking cluster of symptoms that included severely impaired memory, aphasia, erratic behaviour, paranoia and auditory hallucinations, she deteriorated rapidly and appears not to have left hospital. Two years later Alzheimer moved, via Heidelberg, to Munich Medical School to work with the father of modern psychiatry Professor Emil Kraepelin. Alzheimer remained interested in Auguste D's case until her death in Frankfurt on April 8, 1906. Encouraged by Kraepelin he asked for Auguste's brain to be sent to Munich to study in his new neuropathology laboratory. He reported the clinical and pathological findings at a conference in Tübingen on November 3, 1906 under the title of 'On a peculiar disease process of the cerebral cortex' and the proceedings of this meeting were published the following year (Alzheimer, 1907). In his presentation, Alzheimer discussed Auguste D's cognitive and non-cognitive deficits and reported that on post-mortem he found argyrophilic

Table I Growth in papers on Alzheimer's disease 1960s–2000s (from PubMed)

	Total	Basic science	Clinical	Articles in *Brain*
1960s	18	—	—	3*
1970s	290	—	—	2
1980s	5720	54%[†]	46%[†]	10
1990s	18 118	56%[†]	44%[†]	36
2000—2006	13 863	54%[†]	46%[†]	49

*Includes one from 1950s.
[†]Based on a survey of 1000 articles from each decade.

plaques, tangles and atherosclerotic changes in the brain. The invention of silver staining had recently revolutionized neuropathology leading to the identification of plaques and tangles, both of which had been described in the context of senile dementia. The novel aspect in the 1906 case was their occurrence in an unusually young patient, but Alzheimer did not claim to have discovered a new disease. Alzheimer's case notes were lost for almost a century but were discovered in the basement of the University of Munich by Konrad Maurer. This resulted in one of the most famous and fascinating publications of recent times in *The Lancet* (Maurer *et al.*, 1997) which included a photograph of Auguste D and examples of Alzheimer's handwritten notes on Auguste's cognitive status. At that time the slides on which Alzheimer had based his diagnosis were missing but 2 years later they were also discovered by Professor Manuel Graeber. His team were able to extract and test DNA and discovered that she did not carry the e4 allele of the apolipoprotein E gene (Graeber *et al.*, 1998) but have, so far, been unable to screen for genetic mutations associated with early onset disease.

The term Alzheimer's disease was coined by Kraepelin in the 8th edition of his *Handbook of psychiatry* (Kraepelin, 1910) to describe a syndrome of rapidly progressive, young onset, dementia with distinct pathology, that was separable from senile dementia. An analysis of the literature of the time by Berrios (1990) makes it clear that Kraepelin's academic department was under considerable pressure to perform and that the coining of a new disease, discovered by his protégé Alzheimer, was greatly to the department's advantage.
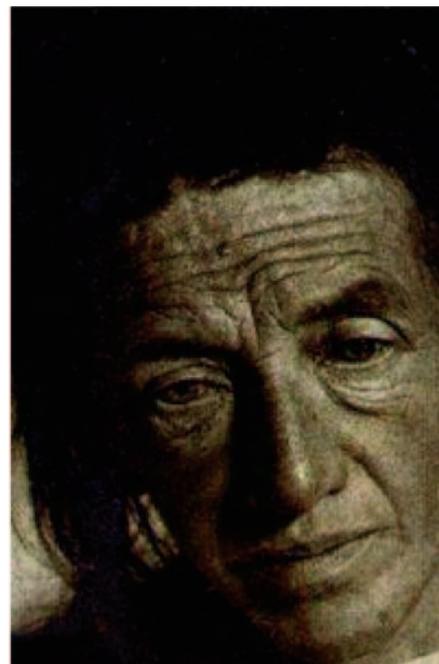

Fig. I Portrait of Alois Alzheimer (1902) and his famous patient Auguste D (from Maurer *et al.*, 1997).

From obscurity to central stage

Kraepelin's declaration of a new disease was controversial and immediately raised issues concerning the relationship between 'Alzheimer's disease' and senile dementia and whether this was truly a separate disorder, as well as the broader question of the relationship between dementia and normal ageing. These two key questions have recurred in the literature over the past century and have yet to be fully resolved (Ballenger, 2006).

For almost 50 years following the 1906 presentation Alzheimer's disease was consigned to a minor role in psychiatry and neurology. This is reflected in the fact that only 10 papers were published in *Brain* between 1906 and 1950 on the topic of dementia, virtually all of which dealt with neurosyphilis and none mentioned Alzheimer's disease. The first paper including Alzheimer's disease in the title was published in 1954 by Corsellis and Brierley (1954) describing an unusual pathological variant and there was then another 10 year gap until the seminal paper describing electron microscopic studies in Alzheimer's disease by Kidd (1964). These two papers are interesting since they were at the centre of the conceptual shift which gradually occurred in the decade after World War II. Until then Alzheimer's disease was regarded as extremely rare and confined to young subjects whereas senile dementia was variously regarded as an exaggerated ageing induced by psychological and/or environmental factors or due to atherosclerotic changes in the brain. This view prevailed into the 1960s as illustrated by a core text, *Lord Brain's Clinical neurology* (2nd edition), which lists Alzheimer's disease as a chief case of presenile dementia, but equates senile dementia and cerebral atherosclerosis. Key to the unification of young onset and more common elderly dementia was the careful clinical delineation of dementia sub-forms coupled with quantitative neuropathology. An important component of this work was spearheaded by Sir Martin Roth in Newcastle whose team demonstrated that the severity of dementia correlated with pathology load (Roth *et al.*, 1966; Blessed *et al.*, 1968). A Ciba Foundation symposium in 1969 brought together researchers from both sides of the Atlantic who presented histopathological and electron microscopy findings and thus set the stage for the ascendancy of Alzheimer's disease (Wolstenholme and O'Connor, 1970).

Modern landmarks in the history of Alzheimer's disease

The 1970s saw an explosion of interest in Alzheimer's disease which centred initially around the application of biochemical techniques and the emergence of the cholinergic hypothesis. Interest in the role of the cholinergic system was triggered by experiments in animal psychopharmacology on the effects of cholinergic blocking and cholinergic enhancing manipulations. Important links between the cholinergic system and cognitive dysfunction were made by Drachman (1974) who reported similarities in the scopolamine-induced cognitive decline in young volunteers to the cognitive deterioration associated with ageing. The cholinergic deficit in Alzheimer's disease was confirmed in 1977 by three separate groups with a series of important publications in *Brain* by Bowen *et al.* (1977*a, b*). Soon afterwards the finding of selective destruction of cell populations in nucleus basalis of Meynert strengthened the cholinergic hypothesis and unified pathology with biochemistry (Whitehouse *et al.*, 1982). The cholinergic discoveries paved the way for the eventual development of the first symptomatic therapies for Alzheimer's disease: the anticholinesterase inhibitors which remain the mainstay of treatment pending the advent of disease-modifying agents. It is now clear that the cholinergic hypothesis was somewhat overstated in that there are more diffuse biochemical changes and, importantly, the cholinergic deficit may not be a particularly early finding in Alzheimer's disease. Indeed, some studies have demonstrated upregulation of choline acetyltransferase activity in the hippocampus and frontal cortex of elderly subjects with very mild Alzheimer's disease (DeKosky *et al.*, 2002). The hypothesis was, however, important as it focused interest on the early cognitive deficits and the need for better assessment methods.

Over the past two decades there has been a shift of emphasis towards the medial temporal lobe as the primary locus of pathology. This shift was again led from pathology with the realization that the earliest changes have a devastating impact on hippocampal connectivity (Hyman *et al.*, 1984) and the pioneering work by Braak and Braak (1991, 1995), in Berlin, who painstakingly worked out a staging of the pathology, particularly tangle formation, with the initial changes occurring in the transentorhinal cortex and subsequent spread into the hippocampal formation proper followed by invasion of posterior isocortical regions (Braak and Braak, 1991, 1995). This pathological staging corresponded to the emergence of more sophisticated neuroimaging techniques which were able to visualize hippocampal and entorhinal atrophy *in vivo* (Jack *et al.*, 1992, 1989; Fox *et al.*, 1996*b*). As will be discussed further latter, the pendulum has swung between a localizationist approach, which emphasizes the focal nature of the early pathology and cognitive deficits, to a more global model of diffuse atrophy in which the hippocampal shrinkage is simply the tip of the iceberg. The application of serial registered MRI images to quantify the rate and distribution of changes over time in individual patients has confirmed the global nature of the brain shrinkage with regional emphasis (Fox *et al.*, 1996*a*, 2001; Scahill *et al.*, 2002).

The advent of metabolic brain imaging in the late 1970s also contributed significantly to our understanding of the disease. A landmark paper published in *Brain* by Frackowiak *et al.* (1981) demonstrated hypometabolism in posterior association cortices and, using 0^{15} positron emission tomography, built on earlier work pioneered in Scandinavia on regional cerebral blood flow (Simard *et al.*, 1971). The cause of these posterior changes has remained an

enigma given the emphasis on medial temporal pathology but modern methods of studying connectivity *in vivo* (e.g. diffusion tensor imaging) seem poised to advance our knowledge (Medina *et al.*, 2006). The advent of PET ligand methods capable of imaging amyloid deposition in the brain (Pittsburgh compound-B) has also shed light on the pathophysiology by showing the widespread deposition of amyloid even early in the course of the disease (Klunk *et al.*, 2004; Archer *et al.*, 2006).

The era of genetics

The past 15 years have been the era of molecular genetic studies of Alzheimer's and have heralded an unprecedented growth in scientific knowledge. Although references were made to inherited forms of Alzheimer's disease during the 1920s and 1930s (e.g. Lowenberg and Waggoner, 1934) their importance was not widely appreciated until the 1970s and 1980s when gradually more autosomal dominant pedigrees were described (Cook *et al.*, 1979; Masters *et al.*, 1981; Bird *et al.*, 1989). By the 1980s molecular genetic techniques, particularly genetic linkage were poised to identify a loci in familial cases. Key to the early hunt was the association between Down's syndrome (trisomy of chromosome 21) and the appearance of Alzheimer's pathology, illustrated by a paper in 1969 published in *Brain* by Olson and Shaw (1969). Shortly before the first reports of genetic linkage, the beta amyloid peptide (the key constituent of amyloid protein found in Alzheimer's disease plaques) were shown to be derived from a larger precursor protein, the amyloid precursor or APP, encoded on the long arm of chromosome 21. APP became the immediate candidate gene when Peter St George-Hyslop *et al.* (1987) demonstrated linkage to the same region of chromosome 21 in four early onset Alzheimer's disease families. As a direct consequence of these observations Goate *et al.* (1991) demonstrated point mutations in the APP gene in one British familial Alzheimer's disease family (Goate *et al.*, 1991). It soon became apparent, however, that APP mutations accounted for only a small proportion of individuals with familial Alzheimer's disease and the race was on to identify other mutations. Linkage was then established to chromosome 14 in some families with early onset disease and Sherrington *et al.* (1995) completed this work when they reported a novel gene, now referred to as presenilin 1 located at chromosome 14 q24.3 which remains the most highly cited paper on Alzheimer's disease. Perhaps the most significant discovery, in terms of overall impact to the burden of disease in the elderly, was the finding of association between gene dose of the apolipoprotein E type 4 allele and the risk of Alzheimer's disease in late onset familial and sporadic cases (Corder *et al.*, 1993; Strittmatter *et al.*, 1993). There is growing evidence that ApoE genotype status may affect the clinical phenotype and rate of progression of Alzheimer's pathology (Mori *et al.*, 2002; Schott *et al.*, 2006).

It is now clear that the vast majority of patients with dominantly inherited Alzheimer's disease present in the presenium, but opinions differ on whether there is a distinct clinical phenotype associated with either early onset Alzheimer's disease in general, or more specifically with genetically determined early onset Alzheimer's disease. This debate has continued ever since Alzheimer's 1906 presentation. A number of clinical studies have suggested that early onset Alzheimer's disease patients have more prominent focal cortical symptoms such as aphasia, apraxia and agnosia than those with Alzheimer's disease of late onset (Seltzer and Sherwin, 1983; Chui *et al.*, 1985) whereas those with late onset disease have been said to have more prominent impairment of memory function. It has also been proposed that early onset patients have a more rapid deterioration. Recent metabolic brain imaging studies have confirmed differential patterns with greater involvement of parietal frontal and subcortical areas in early onset cases as illustrated by a recent *Brain* paper (Kim *et al.*, 2005). As well as their early onset, cases with APP and PS1 mutations are more often associated with motor features notably myoclonus and, in some families, spastic paraparesis (Kennedy *et al.*, 1993; Kwok *et al.*, 1997; Crook *et al.*, 1998). More studies comparing familial and sporadic cases, matched for age, are needed to resolve the important issue of whether Alzheimer's disease should be regarded as a single or multiple disease.

The birth of cognitive studies and the emergence of MCI

On the clinical front, a great deal has been learnt about the cognitive changes associated with Alzheimer's disease. This work led to the emergence of the concept of mild cognitive impairment (MCI) as an amnestic prodrome of full-blown dementia (Petersen *et al.*, 1994, 1999; Fabrigoule *et al.*, 1998; Hodges, 1998; Backman *et al.*, 2001). The cholinergic hypothesis, discussed earlier, focused interest on memory in Alzheimer's disease at a time when cognitive neuropsychological methods were poised to dissect memory into working, episodic and semantic subtypes. Before the 1980s, neuropsychologists had generally considered dementia syndromes to be too messy to study but the situation changed rapidly over a few years. Pioneering studies were undertaken in Kopelman (1989, 1988) and in North American centres, particularly that headed by Nelson Butters, working in collaboration with Robert Katzman and Bob Terry in San Diego. A series of important papers in the 1980s mapped out the cognitive profile and emphasized the severe deficit in episodic memory in early Alzheimer's disease with poor encoding and rapid forgetting of new material (Butters *et al.*, 1983, 1987; Kopelman, 1985; Moss *et al.*, 1986; Heindel *et al.*, 1989; Christensen *et al.*, 1998). It soon became apparent, however, that there is considerable heterogeneity in the cognitive deficits once patients leave the amnesic stage: some patients demonstrate marked impairment of visuo-spatial function, while in others attentional or semantic deficits predominate (Hodges and Patterson, 1995; Perry *et al.*, 2000; Lambon-Ralph *et al.*, 2003). Careful delineation of the cognitive features found in Alzheimer's

disease was also critical to the identification of the non-Alzheimer dementia syndromes particularly semantic dementia (Hodges *et al.*, 1992*a*), other forms of frontotemporal lobar degeneration (Snowden *et al.*, 1992; Evans *et al.*, 1995; Edwards Lee *et al.*, 1997) and dementia with Lewy bodies (Gibb *et al.*, 1987; Hansen *et al.*, 1990; McKeith *et al.*, 1992) many of which were first reported in *Brain*.

In order to identify the earliest cognitive changes, before the stage of global dementia, a number of far sighted investigators began longitudinal studies of patients with isolated memory impairment, normal elderly subjects and enriched populations at high risk because of a family history of genetically determined Alzheimer's disease (Flicker *et al.*, 1991; Fowler *et al.*, 1995; Linn *et al.*, 1995; Tierney *et al.*, 1996; Fox *et al.*, 1998; Petersen *et al.*, 1999; Chen *et al.*, 2000; Albert *et al.*, 2001; De Jager *et al.*, 2003). These studies confirmed that full-blown dementia is preceded by a long phase of slowly progressive cognitive decline and led to the development of the concept of MCI as an amnestic state with a high rate of progression to Alzheimer's disease proper. The introduction of this label is however controversial and the source of considerable confusion. The diagnosis of Alzheimer's disease is only permitted in the presence of progressive cognitive decline, involving two or more areas of cognition, associated with breakdown in social functional or activities of daily living, but it is currently unclear what exactly constitutes a second (above memory) cognitive domain or how to define alterations in daily activities: a judge with poor episodic memory is very disabled whereas an 80-year-old retiree with diffuse cognitive deficits may be coping well at home with the support of their partner. Clinico-pathological studies have established that there is diffuse and relatively advanced pathology even in patients with MCI whose pathology extends beyond the medial temporal lobe (Price and Morris, 1999; Guillozet *et al.*, 2003). Moreover, recent studies have shown that patients with apparently amnesic MCI, defined using simple tasks, perform poorly on more sophisticated cognitive tasks, including tests of attention and semantic memory, thus undermining the concept of MCI as an isolated amnesic disorder (Perry *et al.*, 2000; Dudas *et al.*, 2005). The dividing line between MCI and Alzheimer's disease as currently defined has, therefore, become extremely blurred. The combination of neuropsychological evaluation, with structural and/or metabolic brain imaging, is now highly predictive of those MCI patients destined for more full blown dementia and it seems likely that criteria for Alzheimer's disease will evolve in the next few years to encompass patients at this earlier stage of disease so that effective therapies can be initiated.

Yet another strand in the story has been the status of neuropsychiatric features. Although described by Alzheimer in 1906 they were dropped from descriptions by Kraepelin and were considered for a long time to be secondary, non-core, features of Alzheimer's disease thus distinguishing psychosis and delirium (in which delusions

and hallucinations occurred) from dementia in which such features were not present. Systematic surveys in the 1980s (Berrios, 1989) re-established as a centrality of non-cognitive symptoms and their impact on care-givers.

The remainder of this review examines in more detail the behavioural and neuropsychological findings in Alzheimer's disease highlighting areas of current controversy.

The neuropsychology of Alzheimer's disease: current concepts and controversies

As outlined earlier, a significant shift in thinking occurred in the 1980s; until then Alzheimer's disease was invariably described as causing global cognitive decline. While this remains true of patients in the advanced stages, earlier patients show relatively selective deficits which progress in a relatively predictable pattern through various stages summarized in Table 2. In writing this review it has become clear that the goal of the next decade is to unify the findings from genetic cognitive and imaging studies since these lines of research have developed largely in isolation and that cognitive approaches to understanding the very troublesome neuropsychiatric features of the disease are required.

Episodic memory

Complaints of memory difficulty are by far the commonest initial symptom noticed by the patient, and more particularly by their spouse. As will be discussed later, however, there is a growing number of case reports documenting atypical presentations of Alzheimer's disease (aphasia, visual agnosia, etc.), and it is unclear just how large a minority these represent and whether these atypical presentations are commoner in young onset patients.

It is well established that not all aspects of memory are affected equally in early Alzheimer's disease. The major impairment is in the domain of anterograde episodic memory. The ability to retain new information, such as a story or word-list, after a period is a sensitive measure of early disease (Butters *et al.*, 1987; Welsh *et al.*, 1992; Locascio *et al.*, 1995; Greene *et al.*, 1996; Perry and Hodges, 2000;

Table 2 Stages of cognitive breakdown in typical Alzheimer's disease

	MCI	Mild	Moderate	Severe
Memory				
Working	−	−/+	++	+++
Anterograde episodic	++	+++	+++	+++
Remote	−/+	−/+	++	+++
Semantic	−/+	+	+++	+++
Attention and executive abilities	−/+	++	++	+++
Language (syntax and phonology)	−	−	+	++
Visuospatial and perceptual	−	−/+	++	++
Praxis	−	−	++	++

Key: − absent, + present, −/+ variable.

Clague *et al.*, 2005). Experimental studies have shown that patients have particular difficulty making new cross-modal associations. The Paired Associate Learning Task from the computerized CANTAB battery requires subjects to learn the association between coloured patterns and spatial locations on a computer screen: it is exquisitely sensitive to early Alzheimer's disease and appears to predict patients with MCI who are likely to convert to dementia within 2 years (Sahakian *et al.*, 1988; Fowler *et al.*, 1997; Swainson *et al.*, 2001; Blackwell *et al.*, 2004).

As outlined earlier, it has been assumed that the profound impairment in episodic memory reflects early pathological involvement of the medial temporal lobe when tangles are found in the transentorhinal cortex, effectively disconnecting the hippocampal complex from heteromodal cortical regions, and then later invade the hippocampal formation proper (Hyman *et al.*, 1984; Braak and Braak, 1995). Atrophy of hippocampal related structures can be readily demonstrated *in vivo* using volumetric MRI techniques (Jack *et al.*, 1989, 1992; Fox *et al.*, 1996b). Recent metabolic (FDG–PET) brain imaging cast a somewhat different light by showing substantial hypometabolism of the posterior cingulate region, especially the retrosplenial cortex, which appears devastated even at the phase of MCI (Minoshima *et al.*, 1999; Nestor *et al.*, 2003a, b), a finding in keeping with the recent amnesia literature which highlights this region (Reed *et al.*, 2005). Moreover, a comparison of early Alzheimer's disease with semantic dementia patients suggested a critical role for the posterior cingulate cortex in the genesis of the episodic memory deficit: patients with semantic dementia, who performed well on traditional episodic memory tasks had levels of hippocampal hypometabolism equivalent to that found in Alzheimer's disease but showed sparing of the posterior cingulate (Nestor *et al.*, 2006). In addition, structural imaging using the technique of fluid-registered serial MRI has confirmed volume loss in this region from very early in the course of Alzheimer's disease (Scahill *et al.*, 2002).

In terms of our ability to understand the very earliest cognitive deficits in Alzheimer's disease, patients with sporadic disease provide rather limited opportunities: patients have typically been complaining of memory failure for a number of years and rarely have a pure amnesic syndrome; it is also necessary to follow such patients for years in order to establish that they do indeed have Alzheimer's disease pathologically. By contrast, the study of 'at risk' subjects in families with genetically determined Alzheimer's disease provides the unique opportunity to study the very beginning of the disease. In comparison to the multitude of cognitive studies of sporadic Alzheimer's disease, such investigations are in their infancy, but so far it is clear that impairment in anterograde episodic memory is an early feature in familial Alzheimer's disease which may precede typically a dementia diagnosis by a number of years (Fox *et al.*, 1998). Of relevance to the literature on MCI, and recent imaging findings, is the fact that non-amnestic deficits involving visuo-perceptual abilities, mental speed and attention are also found from a very early pre-clinical stage (Ringman, 2005).

Because patients often become preoccupied with the past, it is commonly believed that such memory is spared in Alzheimer's disease. Systematic research has shown, however, that most patients early in the course of the disease do, in fact, show substantially impaired performance on tests of autobiographical memory, although the degree of impairment is certainly less than that seen on anterograde memory tests. The issue of whether there is a 'so-called' temporal gradient, with sparing of more distant memories, as classically described by Ribot, in amnesic patients remains controversial. Early studies (Sagar *et al.*, 1988; Kopelman, 1989; Greene and Hodges, 1996a, 1997) showed a gentle gradient on autobiographical memory tests but a more recent analysis has suggested a flat pattern with impairment stretching back to childhood, and have suggested that reports of preserved early memories may be artefactual due to the Alzheimer's disease subjects' tendency to relate recurrently the same incidents from earlier in life which renders them more akin to personal semantic facts rather than time episodes (Piolino *et al.*, 2003).

Semantic memory

Work in the early 1990s showed that patients with Alzheimer's disease are also characteristically impaired on tests of semantic memory. Semantic memory refers to our permanent store of representational knowledge including facts, concepts, as well as words and their meaning (Chertkow and Bub, 1990; Hodges *et al.*, 1992b). A recurrent theme over the past decade has been the nature of the semantic deficit, in other words, do patients simply have difficulty accessing knowledge or is there a fundamental loss of knowledge from the brain?

The task which shows the greatest sensitivity in early Alzheimer's disease is category fluency in which subjects generate exemplars from given categories such as animals, fruit or tools. Since category fluency is a task which calls upon a range of cognitive abilities—working memory, executive and phonological skills—as well as semantic memory, it is important to note that initial-letter based (or phonological) fluency is relatively preserved in Alzheimer's disease and that semantic fluency deteriorates at a greater rate than letter fluency as the disease progresses (Rosser and Hodges, 1994; Henry *et al.*, 2004).

It has long been known that naming is also impaired at a fairly early stage in Alzheimer's disease (Bayles and Tolmoeda, 1983; Martin and Fedio, 1983). Analysis of the type of errors has shown that patients with Alzheimer's disease most frequently make semantic, and rarely produce either visual or phonological errors (Hodges *et al.*, 1991). One approach to the issue of impaired access versus degraded knowledge has been to compare performance across a range of semantic memory tests, all of which test

knowledge about the same consistent set of items (e.g. picture naming, word-picture matching, picture sorting, generation of definitions to words etc.). Such studies have shown a striking consistency for individual items across tests (Chertkow and Bub, 1990; Hodges and Patterson, 1995). In other words, if a patient is unable to name a given item in the battery then he (or she) will almost certainly be unable to generate an adequate definition when presented with the name of the same item (Hodges and Patterson, 1995).

A complementary approach has been to use implicit tasks which assess semantic priming effects, typically lexical decision with manipulation of the semantic relatedness between words (co-ordinates: lion–tiger versus attributes: zebra–stripe etc.). This work produced variable, and controversial, results but an emergent finding has been the presence of so-called 'hyperpriming', particularly for semantic co-ordinates. Important work from Caen combined explicit and implicit studies showing that hyperpriming for individual items correlated with impairment on explicit tasks but cross-sectionally and over time (Giffard *et al.*, 2001, 2002).

Another theme in the investigation of semantic deficits in Alzheimer's disease concerns the issue of so-called category specificity. It is well known that patients with temporal lobe damage after herpes simplex encephalitis may show selective loss of semantic knowledge concerning natural kinds (Warrington and Shallice, 1984; Warrington and McCarthy, 1987), whereas other patients' parietal damage can show the opposite pattern, that is selective preservation of knowledge of natural kinds compared with artefacts. Studies of Alzheimer's disease have produced conflicting results, but a large-scale longitudinal and prospective investigation showed an artefact advantage similar to that seen following herpes encephalitis but to a much smaller degree and with considerable inter-individual variability (Garrard *et al.*, 1998, 2001). A multiple single-case strategy revealed not only individuals with consistent advantages for artefacts but also individuals with consistent advantages for natural kinds which appeared to reflect the distribution of pathology as reflected in the profile of other cognitive deficits.

One component of semantic knowledge which seems particularly vulnerable to the ravages of Alzheimer's disease is the knowledge of people: patients commonly complain of difficulty with proper names which might be due to name access or a loss of underlying conceptual information. A number of cognitive studies have suggested that the deficit is primarily semantic and occurs at a very early stage of the disease (Greene and Hodges, 1996*b*; Thompson *et al.*, 2002).

Attentional and executive deficits

By the time most patients are diagnosed with established Alzheimer's disease deficits in attention are usually apparent. Patients are described by carers as distractible, lacking in concentration, slowed up, and easily muddled by tasks which were previously routine, such as setting the washing machine or planning the weekly shopping. At a theoretical level, there has been considerable interest in which aspects of attention are impaired and at what stage of the disease. Attentional processes are often characterized in terms of selective, sustained and divided attention (for review *see* Perry and Hodges, 1999). Although all aspects are impaired at a fairly early stage of the disease, the first component to become impaired appears to be the selective attentional system particularly the inhibitory processes required to perform tasks such as the Stroop test (Perry and Hodges, 1999; Amieva *et al.*, 2004; Pignatti *et al.*, 2005). The putative neural basis of selective attention involves a network of lateral parietal and anterior midline structures (e.g. the cingulate gyrus). Involvement of the basal forebrain cholinergic system may also play an important role in the genesis of attentional dysfunction in Alzheimer's disease (Lawrence and Sahakian, 1995).

Important work by Baddeley *et al.* (1991, 2001) established that there are also deficits on tests of divided attention (the central executive component of Baddeley's working memory model), such as dual-performance tests, in which subjects are required to divide their attention between two simultaneously presented streams of information (e.g. trail making and digit span) which become more evident as the disease progresses.

Sustained attention, or vigilance, may be defined as the ability to focus attention on a task over an unbroken, but prolonged, period of time and is most frequently measured by the speed and accuracy of detecting infrequent and unpredictable targets among more frequent non-targets. In Alzheimer's disease, performance on such tasks declines but only at a later stage of the disease (Sahakian *et al.*, 1988; Perry and Hodges, 1999).

Executive function refers to higher-order cognitive abilities that are called upon to formulate new plans of action, to select and monitor the appropriate sequence of actions. Disorders of executive function have been linked to the dorsolateral prefrontal cortex. Classic tests of executive function include Raven's Progressive Matrices, the Tower of London Test, Trail Making, and the Wisconsin Card Sorting Test. Breakdown in executive ability is virtually always present in patients with established Alzheimer's disease (Kopelman, 1991; Perry and Hodges, 1999). Although MCI is typically characterised as an amnesic syndrome there is growing evidence that most, if not all, subjects who later progress to dementia have attentional and/or executive deficits if appropriate experimental tasks are administered although they are overshadowed by the amnesia (Tales *et al.*, 2005*a*, *b*).

Visuo-spatial and perceptual deficits

At a clinical level, visuo-spatial and perceptual symptoms are usually not early features, but rather follow in the wake of episodic memory and attentional deficits (Perry *et al.*, 2000; Caine and Hodges, 2001). Occasionally, however, visual

symptoms dominate in the so called visual variant of Alzheimer's disease often referred to as posterior cortical atrophy (*see* later). In more typical cases, deficits arise first on complex tasks which require perceptual analysis and spatial planning such as Block Design or copying the Rey Complex Figure. More recent work employing psychophysical techniques have shown deficits in visual motion and rapid serial processing which may be very relevant to driving competency (Rizzo *et al.*, 2000; O'Brien *et al.*, 2001; Kavcic and Duffy, 2003; Uc *et al.*, 2005).

Neuropsychiatric features

The cognitive paradigm which has dominated clinical research in Alzheimer's disease, as reflected in current criteria for both dementia and MCI, has led to a relative neglect of neuropsychiatric phenomena which, as we have seen at the start of this article, were particularly prominent in Auguste D. A key development over the past few years has been the availability of robust carer-based instruments to assess such features particularly the Neuropsychiatric Inventory (Cummings, 1997). The most prominent behavioural symptom is apathy which has been found in between 25% and 50% of cases. Depression is the main psychiatric correlate of apathy in Alzheimer's disease, an expected finding given that loss of interest and motivation is a conspicuous symptom of both syndromes. Apathy, however, should not be construed as a mere symptom of depression given that half of Alzheimer's disease patients with apathy have no concomitant depression. The prevalance of apathy increases with increasing severity of dementia. Several studies have demonstrated a significant association between apathy and both reduced metabolic activity in the frontal lobes and more severe parkinsonism suggesting that neuropathological changes in specific brain areas may underlie the high frequency of apathy in Alzheimer's disease. A recent study has shown that apathy is a behavioural marker of more aggressive dementia chatacterized by faster progression of cognitive, functional and emotional impairment (Starkstein *et al.*, 2006).

Delusions are commoner than hallucinations with estimates of frequency ranging from 20% to 70% (Rao and Lyketsos, 1998). Paranoid delusions, often involving theft, are probably the most common type. Misindentication phenomena and the Capgras delusion, in which patients believe that a close relative has been replaced by an imposter, may occur. Hallucinations, usually visual, are rare in the early stages but increase in prevalence with disease progression reaching almost 50% in some series (Mega *et al.*, 1996). Challenging behaviours including shouting, aggression, agitation, disinhibition and irritability are also common and appear independent of psychosis or depression. Stereotypic ritualized behaviours and changes in eating patterns with a preference for sweet foods that characterize frontotemporal dementia are relatively rare in Alzheimer's disease (Bozeat *et al.*, 2000). Very little work has been done on the cognitive or neural basis of these behavioural changes which impose a huge burden on caregivers.

Insight

Patients with Alzheimer's disease may lack insight into their cognitive difficulties (so-called anosognosia), although this feature has been over-emphasized in the past. A meta-analysis of 16 studies (Markova and Berrios, 2000) highlighted the methodological differences in assessment of insight and of dementia, and the not surprising contrast in conclusions between studies. Nevertheless, certain trends have emerged: most studies suggest that insight is preserved early in the disease and diminishes with progression of the disease although there is marked variability. Analysis of the relationship between disease severity and loss of insight shows mixed results with findings varying between a strong positive correlation (Vasterling *et al.*, 1997), a weak association (Michon *et al.*, 1994) and a lack of relationship (Reed *et al.*, 1993). There appears to be some degree of consensus that Alzheimer's disease patients with prominent frontal involvement—as judged by either SPECT hypoperfusion (Starkstein *et al.*, 1995) or scores on frontal dysfunction tests (Michon *et al.*, 1994) show less insight.

Atypical presentations of Alzheimer's disease

Many reviews give the impression that Alzheimer's disease virtually always presents with amnesia. Indeed this is also a fundamental principal underlying the concept of amnestic MCI. Although it remains true that the majority of cases present in this way, there are a growing number of reports of atypical focal presentations, two of which are particularly prominent in the literature: progressive aphasia and posterior cortical atrophy. Patients with progressive aphasia are classified under the general rubric of frontotemporal dementia (or frontotemporal lobar degeneration) and can be characterized either as progressive non-fluent aphasia or semantic dementia (Hodges and Miller, 2001; Neary *et al.*, 1998). Somewhat paradoxically, given the prominence of semantic deficits in Alzheimer's disease, semantic dementia appears to be associated with Alzheimer's pathology very infrequently (Davies *et al.*, 2005). By contrast, progressive non-fluent aphasia is more often the result of Alzheimer's disease: in a recent Cambridge series a third of cases had Alzheimer's disease pathology (Knibb *et al.*, 2006). In addition to the patients with isolated progressive aphasia a much larger number of patients present to specialist clinics with predominant language impairment but in the context of more generalized cognitive dysfunction and acquire a label of atypical Alzheimer's disease. The frequency of such cases in unbiased community samples is unclear and requires further study.

The other commonly reported variant of Alzheimer's disease was highlighted by Benson (1988) under the title

of posterior cortical atrophy to reflect the distribution of structural changes on imaging. A number of subsequent reports have established that within this broad category a number of different presentations may occur (Mackenzie-Ross *et al.*, 1996). Very occasionally there is progressive visual loss with restriction of fields and a severe apperceptual agnosia. More commonly basic low-level functions (acuity, colour and shape detection etc.) are preserved but patients have severe problems with high-level visual analysis causing alexia colour and object agnosia reflecting involvement of the ventral occipito-temporal pathway. The third, and most common, visual variant presents with features of Balint's syndrome namely simultagnosia, visual disorientation, severe problems with navigation and optic ataxia (Hecaen and De Ajuriaguerra, 1954; McMonagle *et al.*, 2006). The majority of patients with posterior cortical atrophy have Alzheimer's pathology (Galton *et al.*, 2000) but again the prevalence of this atypical presentation is unknown. Interestingly these atypical visual variants appear to be less strongly associated with the presence of apolipoprotein E4 than the usual amnestic presentation (Hashimoto *et al.*, 2001; Schott *et al.*, 2006).

In addition there have been reports of cases presenting with a pure right hemisphere syndrome (Crystal *et al.*, 1982) and with a progressive gait disorder resembling that seen in corticobasal degeneration (Boeve *et al.*, 1999; Rossor *et al.*, 1999). In Cambridge, half of a series of 10 patients with the corticobasal syndrome have had Alzheimer's disease pathology (J. Hodges, unpublished data).

Conclusions

A great deal has been learnt about the cognitive and behavioural aspects of Alzheimer's disease. Much of the recent work has focused on the amnesic and related this to pathology in the medial temporal lobe. While undoubtedly important, there is emergent evidence of more diffuse cognitive impairment and that other regions, such as the posterior cingulate cortex, might be equally important. The prevalence of so-called atypical presentations is also unresolved. Little attention has been given to the cognitive and anatomical basis of the neuropsychiatric features which present such a burden to care-givers. Future studies should attempt to unify genetic, imaging and cognitive aspects with greater emphasis of predictors of slow or fast decline and, hopefully, response to therapies as disease-modifying agents become available.

Acknowledgements

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