

Alzheimer's Disease Versus Normal Ageing: A Review of the Efficiency of Clinical and Experimental Memory Measures

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ABSTRACT

This paper reviews research findings concerning memory performance in Alzheimer's disease (AD) and normal ageing. Studies using clinical (i.e., episodic) memory tests are compared with studies using various experimental memory paradigms (semantic memory, implicit memory, working memory), in order to determine their efficiency to differentiate between AD and normal ageing. In addition, attention is focused on early and preclinical AD. It is argued that traditional clinical memory tests alone are not best able at detecting AD at an early stage. More specifically, tasks calling upon semantic knowledge may aid to an earlier and more efficient assessment of AD.

It is well known that elderly persons as well as dementia patients exhibit a decline in their functioning of memory. In an early stage of dementia, and especially in a preclinical phase, the distinction with memory problems common at an advanced age is difficult. The clinical definition of dementia, as proposed by the *Diagnostic and Statistical Manual of Mental Disorders* (DSM-IV; American Psychiatric Association, 1994), emphasises symptoms of memory impairments. DSM-IV defines these impairments as "an impaired ability to learn new material or the forgetting of previously learned material" (p. 134). Clinical memory tests, for example, used to assess dementia, are constructed according to this definition of memory impairments. In the past decades, the collection of available clinical memory tests has expanded substantially, including many variants on tests measuring the ability to learn new material. These variants usually refer to the various modalities of the material to be memorised or different demands on the reproduction process.

The developments in experimental memory research show a different view. Although memory was originally considered as a single unitary system, many experimental studies of the past decade showed that memory might be better viewed as consisting of various subsystems that are most likely subserved by different (sets of) brain structures (Schacter & Tulving, 1994; Squire, 1992).

This development cannot be seen within clinical memory testing, which still proposes memory as a single entity, though tests can be subdivided according to the modality of the material to be memorised (verbal, visual), the different demands on the reproduction process (free recall, cued recall, recognition), or the length of the interval between the learning phase and the reproduction phase (immediate recall, delayed recall). For example, the Wechsler Memory Scale – III (Wechsler, 1997) contrasts these various aspects of memory testing. Nonetheless, in experimental memory terms, clinical

memory testing is almost exclusively based on the measurement of *episodic memory* – the conscious recollection of previous personal experiences or episodes – tested by, for example, word list learning or recognising pictures. However, both cognitively healthy elderly people and dementia patients in their early stages show deficits in episodic memory performance. Not until the disease progresses, performance differences become evident.

In this paper, it is investigated whether other memory systems than episodic memory (i.e., the traditional clinical memory measures) differentiate better between normal ageing and (early) dementia: e.g., *semantic memory* (the store of facts and general knowledge, including the mental lexicon) and *implicit memory* (the non-conscious influence of past experiences on subsequent performance). Semantic memory in particular, but also certain forms of implicit memory, are alleged to be relatively spared in normal ageing, contrary to early phase dementia (i.e., *Alzheimer's disease* (AD) in particular; e.g., Fleischman & Gabrieli, 1998; Nebes, 1992; Salmon & Heindel, 1992). However, semantic and implicit memory are hardly ever explicitly implemented in clinical memory tests. It should be noted that there are several clinical tests that do measure aspects of semantic memory (e.g., several subtests of verbal intelligence of the WAIS-R (Wechsler, 1981), the Boston Naming Test (Kaplan, Goodglass, & Weintraub, 1983), or various tests of category fluency). However, these tests are hardly ever *interpreted* as measures of semantic memory. Experimental neuropsychological research, on the other hand, pays more and more attention to these memory systems.

The aims of this paper are two-fold. First, clinical (i.e., episodic) and experimental memory measures are compared in their efficiency to differentiate between AD and normal ageing. Therefore, a review will be presented of experimental research findings, reflecting the performance of dementia patients and normal elderly controls on tasks representing the different memory systems. The ability of the DSM-IV criteria and the available clinical memory tests to describe the cognitive profile of AD, known from the experimental studies, will be discussed.

Attention will be focussed on AD, the type of dementia with the highest prevalence. AD is characterised by a gradual onset and a slow progressive cognitive decline. Thus, the course of AD makes it particularly difficult to detect it at an early stage. At the same time, early assessment is crucial for the efficacy of future treatment opportunities. The second aim of this paper is, therefore, to attempt to describe the impairments occurring in an early (or even preclinical) phase of the disease, and the corresponding measures to detect them. Unfortunately, most experimental studies use AD patients who are in an advanced stage of their disease. The few studies that specifically focus on preclinical AD patients use episodic (i.e., clinical) memory measures. Therefore, the studies using diagnosed AD patients but in the earliest stage ('minimal' AD) or with the highest scores on cognitive screening tests (e.g., MMSE > 23) were also selected for a preliminary investigation of this question.

This paper will start with a brief description of, firstly, clinical memory measures and, secondly, experimental memory measures. Thirdly, the review of experimental research findings regarding memory performance of AD patients and normal elderly controls will be presented. Characteristics of each study concerning age, education and stage or severity of AD of the subjects will be available in the Appendix (Table A1). Subsequently, memory performance characteristics of preclinical and very early AD patients, known from the limited number of available studies, will be described. Finally, these findings will be integrated in order to discuss the two questions described above.

CLINICAL MEMORY MEASURES

The collection of available memory tests used in clinical settings may be subdivided into two main types: tests measuring the ability to *learn new information*, and *remote* memory tests requiring the retrieval of old, previously learned information. The majority of clinical memory tests may be categorised as tests of learning new information.

The classification of the tests of learning new information appears to be strongly influenced by

perceptual *modality* of the stimuli, mainly verbal and visual. However, many alleged visual memory tests contain stimuli susceptible to verbal encoding. For example, in Rey's Visual Design Learning Test (Rey, 1968), each item contains two elements that are easily verbalisable (e.g., a dot in a circle, a triangle above a horizontal line). The Visual Spatial Learning Test (Malec, Ivnik, & Hinkeldey, 1991), on the other hand, makes use of a 6×4 grid and seven stimulus items placed on the grid, which provides different nonsense designs that are difficult to verbalise.

Furthermore, the tests are classified according to the degree of inherent *organization* of the material being memorised and to the *mode of reproduction*. Successful free reproduction (i.e., without giving any cues for retrieval) of semantically and phonologically unrelated items requires the initiation of elaborative encoding strategies and active retrieval processes. A relevant and frequently administered example is the Rey Auditory Verbal Learning Test (Rey, 1964). Recalling a previously told story – as in the

California Discourse Memory Test (Kramer, Delis, & Kaplan, 1988) – requires less self-initiated encoding, because the material to be reproduced possesses a meaningful structure itself (which usually aids the retrieval process). Similarly, learning semantically associated pairs of words will take less time and effort than learning unrelated pairs of words (as in the Verbal Paired Associates subtest of the Wechsler Memory Scale – Revised (Wechsler, 1987)). Tasks asking for the recognition of previously presented items out of an array of old and new items demand the least amount of retrieval effort (provided that the items were sufficiently encoded) and this form of testing memory is typically referred to as 'passive' retrieval. At the same time, accurate recognition of target items may be complicated by the introduction of semantically and/or phonologically related nontarget items (e.g., implemented in the Hopkins Verbal Learning Test (Brandt, 1991)).

In addition, many tests include a *delayed recall* trial in order to determine the rate of forgetting of

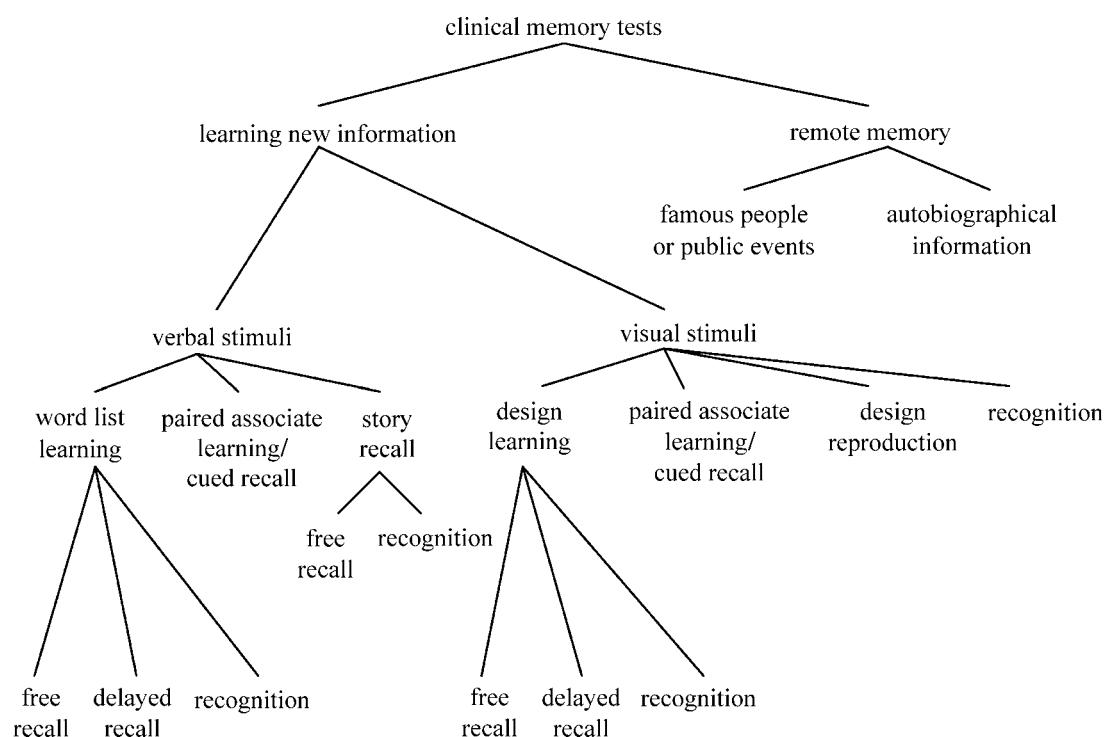


Fig. 1. Classification of clinical memory tests (e.g., after Lezak, 1995).

newly learned information. The degree of retention of material is usually tested after 20–30 min. Figure 1 illustrates a model for classification of clinical memory tests (e.g., see Lezak, 1995, for examples of specific tests).

EXPERIMENTAL MEMORY MEASURES

Current experimental memory research is usually based on the division of memory components presented in Figure 2. The concept of *working* (or short-term) memory and its corresponding subsystems is based on the working memory model proposed by Baddeley and Hitch (1974). Long-term memory is now often divided into *explicit* (conscious) and *implicit* (unconscious) memory (Schacter, 1992; Tulving & Schacter, 1990). This division is also termed the declarative–nondeclarative distinction, where *declarative* (explicit) memory refers to conscious recollections of facts and events, while *nondeclarative* (implicit) memory refers to a heterogeneous collection of nonconscious memory abilities including skills and habits, priming and simple conditioning (Squire, 1992).

Within the concept of explicit memory, or declarative memory, two subsystems may be distinguished, originally defined by Tulving (1972) as episodic and semantic memory. *Episodic* memory refers to the system involved in recollecting particular personal experiences or episodes (events) and is most closely associated with the clinical approaches to learning and memory (categorised as the ability to 'learn new

information'). Episodic memory can be measured by means of free recall (as in list-learning tests), cued recall and recognition tests – whether verbal or nonverbal. *Semantic* memory refers to the store of facts and general knowledge, including mental lexicon (the meaning of words and concepts, vocabulary) or "...the associative network of permanent knowledge about the world which has been built up over one's lifetime" (Ober, Dronkers, Koss, Delis, & Friedland, 1986, p. 76). As opposed to episodic memory, semantic memory is not learning-context dependent: it is not necessary to remember the particular occasion on which one had acquired the particular knowledge item. Examples of semantic memory tasks are verbal (or category) fluency, word identification tasks and (object) naming. Semantic memory is also reflected in the type of clinical memory tests categorised as 'remote' memory tests (though these tests do not represent knowledge of mental lexicon).

Implicit (or nondeclarative) memory can be divided into several learning processes, such as priming, procedural memory and more primitive learning processes (e.g., classical conditioning). These learning processes all share in common that experience alters behaviour nonconsciously without providing access to any memory content (Squire, 1992). *Priming* refers to the improvement in performance on information that one has recently processed, without the need to consciously remember this previous processing. Examples of tasks that intend to measure priming effects are perceptual identification of words, free association, lexical decision, word stem

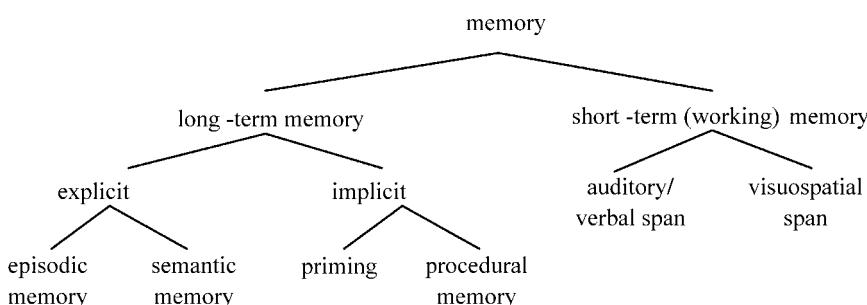


Fig. 2. Components of memory (e.g., after Baddeley & Hitch, 1974; Schacter & Tulving, 1994; Squire, 1992; Tulving, 1972).

completion, word fragment completion and picture completion. *Procedural* memory refers to the acquisition of skills, whether motor, perceptuomotor, (verbal-perceptual or cognitive skills. 'Skill learning' implicates the acquisition of procedures and operations that occurs gradually with repeated exposure to items. Skill learning is demonstrated by general improvement on a task as a function of practice rather than improvement on a specific item within that task (e.g., when new words that have not been presented before in the experiment are read faster across successive trials). Skill learning may be tested by the serial reaction time task, mirror tracing, the pursuit rotor task, reading transformed script or maze learning.

REVIEW OF MEMORY FUNCTIONING IN AD VERSUS NORMAL AGEING

This section presents a brief summary of relevant experimental research findings on differences in memory performance between AD and normal ageing. Journal articles were obtained from computerised database searches of PsychInfo between 1983 and 1998. The key words were: Alzheimer's disease, ageing, episodic memory, cued recall, free recall, semantic memory, fluency, short-term memory, priming, word identification, skill learning and mirror reading. Some articles were also located by citation. Studies were included only if a group of AD patients was directly compared with an appropriate control group. The findings will be organised according to the division of memory components, as was illustrated in Figure 2. More detailed information of each study, regarding demographic variables (i.e., age and education) and severity of disease, can be found in Table A1 of the Appendix.

Episodic Memory

AD patients perform worse than older normal control subjects on *free recall* of word lists (e.g., Eslinger & Damasio, 1986; Martin, Brouwers, Cox, & Fedio, 1985; Spinnler, Della Sala, Bandera, & Baddeley, 1988). Greene, Baddeley, and Hodges (1996), using the Doors and People Test (Baddeley, Emslie, & Nimmo-Smith, 1994),

did not find a difference between verbal and visual recall. Furthermore, they reported no differences in forgetting rate between older normal control subjects and AD patients, when comparing immediate and delayed recall trials. In addition, AD patients exhibited many intrusions in word recall (Helkala, Laulumaa, Soininen, & Riekkinen, 1989).

Semantic *cueing* does not improve recall performance of AD patients, possibly because of deficient semantic encoding (e.g., Bird & Luszcz, 1991; Bondi & Kaszniak, 1991; Chertkow & Bub, 1990; Monti et al., 1996; Russo & Spinnler, 1994). Sailor, Bramwell, and Griesing (1998) suggested that AD patients have a specific deficit in the ability to evaluate semantic relations. They are no longer able to discriminate between two related concepts, because the attribute knowledge that distinguishes these concepts is lost.

AD patients do not perform relatively better on verbal *recognition* tasks than on recall tasks (e.g., Abbenhuis, Raaijmakers, Raaijmakers, & Van Woerden, 1990; Deweer, Pillon, Michon, & Dubois, 1993; Eslinger & Damasio, 1986; Fleischman et al., 1996; Grosse, Wilson, & Fox, 1990; Heindel, Butters & Salmon, 1988; Koivisto, Portin, & Rinne, 1996; Russo & Spinnler, 1994;). AD patients seem incapable of learning due to deficient encoding rather than due to impaired retrieval since their free recall performance is as poor as their recognition performance (Greene et al., 1996). Greene et al. found their patients to be equally impaired on visual and verbal recognition trials of the Doors and People test. Eslinger and Damasio (1986) reported that AD patients were also unable to recognise previously presented pictures of unfamiliar faces. Furthermore, Keane, Gabrieli, Growdon, and Corkin (1994) found that AD patients performed poorly on the recognition of pseudowords. Noteworthy for the recognition performance of AD patients is that they make relatively many false positive errors, compared to false negative errors (Deweer et al., 1994). They appear unable to inhibit irrelevant associations (Helkala et al., 1989). Brandt, Corwin, and Krafft (1992) explained the AD patients' high number of false positive errors by their inability to discriminate between different semantic relations in the

presented material: they were sensitive to category membership of words, but could not discriminate between different semantic attributes of words *within* a given category.

In addition to AD patients, normal elderly people also exhibit episodic memory problems. Normal elderly subjects typically have problems with free recall conditions (e.g., Java & Gardiner, 1991; Jelicic, Craik, & Moscovitch, 1996; Spinnler et al., 1988), but they exhibit normal benefit from (semantic) cueing and inherently structured material (e.g., Bäckman & Wahlin, 1995; Hart, Colenda, Dougherty, & Wade, 1992; Monti et al., 1996). Their recognition performance is a little less efficient than that of younger subjects, but this difference is negligible compared to their impairment on free recall tasks (e.g., LaVoie & Light, 1994).

It may be concluded that AD patients suffer from a general episodic memory deficit: they cannot benefit from cueing or inherent structure and their recognition ability is as impaired as their free recall performance. AD patients show impaired learning rather than accelerated forgetting or disrupted retrieval. In addition, AD patients perform deficiently on episodic memory tasks, regardless of the perceptual modality of the stimuli used in these tasks. The relative insignificance of delayed recall trials and perceptual modality is an important finding considering that clinical memory testing is strongly influenced by these factors (see Fig. 1).

However, it is rather unlikely that the deficit in the benefit from semantic cueing or recognition (including false positive errors) occurs in a very early stage of AD (e.g., Hedges & Patterson, 1995). Studies reviewed in this section usually examined AD patients whose diagnosis is based on symptoms occurring for several years, rather than very early (or even preclinical) stage AD patients whose diagnosis was confirmed subsequently (see also Appendix, Table A1).

Semantic Memory

As a measure of semantic memory many studies use the *verbal* (or *category*) *fluency* task, in which the subject must name as many exemplars of a particular category – for example, animals, vehicles, fruits and vegetables or supermarket

items – as he can think of within a certain time limit. AD patients consistently perform deficiently on verbal fluency, compared to normal elderly controls (e.g., Beatty, Testa, English, & Winn, 1997; Hedges, Salmon, & Butters, 1990; Hedges & Patterson, 1995; Mickanin, Grossman, Onishi, Auriacombe, & Clark, 1994; Monsch et al., 1992; Sailor et al., 1998; Salmon, Heindel, & Butters, 1992). AD may lead to a specific disruption in semantic knowledge, characterised by a difficulty in differentiating between items within the same semantic category concurrent with relative preservation of broader categorical information (Martin & Fedio, 1983). This is called the *bottom-up breakdown* of semantic knowledge and is often used to explain the nature of the performance by AD patients (e.g., Binetti et al., 1995; Monsch et al., 1994; Ober et al., 1986; Rosser & Hedges, 1994; Salmon, Shimamura, Butters, & Smith, 1988; Tröster, Salmon, McCullough, & Butters, 1989). Weingartner, Kawas, Rawlings, and Shapiro (1993) noted that changes in semantic memory are detectable *before* the diagnosis of AD can be made: first, the patients are not able to name low-frequency exemplars and later they lose more common elements. It is concluded that in AD, loss of knowledge is the cause of impaired verbal fluency performance, rather than deficient initiation of retrieval (e.g., Monsch et al., 1994; Randolph, Braun, Goldberg, & Chase, 1993; Rosser & Hedges, 1994).

Normal elderly subjects typically perform better on the category fluency task than on the *letter fluency* task, in which as many words beginning with a particular letter as one can think of must be named within a certain time limit. AD patients show the reverse pattern: they perform better on letter fluency than on category fluency, although both types of performance are impaired (e.g., Mickanin, Grossman, Onishi, Auriacombe, & Clark, 1994; Monsch et al., 1994; Rosser & Hedges, 1994). This pattern of performance usually differentiates AD patients and normal elderly controls and illustrates the clear semantic memory problems of AD patients, relative to normal elderly controls. In addition, AD patients may be detected by their qualitative performance on the category fluency task: in addition to

naming few correct exemplars in general, they typically name the most common elements (i.e., preservation of broad category information) and produce few different subcategories and few items per subcategory and relatively many category labels (e.g., Beatty et al., 1997; Martin & Fedio, 1983; Ober et al., 1986; Tröster et al., 1989).

As was mentioned before, verbal fluency is the most frequently and extensively used task to examine semantic memory. Alternative tasks include: confrontation naming (e.g., the Boston Naming Test); vocabulary (e.g., in WAIS-R); naming in response to verbal description and semantic feature questions (Hodges & Patterson, 1995); sentence verification (answering category and property statements; Sailor, Bramwell, & Griesing, 1998). All these tasks showed deficits for AD patients, compared with normal elderly controls.

Hodges and Patterson concluded that semantic memory is also impaired in a very early stage – ‘minimal’ AD patients with a *Mini-Mental State Examination* score (Folstein, Folstein, & McHugh, 1975) above 23. Thus, it may be argued that semantic memory performance might be a better early marker for AD than (purely) episodic memory performance (i.e., episodic memory performance that is relatively unaffected by semantic processing capacities, as in free recall of inherently unstructured lists of words). This suggestion is supported by the finding that normal elderly controls also show impaired performance in free recall conditions, (as was discussed in the previous section). However, elderly controls perform normally on tasks sensitive to semantic processing capacities, which is in contrast with AD patients’ performance. In the section on very early and preclinical AD, these issues will be discussed in more detail.

Short-term (or Working) Memory

No evident differences in the *auditory/verbal span* between early (or minimal) AD patients and normal elderly controls were found (e.g., Carlesimo, Fadda, Lorusso, & Caltagirone, 1994; Hodges & Patterson, 1995; Morris, 1994). Only in moderate dementia patients performance was significantly poorer than in normal elderly subjects

(Orsini, Trojano, Chiacchio, & Grossi, 1988). However, AD patients (also when in an early stage) exhibited a significantly smaller *visuospatial span* than normal elderly controls (e.g., Carlesimo et al., 1994; Orsini et al., 1988; Spinnler et al., 1988; Trojano, Chiacchio, De Luca, & Grossi, 1994). This deficit was also shown when the sequence of to be recalled patterns was not important (Grossi, Becker, Smith, & Trojano, 1993). Apparently, AD patients suffer from a specific disorder of visual working memory.

Implicit Memory: Priming Effects

Relative to normal elderly controls, AD patients exhibit a normal repetition priming effect, when tested by means of perceptual identification of words (e.g., Abbenhuis et al., 1990; Gabrieli et al., 1994; Keane, Gabrieli, Fennema, Growdon, & Corkin, 1991; Koivisto et al., 1996; Meiran & Jelicic, 1995; Russo & Spinnler, 1994). In addition, preserved priming effects were found in other tasks as well: perceptual identification of pseudowords (Keane et al., 1994), reading mirror-words (Deweer et al., 1993, 1994; Grober, Ausubel, Sliwinski, & Gordon, 1992), perceptual identification of incomplete pictures (Gabrieli et al., 1994). In general, perceptually based priming effects are preserved in normal ageing as well as in AD, despite poor explicit memory for the stimuli used.

Priming effects on word stem completion tasks are less consistent for AD patients. Most studies concluded that AD patients perform deficiently (e.g., Bondi & Kaszniak, 1991; Butters, Heindel, & Salmon, 1990; Carlesimo, Fadda, Marfia, & Caltagirone, 1995; Gabrieli et al., 1994; Keane et al., 1991, 1994; Meiran & Jelicic, 1995; Salmon et al., 1988; Shimamura, Salmon, Squire, & Butters, 1987). But some studies report the contrary. For example, Grosse et al. (1990), as well as Fleischman et al. (1996), demonstrated intact word stem completion priming by AD patients after a semantic/conceptual encoding task – though numerous studies mentioned above also used semantic encoding tasks – despite poor recognition of the material. Fleischman et al. could not explain their findings by differences between studies in study-test interval, number of study-phase exposures, encoding modalities

engaged or item type. They suggested, instead, that the pattern of intact and impaired word stem completion priming across independent AD studies reflects individual differences in the locus and extent of brain dysfunctions. Another explanation lies in the characteristics of the normal control subjects. Davis et al. (1990) found that age-related word stem completion priming deficits started to appear around age 70. Fleischman et al. concluded that repetition priming in control subjects at this age might be as variable as it is in early-stage AD, which could complicate the search for group differences in word stem completion priming.

Overall, AD patients show preserved perceptual (identification) priming effects, but deficient priming in word stem completion and category exemplars tasks. The dissociation in the priming performance of AD patients is consistent with the perceptual/conceptual (e.g., Keane et al., 1991) and the identification/generation hypotheses (Gabrieli et al., 1994). Thus, conceptual or generation priming tasks may better differentiate between AD and normal ageing than perceptual or identification priming tasks.

Implicit Memory: Procedural Memory or Skill Learning

AD patients exhibit a, relative to normal elderly controls, normal improvement over trials on perceptual-motor learning tasks (such as pursuit rotor, mirror tracing, serial reaction time or more cognitively mediated tasks such as maze learning and weight biasing) and show normal transfer to comparable trials – despite absent explicit learning (e.g., Butters et al., 1990; Eslinger & Damasio, 1986; Gabrieli, Corkin, Mickel, & Growdon, 1993; Grosse, Gilley, & Wilson, 1991; Heindel et al., 1988; Heindel, Salmon, Shults, Walicke, & Butters, 1989; Knopman, 1991; Knopman & Nissen, 1987).

Verbal-perceptual skills lead to quite similar results: in addition to motor skills, AD patients are also able to learn mirror reading in a normal way (comparable to normal elderly controls), despite impaired explicit recognition of presented items (e.g., Deweer et al., 1993, 1994; Salmon et al., 1992). However, Grober et al. (1992) found no learning ability for AD patients on the mirror

reading skill. They explained this result in terms of the patients' underlying deficit in abstract reasoning that precludes the development of appropriate pattern analysing strategies needed to transform rotated text. In contrast to the AD patients, older normal control subjects in this study were found to be able to learn the mirror reading skill. Noteworthy is that the AD patients in the experiment by Grober et al. were significantly older than the older normal control subjects (83.4 and 76.9, respectively). Most subjects in the other studies were around 70 years old.

FOCUS ON VERY EARLY AND PRECLINICAL AD

Though some remarks on the subject of early assessment of AD were already made in the previous sections, this section will pay more specific attention to it. Unfortunately, most experimental studies reviewed above use AD patients who are in an advanced stage of their disease (see Appendix, Table A1). Studies investigating *preclinical* AD patients usually recruit a large cohort of non-demented older subjects, who are administered a battery of neuropsychological tests at several times of measurement. This cohort is assessed longitudinally until a sufficient number of subjects have been diagnosed clinically with probable or possible AD (Collie & Maruff, 2000). Deficits on the following tests may be indicative for developing AD, several years before the diagnosis was made: (delayed) story recall (Elias et al., 2000; Collie & Maruff, 2000), Similarities (WAIS-R; Elias et al., 2000), (verbal) paired-associate learning (Elias et al., 2000; Collie & Maruff, 2000), (delayed) free recall (and recognition) of words (Bäckman, Small, & Fratiglioni, 2001; Collie & Maruff, 2000; Grober, Lipton, Hall, & Crystal, 2000; Masur, Sliwinski, Lipton, Blau, & Crystal, 1994; Linn et al., 1995), tactile recall memory (Masur et al., 2000), immediate visual memory (Zonderman et al., 1995), Digit Symbol (WAIS-R; Masur et al., 2000) and verbal fluency (Masur et al., 2000). However, the neuropsychological test battery in this class of studies is usually limited to measures of (verbal)

episodic memory (i.e., clinical memory tests), while other memory systems are not investigated. Nonetheless, one may argue that semantic memory plays an important role in several tests listed above: Similarities (i.e., capacity of mental lexicon), paired-associate learning (i.e., recall benefit in pairs of words that are semantically related), story recall (i.e., memory for meaningful material, dependent on degree of text comprehension), and verbal fluency (i.e., performance is dependant on processes of semantic categorisation and differentiating between various subcategories within a concept). However, in these studies, these tests are usually not interpreted as measures of semantic memory. Thus, it may be argued that important information could be missed by concluding that (purely) episodic memory processes are crucial for the prediction of dementia. In addition, other than so-called episodic memory tests are rarely administered in these studies – at least, other memory components are not explicitly investigated in order to determine the most sensitive measures of preclinical dementia. Therefore, conclusions in this respect should be drawn cautiously.

Since the studies investigating preclinical AD patients do not examine memory according to the 'explicit-implicit' view (Schacter, 1992; Tulving & Schacter, 1990), a selection was made from the experimental studies reviewed above that used diagnosed AD patients but in their earliest stages ('minimal' AD) or with high scores on cognitive screening tests (i.e., MMSE > 23). The study of Weingartner et al. (1993), reviewed in the section on semantic memory, was the only study that investigated preclinical AD patients (in a category fluency task, 2 years before the diagnosis was made). They concluded that one of the early cognitive symptoms of AD is changes in availability of uncommon exemplars of semantic networks.

Hodges and Patterson (1995) and Greene et al. (1996) both define a group of '*minimal*' AD patients: patients diagnosed with AD who scored in the 24–30 ranges of the MMSE. Greene et al. present a systematic investigation of various aspects of episodic memory. They found that the '*minimal*' AD patients performed significantly worse than normal elderly controls on immediate

and delayed trials of story recall, free recall and recognition (verbal and nonverbal tests). Greene et al. conclude that the '*minimal*' AD patients suffer from general episodic memory disorders, characterised by defective learning processes rather than faster forgetting or impaired retrieval. No effect was found for modality of material to be memorised.

Hodges and Patterson investigated how early in the course of the disease and how consistently semantic memory problems occur in AD. The '*minimal*' AD patients demonstrated impaired performance on various tests of semantic memory (e.g., category fluency, naming, naming to verbal description, semantic feature questions) and on episodic memory (i.e., delayed story recall). Recognition memory was less impaired in '*minimal*' AD, but may be a better index of severity of the disease. Tests of visuospatial ability and verbal short-term memory (i.e., digit span) did not show significant differences with normal elderly controls. It may be noted that in the prospective study by Linn et al. (1995; mentioned above), '*preclinical*' AD patients performed better on a digit span test than normal subjects. Hodges and Patterson conclude that semantic memory is affected very early in the course of AD, though there was considerable variability in the extent of semantic impairment among patients with the same overall level of dementia. This finding regarding the early semantic memory impairment in AD is supported by Rosser and Hodges (1994), who examined category fluency performance in early AD patients (mean score Dementia Rating Scale (Mattis, 1976): 121.4). In addition, Sailor et al. (1998) found their early AD patients (mean MMSE score: 23.7) to be impaired in several tasks of semantic memory. Furthermore, Hodges et al. (1990) demonstrated impaired performance of their early AD patients (mean MMSE score: 24.4) on a category fluency test and some tests of semantic knowledge (e.g., Boston Naming Test, WAIS-R subtests Vocabulary and Similarities). Early semantic memory impairment was also found by Almkvist and Bäckman (1993), who reported that detection of 'very mild dementia' was best accomplished by three tests assessing episodic memory, semantic memory and visuospatial

functioning (according to a stepwise discriminant analysis).

Few studies can be selected that investigated implicit memory performance in early AD. Koivisto et al. (1996) found intact perceptual priming effects in their early AD patients (mean MMSE score: 22.9). Monti et al. (1996) found impaired priming for category exemplars in their early AD patients (mean MMSE score: 23.3), while normal elderly controls showed equivalent priming effects as younger normal controls. The AD patients did not benefit from deep encoding in either an explicit memory measure (i.e., cued recall) or an implicit memory measure (i.e., the conceptual priming task). Monti et al. argue that AD, contrary to normal ageing, is characterised by impaired conceptual processing. On the other hand, Fleischman et al. (1996), using the word stem completion task, found similar priming effects for their early AD patients (mean MMSE score: 23.3) and their controls, while usually impaired priming effects are found in AD. As was mentioned above, the age of the subjects tested may be an important factor, since priming effects in normal control subjects aged 70 or above may be as variable as in early AD.

Since hardly any studies are available that examine priming effects in very early AD patients, it is difficult to discuss the value of priming tasks for early assessment. Conceptually based priming tasks might lead to differences between very early or preclinical AD patients and their controls, since these tasks may be dependent on the functioning of semantic memory (which is most likely impaired in a very early stage of the disease). However, much more research must be done before reliable conclusions can be drawn.

DISCUSSION

From the review of experimental findings, it may be concluded that, in addition to episodic memory problems, there are also major differences in memory functioning between normal ageing and AD in the field of their semantic capacities (i.e., the structure of semantic knowledge). AD patients exhibit, relative to normal elderly controls, poor semantic encoding of to be learned information.

This will also affect episodic memory performance, especially in the case of material with an inherent semantic structure or in semantic cueing tasks: AD patients cannot benefit from such cues, contrary to normal elderly controls. AD patients might not be able to discriminate between two related concepts, because the attribute knowledge that distinguishes the two concepts is lost (e.g., Martin & Fedio, 1983; Sailor et al., 1998). In addition, AD patients' deficits are evident in recognition tasks, particularly when semantically related distractors are used – their responses consist of numerous false positive errors. AD patients seem unable to inhibit irrelevant associations.

Many studies examining the impaired category fluency performance in AD, report a 'degraded structure of semantic knowledge.' In AD, the qualitative characteristics of performance are striking: they do not simply name few correct exemplars in general, but they also show hardly any exploration or awareness of subcategorical information (i.e., the bottom-up breakdown of the semantic knowledge network). Furthermore, they name many subcategory labels and they show many perseverations, relative to their total production of exemplars.

In addition, priming experiments based on more conceptually (i.e., semantically) based encoding tasks reflect deficits in AD patients' performance as well, once again due to their impaired semantic capacities. Also their poor visuospatial span, relative to their auditory/verbal span, has been reported frequently.

Contrasted to AD, poor episodic memory performance in normal ageing mainly concerns deficient initiation of retrieval strategies, rather than poor encoding processes. This may also relate to their compromised performance on semantic memory, as in category fluency, but primarily results in a slow retrieval of relevant exemplars without a typical profile of responses. Normal elderly controls show relatively intact implicit memory and short-term memory, at least until the age of 70.

However, most patients used in the studies reviewed above were in an advanced stage of their disease. As can be noted from the studies listed in the Appendix, symptoms have been reported for

several years and the scores on cognitive screening tests are generally low. From the tentative review of preclinical and very early AD patients, it may be concluded that tests sensitive to semantic knowledge are crucial for detecting AD at the earliest possible stage. These tests may include memorising material with an inherent semantic structure (e.g., story recall), semantic cueing, or category fluency. Possibly, reliable priming tasks that call upon semantic processing may also be useful.

Other important factors that may influence patterns of performance are the age and level of education of the subjects under investigation. As is illustrated in the Appendix, the usual sample of healthy elderly subjects and dementia patients is restricted to a relatively young age (around 68 years old) and high educational level (e.g., college education; around 12 years of attained education), which both are not representative for the average elderly population. Grosse et al. (1991) investigated the contribution of age of onset to semantic and episodic memory in AD, while controlling for dementia severity and education. The authors found that late onset AD (a mean age of 75.4 years – as opposed to early onset AD: 60.9 years) is associated with relatively greater impairment of semantic memory (i.e., confrontation naming and sentence frame completion). Bäckman, Small, Wahlin, and Larsson (2000) reported that not much research has been done on cognitive functioning in ‘very old age,’ i.e., 75 years and above, although this age group is becoming more and more relevant because life expectancy continues to increase. In addition, prevalence of dementia is greatest in this age group: it increases exponentially with increasing age. Thus, differentiation of effects of normal ageing versus early dementia is a central issue in subjects of very old age. Furthermore, this differentiation may be more difficult when the subjects are of ‘very old age,’ rather than of ‘young-old’ age, because normal ageing effects on cognitive performance may be more pronounced at this age, thereby complicating the differential diagnosis. In addition, low educational background complicates the investigation of very old persons: their level of cognitive functioning is easily mistaken for pathological ageing effects. However, the present

elderly population usually has not had the advantage of a good education.

As was discussed above, clinical memory tests focus on measuring episodic memory performance, although these tests do not use the label ‘episodic memory.’ The DSM-IV features of dementia regarding memory impairments (superficially) describe episodic memory disorders, again without labelling them as such. The global DSM-IV features fail to describe the more specific memory performance characteristics of AD patients and they even fail to describe the precise *episodic* memory performance characteristics, reported in numerous experimental studies. More specific information for assessment is gathered from the available clinical memory tests that provide redundant measures of episodic memory performance, although their interpretation is not completely consistent with current theoretical concepts. Other neuropsychological tests may provide additional information on memory functioning (such as the category fluency test on semantic memory), but scoring procedures should be modified to obtain more specific information (e.g., scoring the use of different subcategories instead of merely considering the sum of correct exemplars generated within 1 min). Nevertheless, the available clinical memory tests fail to offer a broad view of memory functioning of normal elderly subjects and dementia patients: tests other than of purely episodic memory are needed to be able to observe the essential differences. At least, the interpretation of test results should focus on aspects of performance that are sensitive to semantic processing capacities rather than simply interpreting results in terms of ‘memory deficits.’ Particularly in early assessment, tests calling upon semantic knowledge may aid to an earlier and more efficient assessment of AD.

In sum, one may conclude that current theoretical knowledge about memory functioning is not well reflected in clinical assessment, which may, at least in this case, lead to a less systematic investigation of differential performance of cognitively healthy and impaired elderly subjects. As a result, important information could be missed and the interpretation of test results may be more hazardous than necessary. Using a broader set of

memory tasks might lead to an improved differential diagnosis, especially for the early detection of dementia.

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APPENDIX

Table A1. Summary of Experimental Research Findings on Memory Performance in Alzheimer's Disease Patients (AD), Relative to Normal Elderly Controls (NC), Including Characteristics of Both Groups of Subjects (*n*, Mean Age, Mean Years of Education and Stage of the Disease).

Memory component	Study	<i>n</i> (AD)/ <i>n</i> (NC)	Age (AD)	Age (NC)	Education (AD)	Education (NC)	Stage of AD/MMSE ¹ or DRS ² -score, etc./duration of illness	Result AD (vs. NC)
Episodic memory: free recall	Martin et al. (1985)	14/11	58.2	61.5	14.7	13.8	1–10 year reported duration of sympt. ($M = 3.8$)	Impaired
	Eslinger and Damasio (1986)	8/8	71.4	70.8	10**	16**	2 $\frac{1}{2}$ –9 year illness ($M = 4$)	Impaired
	Spinnler et al. (1988)	29/58	67	67	8.9	11	1–4 year illness	Impaired
	Helkala et al. (1989)	32/23	68	68	?	?	18 mild, 13 moderate, 1 severe; 1–3 year illness	Impaired
	Greene et al. (1996)	33 ³ /30	73.1; 66.2	67.9	12.5; 10.3	11	Minimal pts: MMSE 24–30 ($M = 26.2$); mild pts: MMSE 17–23 ($M = 20.3$)	Impaired
Episodic memory: cued recall	Bird and Luszcz (1991)	22/22	82.2	84.3	?	?	MMSE: $M = 16.9$; mild-moderate	Impaired
	Bondi and Kaszniak (1991)	12/16	70.7	69.6	13.6	15.2	MMSE: $M = 18$; DRS: $M = 103.8$	Impaired
	Russo and Spinnler (1994)	12/12	71.8	72.3	9.3	10.1	Mild; probable DAT	Impaired
	Monti et al. (1996)	24/24	73.4	70.3	13.2	13.8	MMSE > 17 ($M = 23.3$)	Impaired
	Sailor et al. (1998)	14/19	75.5	71	13.2	15.8	MMSE: $M = 23.7$	Impaired
Episodic memory: recognition	Eslinger and Damasio (1986)	8/8	71.4	70.8	10**	16**	2 $\frac{1}{2}$ –9 year illness ($M = 4$)	Impaired
	Heindel et al. (1988)	10/10	76.5	67.5	11.6	12.4	DRS: $M = 117.8$	Impaired
	Helkala et al. (1989)	32/23	68	68	?	?	18 mild, 13 moderate, 1 severe; 1–3 year illness	Impaired
	Abbenhuis et al. (1990)	11/11	74.7	74.2	7.2	7.9	Probable DAT, moderately/severely impaired	Impaired
	Grosse et al. (1990)	12/15	72.3	73	15	14.3	MMSE < 24 ($M = 19.8$); DRS < 130	Impaired
	Deweerd et al. (1993)	17/9	73.4	71	8.4	8.4	MMSE: $M = 21.6$; DRS: $M = 112.6$	Impaired
	Deweerd et al. (1994)	30 ⁴ /19	80.2; 73.6	73.4	6.5; 8.4	8	MMSE: inst. pts: $M = 15.9$; outpts: $M = 21.6$	Impaired
	Keane et al. (1994)	12/12	70.4	64.5	12.9	13	Blessed Dementia Scale: $M = 15.2$ (mild-severe)	Impaired
	Russo and Spinnler (1994)	12/12	71.8	72.3	9.3	10.1	Mild; probable DAT	Impaired
	Fleischman et al. (1996)	28/24	72.8	71.5	14	14.3	MMSE > 16 ($M = 23.3$); mild	Impaired
Semantic memory: category fluency	Greene et al. (1996)	33 ³ /30	73.1; 66.2	67.9	12.5; 10.3	11	Minimal: MMSE 24–30 ($M = 26.2$); mild: MMSE 17–23 ($M = 20.3$)	Impaired
	Koivisto et al. (1996)	8/12	70.3	69.3	7.4	7	2.1 year illness; MMSE: $M = 22.9$	Impaired
Semantic memory: category fluency	Martin and Fedio (1983)	14/11	58.2	61.5	14.7	13.8	1–10 year reported duration of sympt. ($M = 3.8$)	Impaired
	Ober et al. (1986)	19/11	63.5	64.3	?	?	10 mild, 9 moderate/severe	Impaired
	Salmon et al. (1988)	13/13	71.2	66.5	12.4	14	DRS: $M = 116.6$	Impaired
	Tröster et al. (1989)	40/20	71.4	70.4	13.6	13.9	20 mild (DRS: 117.4), 20 moderate (DRS: 101.9)	Impaired
	Chertkow and Bub (1990)	10/10	76.3	73	11.6	11.2	MMSE < 25 ($M = 17.3$)	Impaired
	Hodges et al. (1990)	14/14	73.6	73.1	12.9	13.3	MMSE: 19–28 ($M = 24.4$)	Impaired
	Monsch et al. (1992)	89/53	72.1	71.2	13.5	13.6	21 pts. of sample 'mild': MMSE > 17 ($M = 22.5$), DRS > 114; whole sample: MMSE: $M = 18$ (incl. 'mild')	Impaired

Table A1. (continued).

Memory component	Study	n(AD)/n(NC)	Age (AD)	Age (NC)	Education (AD)	Education (NC)	Stage of AD/MMSE ¹ or DRS ² -score, etc./duration of illness	Result AD (vs. NC)
	Salmon et al. (1992)	—	—	—	—	—	Review	Impaired
	Randolph et al. (1993)	11/11	64.3	68.5	16.4	16.6	DRS: $M = 114.8$	Impaired
	Weingartner et al. (1993)	6/6 ⁵	78.8	78.8	?	?	MMSE: T1: $M = 25.33$, T2: $M = 20.6$; T1-T2: 2.3 year	Impaired T1
	Mickanin et al. (1994)	22/21	70.9	66.1	13.5	17	2-10 year illness ($M = 3.9$); mod. /sev.; MMSE: $M = 20.6$	Impaired
	Monsch et al. (1994)	44/44	71.5	70	14.2	14.2	DRS: $M = 113.3$	Impaired
	Rosser and Hodges (1994)	10/25	67.2	69	11.1	10.7	DRS: $M = 121.4$	Impaired
	Binetti et al. (1995)	70/35	70.5	67.4	6.5	6.8	40 mild (MMSE 21.4), 30 mod. /sev. (MMSE 12.3)	Impaired
	Hodges and Patterson (1995)	52 ⁶ /24	63.4-72.2	69.7	10.9-11.4	10.7	Minimal (MMSE > 23), mild (MMSE 17-23), moderate (MMSE < 17)	Impaired (incl. min.)
	Beatty et al. (1997)	35/38	76.5	73.7	14.1	13.4	MMSE: $M = 18.5$	Impaired
	Sailor et al. (1998)	14/19	75.5	71	13.2	15.8	MMSE: $M = 23.7$	Impaired
Working memory: auditory/verbal span	Orsini et al. (1988)	51/30	63.5	63.7	7	8.4	24 mild, 27 moderate	Mod. impaired
	Carlesimo et al. (1994)	18/26	60.9	61.3	8.9	9.3	Global Performance Index: $z = -1.42$	Intact
	Morris (1994)	—	—	—	—	—	Review	Intact
	Hodges and Patterson (1995)	52 ⁸ /24	63.4-72.2	69.7	10.9-11.4	10.7	Minimal (MMSE > 23), mild (MMSE 17-23), moderate (MMSE < 17);	Intact (incl. minimal)
Working memory: visuospatial span	Orsini et al. (1988)	51/30	63.5	63.7	7	8.4	24 mild, 27 moderate	Impaired
	Spinnler et al. (1988)	29/58	67	67	8.9	11	1-4 years duration of illness	Impaired
	Grossi et al. (1993)	39/62	67.3	66.9	10.4	11.3	MMSE: $M = 21.4$	Impaired
	Carlesimo et al. (1994)	18/26	60.9	61.3	8.9	9.3	Global Performance Index: $z = -1.42$	Impaired
	Trojano et al. (1994)	30/30	65.8	63	7.4	7.6	Probable DAT; MMSE: $M = 22.6$	Impaired
Implicit memory: perceptual/identification priming tasks	Abbenhuis et al. (1990)	11/11	74.7	74.2	7.2	7.9	Probable DAT, moderately/severely impaired	Intact
	Keane et al. (1991)	12/12	69.8	64.6	14.3	14.1	Mild-severe (Blessed Dementia Scale: $M = 18.7$)	Intact
	Grober et al. (1992)	18/18	83.4*	76.9*	10	10.8	Blessed Mental Status Test: $M = 13.5$ errors	Intact
	Gabrieli et al. (1994)	13/13	64.5	67.2	14.4	15.5	Mild-severe (Blessed Dementia Scale: $M = 19.1$)	Intact
	Keane et al. (1994)	12/12	70.4	64.5	12.9	13	Blessed Dementia Scale: $M = 15.2$ (mild-severe)	Intact
	Russo and Spinnler (1994)	12/12	71.8	72.3	9.3	10.1	Mild; probable DAT	Intact
	Meiran and Jelicic (1995)	—	—	—	—	—	Meta-analysis	Intact
	Koivisto et al. (1996)	8/12	70.3	69.3	7.4	7	2.1 year illness; MMSE: $M = 22.9$	Intact

Table A1. (continued).

Memory component	Study	n(AD)/n(NC)	Age (AD)	Age (NC)	Education (AD)	Education (NC)	Stage of AD/MMSE ¹ or DRS ² -score, etc./duration of illness	Result AD (vs. NC)
Implicit memory: conceptual/generation priming tasks	Shimamura et al. (1987)	8/9	72	69.6	13.8	13.9	Mild-moderate; DRS: $M = 118$; MMSE: $M = 20.4$	Impaired
	Salmon et al. (1988)	13/13	71.2	66.5	12.4	14	DRS: $M = 116.6$	Impaired
	Butters et al. (1990)	—	—	—	—	—	Review	Impaired
	Grosse et al. (1990)	12/15	72.3	73	15	14.3	MMSE < 24 ($M = 19.8$); DRS < 130	Intact
	Bondi and Kaszniak (1991)	12/16	70.7	69.6	13.6	15.2	MMSE: $M = 18$; DRS: $M = 103.8$	Impaired
	Keane et al. (1991)	10/10	70.5	68.2	13.6	12.7	Blessed Dementia Scale: $M = 18.7$ (mild-severe)	Impaired
	Gabrieli et al. (1994)	15/15	68.3	63.1	14.1	15.1	Mild-severe (Blessed Dementia Scale: $M = 16.4$)	Impaired
	Keane et al. (1994)	12/12	70.4	64.5	12.9	13	Blessed Dementia Scale: $M = 15.2$ (mild-severe)	Impaired
	Carlesimo et al. (1995)	11/18	63.8	66.5	6.1	8	Global Performance Index: $z = -2.79$	Impaired
	Meiran and Jelicic (1995)	—	—	—	—	—	Meta-analysis	Impaired
	Fleischman et al. (1996)	28/24	72.8	71.5	14	14.3	MMSE > 16 ($M = 23.3$); mild	Intact
Procedural memory	Eslinger and Damasio (1986)	8/8	71.4	70.8	10**	16**	2 ¹ /9 year illness ($M = 4$)	Intact
	Knopman and Nissen (1987)	35/13	70.4	68.5	?	?	MMSE < 26	Intact
	Heindel et al. (1988)	10/10	76.5	53.4	11.6	14.9	DRS: $M = 117.8$	Intact
	Heindel et al. (1989)	16/12	74.3	71.3	12.2	14.8	DRS: $M = 118.3$	Intact
	Butters et al. (1990)	—	—	—	—	—	Review	Intact
	Grosse et al. (1991)	12/15	72.3	73	15	14.3	MMSE < 24 ($M = 19.8$); DRS < 130	Intact
	Knopman (1991)	8/14	72.8	69.4	14.7	16.1	MMSE: $M = 20.7$	Intact
	Grober et al. (1992)	18/18	83.4*	76.9*	10	10.8	Blessed Mental Status Test: $M = 13.5$ errors	Impaired
	Salmon et al. (1992)	—	—	—	—	—	Review	Intact
	Deweerd et al. (1993)	17/9	73.4	71	8.4	8.4	MMSE: $M = 21.6$; DRS: $M = 112.6$	Intact
	Gabrieli et al. (1993)	9/8	71.9	66	12.9	13.4	Blessed Dementia Scale: $M = 14.1$ (mild-severe)	Intact
	Deweerd et al. (1994)	30 ⁴ /19	80.2; 73.6	73.4	6.5; 8.4	8	MMSE: inst. pts: $M = 15.9$; outpatients: $M = 21.6$	Intact

¹MMSE = Mini-Mental State Examination (Folstein, Folstein, & McHugh, 1975).²DRS = Dementia Rating Scale (Mannis, 1976).³17 'minimal' dementia patients, 16 'mild' dementia patients.⁴13 institutionalised patients, 17 outpatients.⁵At Time 1: 76 nondemented ss. At Time 2 (2.3 years later), 6 ss. were demented; the NC ss. were matched to the demented ss. in age, education and sex.⁶17 'minimal' dementia pts. (age 72.2, education 11.2), 17 'mild' dementia pts., (age 67, education 11.4), 18 'moderate' dementia pts. (age 63.4, education 10.9).