Presymptomatic cognitive deficits in individuals at risk of familial Alzheimer’s disease
A longitudinal prospective study

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Summary
A longitudinal study of asymptomatic individuals at risk of autosomal dominant familial Alzheimer’s disease was performed to assess the earliest clinical and neuropsychological features of the disease. Over a 6-year period, 63 subjects underwent serial assessments. During the study, 10 subjects developed symptoms of episodic memory loss and subsequently progressed to fulfil criteria for possible or probable Alzheimer’s disease. The mean time (± SD) from first assessment to the appearance of symptoms was 2.6 ± 1.4 years. The subjects who remained well were similar to those who became clinically affected in terms of age, family history and initial Mini-Mental State Examination. Individuals who later became clinically affected already had significantly lower verbal memory (P = 0.003) and performance IQ (P = 0.030) scores at their first assessment, when they were ostensibly unaffected. Subsequent assessments showed progressive decline in multiple cognitive domains. Blinded assessment of serial imaging revealed the appearance of diffuse cerebral and medial temporal lobe atrophy in subjects only once they were clinically affected. These findings imply that in familial Alzheimer’s disease cognitive decline predates symptoms by several years and that verbal memory deficits precede more widespread deterioration. This may have implications for the detection and treatment of Alzheimer’s disease at an early stage.

Keywords: Alzheimer’s disease; memory; presymptomatic; at risk; familial

Abbreviations: CDR = Clinical Dementia Rating; MMSE = Mini-Mental State Examination; NART = National Adult Reading Test

Introduction
Alzheimer’s disease is a progressive neurodegenerative condition characterized by relentless cognitive decline. Mean survival is typically 6–8 years from diagnosis, and there is an insidious onset of symptoms which is thought to precede the diagnosis by 2–3 years (Jost and Grossberg, 1995). Episodic memory loss is usually the presenting symptom, but cognitive deficits become widespread with most higher cortical functions affected within a few years (Flicker et al., 1991; Rossor, 1993). The prospect and advent of treatments for the disease has led to increasing interest in identifying its earliest stages (Kelly et al., 1997). Important unresolved questions related to instituting early treatment include: when does the pathological process of Alzheimer’s disease begin and what are its earliest detectable features?

While the clinical features of the established disease have been well studied, relatively little is known about the early symptomatic phase of the disease and even less about presymptomatic disease manifestations. In order to assess presymptomatic changes, asymptomatic individuals need to be followed prospectively through the period of symptom onset to established diagnosis. Identification of individuals at increased risk of the disease allows more detailed assessment, since fewer subjects need to be followed to detect the same number of affected individuals. Increasing age and a family history of Alzheimer’s disease are the most important risk factors established for the disease (van Duijn and Hofman, 1992). Pedigrees with an autosomal dominant pattern of inheritance of Alzheimer’s disease have been recognized for many years, and recently three genetic loci responsible for early-onset disease (before the age of 65 years) have been described (Hardy, 1997). Individuals with a family history of early-onset autosomal dominant Alzheimer’s disease provide an at-risk population where prospective detailed study of the earliest changes can feasibly be achieved since

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each individual carries a 50% chance of developing the disease and the age at onset within a family is relatively constant (Fox et al., 1997).

Established criteria for dementia require cognitive decline to be demonstrated in more than one area of cognition (American Psychiatric Association, 1994). Depending on the pattern and rate of the degenerative process, isolated neuropsychological deficits may, in theory, be detectable some time before other areas of cognition are affected. Several studies have shown that elderly individuals who have symptoms of memory loss and apparently isolated memory deficits are at an increased risk of developing dementia (Tierney et al., 1996; Bowen et al., 1997; Howieson et al., 1997). Tierney et al. (1996) followed 123 patients who complained of memory problems sufficient to interfere with daily functioning but who did not fulfil criteria for dementia. Of these, 29 became demented within 2 years. Bowen et al. (1997) found that 10 out of 21 patients with memory complaints and isolated memory loss without an identifiable cause developed dementia within 5 years. Howieson et al. (1997) in a study of individuals >80 years of age found that verbal memory decline preceded dementia. There are, however, very few studies which have recruited individuals before the onset of memory or other cognitive complaints to identify the first symptoms, cognitive deficits and other features in Alzheimer’s disease. Flicker et al. (1993) found that 50 elderly individuals (used as controls for comparison with a group of Alzheimer’s disease patients), six subjects were cognitively impaired at follow-up 2 years later. These subjects had significantly lower memory scores at baseline when compared with those individuals whose cognitive performance did not decline. Longitudinal follow-up of elderly individuals in the Framingham cohort suggested that a ‘pre-clinical’ phase of detectable cognitive deficits may precede the clinical diagnosis of probable Alzheimer’s disease (Linn et al., 1995); verbal recall scores were lower in the subjects who later developed dementia compared with those who remained well. However, the initial neuropsychological testing in this large study was necessarily a brief 20–25 min screening assessment which could not cover a wide range of cognitive domains. Studies which have examined the early cognitive decline in Alzheimer’s disease using elderly subjects have to contend with the variability of age-related decline in cognition and confounding effects of co-morbidity such as vascular disease. Study of the relatively younger familial Alzheimer’s disease group avoids both these problems. Furthermore, in those family members who develop dementia, the diagnosis of Alzheimer’s disease is not in question. In order to examine the onset and nature of the very earliest changes in familial Alzheimer’s disease in detail, we conducted a prospective longitudinal study from 1991 to 1997 of asymptomatic individuals at risk of young onset disease. We report here the clinical and neuropsychological features of these subjects and describe the differences between those who developed the disease and those who remained well.

Methods

Case selection

Asymptomatic at-risk members of early-onset familial Alzheimer’s disease pedigrees were recruited to a longitudinal study. Individuals were asked to participate in the study if they had at least two family members in two different generations, including a first degree relative, affected with Alzheimer’s disease before the age of 65 years and if they were themselves within 5 years of the historical age at onset for their family. At recruitment, a careful history for the presence of symptoms was taken from the subject and from the subject’s spouse or other close family member. Subjects were excluded if they fulfilled established criteria for possible or probable Alzheimer’s disease (McKhann et al., 1984). Subjects were only included if both they and other informants felt they had no symptoms of cognitive decline. All subjects were also screened using the Mini-Mental State Examination (MMSE) and the Clinical Dementia Rating (CDR) scale (Folstein et al., 1975; Hughes et al., 1982) and were only included if they scored ≥24/30 on the MMSE and zero (healthy) on the CDR. Informed written consent was obtained from all subjects, and the study received ethical approval from participating centres. All study participants were informed that it would not be possible to provide any information about the outcomes of these research assessments. However, if they were concerned about becoming symptomatic a referral to a specialist dementia clinic would be arranged. All investigators were blinded to information about individual genetic status. Subjects who requested referral were fully investigated using standard clinical protocols to exclude alternative diagnoses.

Clinical assessment

Study subjects were asked to attend annual assessments, accompanied by a close informant. Each assessment consisted of a clinical interview, neurological examination, neuropsychological assessment and MRI examination. In addition, the accompanying informant was interviewed independently.

The Medical Research Council (UK) guidelines for assessment of research patients provided the basis for the clinical interview (Medical Research Council, 1986). Specific questions covered activities of daily living, whether the subject was working, the nature of the work and whether there had been any recent difficulties in coping with the demands of the job or home. Memory functions were specifically enquired about, including difficulties in remembering telephone messages, errands or lists of items such as shopping. The subject and informant were independently asked how the subject’s memory compared with that of other individuals of a similar age. Enquiries were also made about any changes in other cognitive functions or in behaviour. On each assessment, MMSE and CDR scores were recorded. General and neurological examinations were performed, including assessments of myoclonus and praxis.
Presymptomatic memory deficits in Alzheimer's disease

Neuropsychology

Neuropsychological assessments were performed independently but on the same day as the clinical interview. The test battery included measures of current intelligence, verbal and visual memory, naming, perception, arithmetic, spelling, psychomotor speed and attention. The tests administered were a short version of the Wechsler Adult Intelligence Scale—Revised, consisting of four verbal subtests (verbal IQ: assessed from vocabulary, arithmetic, digit span and similarities) and three performance subtests (performance IQ: assessed from block design, picture completion and picture arrangement) (Warrington et al., 1986); the Recognition Memory Test (Warrington, 1984); the Graded Naming Test (McKenna and Warrington, 1983); the Visual Object and Spatial Perception Test (Warrington and James, 1991); Psychomotor Speed Tests (Willison and Warrington, 1992), the Graded Difficulty Arithmetic Test (Jackson and Warrington, 1986) and the Graded Difficulty Spelling Test (Baxter and Warrington, 1994). The selection of tests was based on the availability of age-scaled normative data. The National Adult Reading Test (NART) was administered to obtain a measure (reading IQ equivalent) of optimum level of intellectual function (Nelson, 1991). In at-risk subjects, who often had to travel some distance for assessments, we felt it was important to keep the assessment as short as possible and yet be comprehensive. This test battery takes between 1.5 and 2 h to administer and we focused for the most part on tests of graded difficulty on which normal subjects do not score at ceiling.

Two derived scores were calculated from these test results: (i) the 'dementia index' the difference between the NART and full-scale IQ and (ii) the composite cognitive score. The composite cognitive score was calculated by converting all individual test scores (except the NART) to one of five grades based on age-specific standardized scores as follows: grade 5 above the 50th percentile; grade 4 between the 25th and 50th percentiles; grade 3 between the 5th and 25th percentiles; grade 2 between the 5th and 1st percentiles and grade 1 below the 1st percentile. The mean of these grade scores was recorded as an overall index of cognitive competence.

MRI was performed on a Signa 1.5-T unit (General Electric, Milwaukee, Wisc., USA). All scans included a routine sagittal ($T_1$-weighted) scout sequence and an axial dual-echo sequence ($T_2$- and proton density-weighted). In addition, volumetric imaging was performed in the coronal plane, using a spoiled gradient echo technique with a 24-cm field of view yielding 124 contiguous 1.5 mm thick slices through the head on a $256 \times 128$ image matrix with acquisition parameters (TR, TE, NEX and FLIP = 35, 5, 1 and 35 ms, respectively). All scans were reported by a consultant neuroradiologist who was blind to any clinical details, apart from the subjects' ages, and to the fact that they were part of the at-risk group in a study of familial Alzheimer's disease.

Outcome measures and assignment to affected and unaffected groups

At the end of the 6-year study, these at-risk subjects were classified on purely clinical criteria into two groups for analysis purposes without reference to the neuropsychological test results.

Individuals were assigned to the affected group in our at-risk population if they had developed symptoms of Alzheimer's disease, with clear evidence of progression. The date of onset of symptoms was determined from the interviews with close family members. The dates at which subjects fulfilled criteria for possible and probable Alzheimer’s disease (McKhann et al., 1984) were determined by the examining neurologist using the results of the assessments and investigations performed as part of the clinical referral.

The individuals assigned to the unaffected group in our at-risk population were those who were deemed to have remained well, i.e., they, their families and the examining neurologist all felt there was no change in cognitive function or activities of daily living. In addition, there was no deterioration in their CDR score and their MMSE scores were still within the normal range.

Statistical analyses

The scores of the at-risk individuals who became affected and the at-risk individuals who remained well were compared using the Mann–Whitney U test (two tailed) with the SPSS (statistical package for the social sciences) software (McGraw-Hill, New York, USA).

Results

Study population

Sixty-three subjects who fulfilled entry criteria and who attended for follow-up were included in the study. Thirty-two were female, 55 were right handed, seven were left handed and one was ambidextrous. The age of the study subjects at initial assessment ranged from 31 to 63 years with a mean (± SD) of 44.7 ± 8.1 years. At initial assessment the mean MMSE score of the subjects was 29.2 ± 1.2 (range 24–30) out of a possible maximum of 30.

All subjects fulfilled the entry criteria for a family history of autosomal dominant familial Alzheimer’s disease; the number of family members known to have been affected with early-onset dementia ranged from 3 to 13, with a mean of 7.3. All pedigrees had Alzheimer’s disease proven by autopsy in at least one affected individual. Nineteen of the at-risk subjects were from three large pedigrees where point mutations at position 717 in the amyloid precursor protein gene have been identified in affected family members: V717I in families F23 and F172 and V717G in family F19 (for further details on this family, see Fox et al., 1996b). Twenty-five subjects were from families where mutations in the presenilin 1 gene have been identified: two families showed...
Table 1  Test scores at initial assessment for all subjects

<table>
<thead>
<tr>
<th>Neuropsychological test</th>
<th>Maximum score</th>
<th>Control scores (50th percentile)</th>
<th>Scores of subjects at risk</th>
<th>Number (%) scoring &lt;5%</th>
<th>Number (%) scoring &lt;25%</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>Mean ± SD</td>
<td>Range</td>
<td></td>
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<tr>
<td>General intellectual function</td>
<td></td>
<td></td>
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<td></td>
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</tr>
<tr>
<td>Verbal IQ</td>
<td>100</td>
<td>97.6 ± 11.0</td>
<td>74–127</td>
<td>1 (1.6%)</td>
<td>16 (25%)</td>
</tr>
<tr>
<td>Performance IQ</td>
<td>100</td>
<td>99.7 ± 14.7</td>
<td>71–138</td>
<td>5 (7.9%)</td>
<td>17 (27%)</td>
</tr>
<tr>
<td>NART IQ</td>
<td>100</td>
<td>101.1 ± 10.9</td>
<td>71–123</td>
<td>1 (1.6%)</td>
<td>8 (13%)</td>
</tr>
<tr>
<td>Memory</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Recognition Memory Test: words</td>
<td>50</td>
<td>45.4 ± 4.1</td>
<td>33–50</td>
<td>3 (4.8%)</td>
<td>15 (24%)</td>
</tr>
<tr>
<td>Recognition Memory Test: faces</td>
<td>50</td>
<td>44.1 ± 4.0</td>
<td>33–50</td>
<td>2 (3.2%)</td>
<td>12 (19%)</td>
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<tr>
<td>Naming skills</td>
<td></td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>Graded Naming Test</td>
<td>30</td>
<td>21.2 ± 5.4</td>
<td>5–29</td>
<td>6 (9.5%)</td>
<td>13 (21%)</td>
</tr>
<tr>
<td>Literacy skills</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>Arithmetic</td>
<td>24</td>
<td>12.5 ± 5.5</td>
<td>0–23</td>
<td>3 (4.8%)</td>
<td>9 (14%)</td>
</tr>
<tr>
<td>Spelling</td>
<td>30</td>
<td>19.6 ± 6.4</td>
<td>5–29</td>
<td>3 (4.8%)</td>
<td>16 (25%)</td>
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<tr>
<td>Perception: Visual Object and Spatial Perception Test</td>
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<tr>
<td>Silhouettes</td>
<td>30</td>
<td>22.6 ± 4.0</td>
<td>11–29</td>
<td>1 (1.6%)</td>
<td>15 (24%)</td>
</tr>
<tr>
<td>Cubes</td>
<td>10</td>
<td>9.0 ± 1.2</td>
<td>5–10</td>
<td>1 (1.6%)</td>
<td>17 (27%)</td>
</tr>
<tr>
<td>Speed and attention (s)</td>
<td></td>
<td></td>
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<tr>
<td>Digit Copying</td>
<td>42</td>
<td>41.5 ± 12.4</td>
<td>27–95</td>
<td>1 (1.6%)</td>
<td>18 (29%)</td>
</tr>
<tr>
<td>Composite cognitive score</td>
<td>5</td>
<td>4.3 ± 0.6</td>
<td>2.4–5.0</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Dementia Index: NART Full-Scale IQ</td>
<td></td>
<td>3.0 ± 0.9</td>
<td>−17 to +30</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

M139V (see Fox et al., 1997); two families E280G and one family each E120A, I143F, P267S and S290C). The remaining subjects were from early-onset familial Alzheimer’s disease pedigrees which have, as yet, not been genetically characterized (details of family F134 reported by Newman et al., 1994). The estimated mean (± SD) historical age at onset of the disease within the families of the at-risk subjects was 46 ± 7 years, and the range was from 36 to 58 years.

At initial assessment, the neurological examination was normal in all subjects apart from one subject who had early symptoms of idiopathic Parkinson’s disease. This subject had recently been commenced on selegeline (10 mg/day).

**MRI**

Initial imaging was adequately performed on 53 of the 63 study subjects. Nine subjects did not have an MRI because they were either unwilling or unable to tolerate an adequate study, and one subject’s girth was such he could not fit in the scanner. No neoplastic or other structural lesions were detected and there was no evidence of significant vascular pathology in any subject. White matter changes of questionable significance were reported in 10 subjects; these mainly consisted of small scattered peripheral lesions. None of the initial scans were reported as showing definite atrophy; possible mild diffuse atrophy was reported in five subjects.

**Neuropsychology at initial assessment**

The neuropsychological tests administered are shown in Table 1. Where appropriate the maximum possible score for each test is given, and the 50th percentile score derived from large age-matched control populations is also listed for each test to serve as a reference point. The means of the scores obtained by the whole subject group at initial assessment are shown together with standard deviations, range of scores obtained and the numbers of subjects scoring below the standardized 5th and 25th percentile score on each measure. On all the measures, the mean scores obtained by the study group at the initial assessment closely matched the 50th percentile score of the standardization sample. A representative sample of the normal population should achieve a mean score close to the standardized 50th percentile, 5% of the sample would be expected to score below the 5th percentile and 25% would be expected to score below the 25th percentile. The expected mean dementia score (NART minus full-scale IQ) should be zero unless subjects had experienced cognitive decline, in which case the score becomes progressively more positive.

**Follow-up**

The subjects were followed for a mean of 4 years (range 1–6 years). During this period 10 subjects (five male and five female) became clinically affected (see below and Table 2) All 10 had progressive symptoms of memory loss and fulfilled NINCDS–ADRDA (National Institute of Neurological and Communicative Disorders and Stroke–Alzheimer’s Disease and Related Disorders Association) criteria (McKlenn et al., 1984) for possible Alzheimer’s disease and seven subsequently fulfilled criteria for probable Alzheimer’s disease with progressive impairment in more than one
cognitive domain interfering with activities of daily living. Eight of the these subjects had MRI studies reported as showing the development of definite diffuse cortical atrophy with involvement of the medial temporal lobe structures; in two of these eight subjects the development of atrophy was only detectable by comparison with earlier scans. Two subjects in the affected group had serial MRI scans reported as showing ‘no abnormality’.

Two other subjects requested clinical referral for investigation because they were concerned about possible memory problems. After full clinical assessment including normal repeat MRI these subjects were considered to be unaffected (a view shared by their spouses) and have since had no further symptoms and no assessments showing cognitive decline; they remain under follow-up as at risk for familial Alzheimer’s disease. These subjects were included in the ‘unaffected’ group (n = 53) for analysis purposes.

### AFFECTED SUBJECTS

For the 10 affected subjects the mean time (± SD) from initial assessment to first symptomatic assessment was 3.1 ± 1.5 years (range 1–5 years). Symptoms of very mild episodic memory problems were the most common symptom declared and this had been noticed by the spouse or close family member, on average, 6 months before the first symptomatic assessment. All but one of the subjects who became affected scored 29/30 or 30/30 on the MMSE at initial assessment. The one subject who scored 25/30 maintained this score for the next 2 years, a similar score to other members of his family who have remained well. There were no significant differences between the subjects who became clinically affected and those who remained well in terms of age, gender, handedness or MMSE at initial assessment (Table 2).

The mean scores for each of the neuropsychological tests performed at initial assessment for the subjects who remained unaffected and those who became clinically affected are given in Table 3. Those subjects that later became affected had significantly lower initial scores on the recognition memory test for words (Z = −2.95, P = 0.003). In addition the affected group had lower performance IQ at initial assessment compared with those who remained well (Z = −2.17, P = 0.030). On other individual neuropsychological test scores there were no significant differences between the two groups at initial assessment, but there was a significant difference between the two groups on the composite cognitive score (Z = −2.04, P = 0.033).

Two of the at-risk subjects who became affected had initial memory scores below the 5th percentile at first assessment. When the at-risk affected group was reanalysed excluding these two subjects, the group of eight other at-risk individuals who later became affected still scored lower on verbal memory testing at initial assessment compared with the at-risk group who remained well (Z = −2.21, P = 0.027).

The test results of the neuropsychological assessments carried out on the affected group once they were considered to be clinically affected and fulfilled NINCDS–ADRDA criteria either for possible or probable Alzheimer’s disease are given in Table 4. These results are compared with the results of the group that remained well. The affected group now scored lower than the unaffected group on all tests. Tests of memory, general intellectual function, speed and attention were most significantly reduced with a relatively smaller difference on tests of naming, literacy and visuospatial skills. At this stage all the affected subjects had had a fall of two or more points in their MMSE scores, with the group mean having now fallen from 29.2 to 20.9 and individual scores ranging from 15 out of 30 to 28 out of 30.

### DISCUSSION

The results of this study suggest that measurable cognitive decline is present 2–3 years before symptoms are manifest and 4–5 years before individuals fulfil criteria for probable Alzheimer’s disease. While none of the 10 subjects who became affected has come to post-mortem examination the diagnosis of Alzheimer’s disease is relatively secure since alternative pathologies such as vascular disease would be unlikely in this young cohort and there was no evidence of ischaemia on MRI. Other degenerative dementias are also unlikely because each individual had a family history of autopsy-proven Alzheimer’s disease. Eight of the 10 subjects showed progressive decline in more than one cognitive domain, fulfilling clinical criteria for probable Alzheimer’s disease. In the two most mildly affected subjects, neuropsychological impairment was still confined to memory at the last assessment, thereby fulfilling criteria for possible rather than probable Alzheimer’s disease; only continued follow-up will confirm more widespread progression.

The group of subjects who went on to develop Alzheimer’s

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### Table 2 Characteristics at initial assessment of subjects

<table>
<thead>
<tr>
<th></th>
<th>Unaffected group (n = 53)</th>
<th>Affected group (n = 10)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Male : female</td>
<td>26 : 27</td>
<td>5 : 5</td>
</tr>
<tr>
<td>Mean age ± SD (years)</td>
<td>45.1 ± 8.1</td>
<td>42.1 ± 8.1</td>
</tr>
<tr>
<td>Mean MMSE (±SD)</td>
<td>29.1 ± 1.2</td>
<td>29.2 ± 1.5</td>
</tr>
<tr>
<td>Range MMSE (maximum 30)</td>
<td>24–30</td>
<td>25–30</td>
</tr>
</tbody>
</table>

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disease had significantly reduced scores on the recognition memory test for words when first assessed between 1 and 5 years before becoming symptomatic. Two subjects already had impaired scores (below the 5th percentile) on this test when first assessed; these were the subjects who were the first to become symptomatic, 1 year later. Even excluding these two subjects, the mean initial verbal memory scores were significantly lower in the remaining eight subjects compared with those of the subjects who remained well. It should be emphasized that these eight subjects, when considered on an individual basis, were considered to be performing at adequate levels on the memory tests in that they all scored within the normal range of the standardized population on both verbal and visual memory tests. It is only when considered as a group that the lower memory scores become statistically significant. Each individual would probably have been considered to be within normal limits in a clinical setting. Not surprisingly the MMSE was insensitive to change at this early stage.

The performance IQ was the only other cognitive measure on which the 10 individuals who subsequently became affected scored significantly lower than the group of at-risk subjects who remained well. On several measures there was a trend towards a significant difference between the groups. However, the difference between the groups on naming was minimal. This argues against an impairment of semantic memory being an early feature of familial Alzheimer’s disease.

Widespread cognitive deficits were recorded by the time the 10 affected individuals first fulfilled the criteria for probable Alzheimer’s disease (McKhann et al., 1984). Memory for both visual and verbal material was impaired

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### Table 3 Neuropsychological scores for affected and unaffected groups at initial assessment

<table>
<thead>
<tr>
<th>Test</th>
<th>Maximum score</th>
<th>Unaffected subjects</th>
<th>Affected subjects</th>
<th>Z-score*</th>
<th>P-value*</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>Mean ± SD</td>
<td>Median (range)</td>
<td>Mean ± SD</td>
<td>Median (range)</td>
</tr>
<tr>
<td>Verbal IQ</td>
<td>98.7 ± 11.1</td>
<td>97 (74–127)</td>
<td>91.7 ± 8.7</td>
<td>90.5 (81–102)</td>
<td>–1.80 0.072</td>
</tr>
<tr>
<td>Performance IQ</td>
<td>101.4 ± 14.5</td>
<td>98 (75–138)</td>
<td>90.5 ± 13.0</td>
<td>88.5 (71–113)</td>
<td>–2.17 0.030</td>
</tr>
<tr>
<td>NART</td>
<td>101.7 ± 10.2</td>
<td>102 (71–123)</td>
<td>98.4 ± 14.1</td>
<td>100.5 (80–117)</td>
<td>–0.67 0.502</td>
</tr>
<tr>
<td>Memory: words</td>
<td>50</td>
<td>46.2 ± 3.4</td>
<td>41.3 ± 5.1</td>
<td>41 (33–48)</td>
<td>–2.95 0.003</td>
</tr>
<tr>
<td>Memory: faces</td>
<td>50</td>
<td>44.5 ± 4.0</td>
<td>42.2 ± 4.2</td>
<td>42.5 (33–49)</td>
<td>–1.50 0.133</td>
</tr>
<tr>
<td>Naming</td>
<td>30</td>
<td>21.3 ± 5.3</td>
<td>20.7 ± 6.2</td>
<td>22 (5–26)</td>
<td>–0.17 0.865</td>
</tr>
<tr>
<td>Arithmetic</td>
<td>24</td>
<td>12.9 ± 5.6</td>
<td>10.3 ± 4.8</td>
<td>11 (3–20)</td>
<td>–1.47 0.142</td>
</tr>
<tr>
<td>Spelling</td>
<td>30</td>
<td>20.2 ± 5.8</td>
<td>16.4 ± 8.5</td>
<td>18 (6–28)</td>
<td>–1.30 0.192</td>
</tr>
<tr>
<td><strong>Visual Object and Spatial Perception Test</strong></td>
<td></td>
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<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Silhouettes</td>
<td>30</td>
<td>22.9 ± 3.8</td>
<td>20.9 ± 4.4</td>
<td>21.5 (11–26)</td>
<td>–1.15 0.249</td>
</tr>
<tr>
<td>Cubes</td>
<td>10</td>
<td>9.0 ± 1.2</td>
<td>8.9 ± 1.0</td>
<td>9 (7–10)</td>
<td>–0.64 0.522</td>
</tr>
<tr>
<td>Digit Copying (s)</td>
<td>41.4 ± 13.0</td>
<td>41.9 ± 9.4</td>
<td>42 (27–61)</td>
<td>–0.67 0.506</td>
<td></td>
</tr>
<tr>
<td>Composite Cognitive Score</td>
<td>4.3 ± 0.6</td>
<td>4.3 (2.4–5.0)</td>
<td>3.9 ± 0.5</td>
<td>3.9 (3.0–4.7)</td>
<td>–2.04 0.033</td>
</tr>
<tr>
<td>Dementia Index</td>
<td>2.0 ± 9.3</td>
<td>8.1 ± 9.9</td>
<td>9.0 (–7 to +24)</td>
<td>–1.67 0.096</td>
<td></td>
</tr>
</tbody>
</table>

*Mann–Whitney U test.

### Table 4 Neuropsychological scores for affected and unaffected groups at diagnostic assessment

<table>
<thead>
<tr>
<th>Test</th>
<th>Maximum score</th>
<th>Unaffected subjects</th>
<th>Affected subjects</th>
<th>Z-score*</th>
<th>P-value*</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>Mean ± SD</td>
<td>Median (range)</td>
<td>Mean ± SD</td>
<td>Median (range)</td>
</tr>
<tr>
<td>Verbal IQ</td>
<td>101.5 ± 12.2</td>
<td>98 (80–129)</td>
<td>85.2 ± 11.6</td>
<td>85.5 (70–110)</td>
<td>–3.55 0.000</td>
</tr>
<tr>
<td>Performance IQ</td>
<td>107.8 ± 17.2</td>
<td>109 (74–146)</td>
<td>85.4 ± 16.1</td>
<td>82 (66–116)</td>
<td>–3.28 0.001</td>
</tr>
<tr>
<td>Memory: words</td>
<td>46.6 ± 3.2</td>
<td>48 (39–50)</td>
<td>32.1 ± 6.2</td>
<td>30 (25–45)</td>
<td>–4.50 0.000</td>
</tr>
<tr>
<td>Memory: faces</td>
<td>43.6 ± 3.9</td>
<td>44 (34–50)</td>
<td>37.7 ± 4.6</td>
<td>37 (32–45)</td>
<td>–3.19 0.001</td>
</tr>
<tr>
<td>Naming</td>
<td>22.5 ± 5.6</td>
<td>24 (7–30)</td>
<td>19.8 ± 5.5</td>
<td>20 (7–26)</td>
<td>–1.70 0.090</td>
</tr>
<tr>
<td>Arithmetic</td>
<td>13.1 ± 6.0</td>
<td>14 (2–24)</td>
<td>7.2 ± 6.5</td>
<td>6 (1–21)</td>
<td>–2.51 0.012</td>
</tr>
<tr>
<td>Spelling</td>
<td>19.8 ± 6.5</td>
<td>21.5 (6–29)</td>
<td>16.3 ± 8.3</td>
<td>16 (4–28)</td>
<td>–1.18 0.237</td>
</tr>
<tr>
<td><strong>Visual Object and Spatial Perception Test</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Silhouettes</td>
<td>23.6 ± 3.8</td>
<td>24 (15–30)</td>
<td>21.1 ± 5.8</td>
<td>22 (11–28)</td>
<td>–1.15 0.249</td>
</tr>
<tr>
<td>Cubes</td>
<td>9.4 ± 1.0</td>
<td>10 (5–10)</td>
<td>7.1 ± 3.6</td>
<td>8.5 (6–10)</td>
<td>–2.21 0.027</td>
</tr>
<tr>
<td>Digit Copying (s)</td>
<td>41.4 ± 9.9</td>
<td>40 (27–64)</td>
<td>54.8 ± 16.7</td>
<td>52.5 (33–82)</td>
<td>–2.41 0.016</td>
</tr>
<tr>
<td>Composite Cognitive Score</td>
<td>4.4 ± 0.5</td>
<td>4.6 (2.7–5.0)</td>
<td>3.2 ± 0.8</td>
<td>3.0 (1.7–4.3)</td>
<td>–3.60 0.000</td>
</tr>
<tr>
<td>Dementia Index</td>
<td>–2.9 ± 10.6</td>
<td>–3.0 (–28 to +21)</td>
<td>13.9 ± 11.7</td>
<td>12.5 (–2 to +33)</td>
<td>–3.63 0.000</td>
</tr>
</tbody>
</table>

*Mann–Whitney U test.
and there had been a significant decrement in the arithmetic, speed and verbal IQ measures compared with the unaffected group. It is noteworthy that there was still no significant difference between the groups on naming. The two composite measures of overall impairment reflected the widespread cognitive decline in that there were highly significant differences between the affected and unaffected groups on both the composite cognitive score and the dementia index. Even at this stage these individuals would have been considered by many studies to be only mildly affected in that the mean MMSE score for the group was still 21 out of 30.

Studies that have examined the neuropsychological deficits in ‘mild’ Alzheimer’s disease have shown that deficits are already widespread, but they have suggested that memory tests make the largest contribution to discriminating early Alzheimer’s disease from healthy ageing (Storandt and Hill, 1989; Flicker et al., 1991). Our results accord with this suggestion in that they imply that memory decline is one of the earliest measurable cognitive deficits in Alzheimer’s disease. It is interesting to note that we found verbal memory to be more vulnerable than non-verbal memory. In our study we used the recognition memory test for faces which is an entirely similar test of non-verbal memory to the recognition memory test for words, and indeed is a slightly more stringent test. Thus it is unlikely that this result reflects different test sensitivities. Nonetheless the verbal test was a much better predictor of which subjects would develop Alzheimer’s disease. Alternatively this finding may be considered to be an indication of left (or dominant) hemispheric vulnerability in Alzheimer’s disease. Some support for the implication of left hemispheric vulnerability comes from the report of verbal memory loss being more common than similar selective visual memory deficits in patients with cerebral atrophy (Warrington, 1984), as well as from other neuropsychological (Capitani et al., 1990; Becker et al., 1992; Greene et al., 1996), neurochemical (Rossor et al., 1982) and functional imaging (Loewenstein et al., 1989; Kennedy et al., 1995b) studies in sporadic and familial Alzheimer’s disease.

At initial assessment all the at-risk individuals who were scanned had essentially normal imaging. Visual inspection of MRI was not found to be predictive of dementia in these very early cases. The use of quantitative analysis of volume loss using registration of serial MRI may improve the detection and localization of increased rates of atrophy in the earliest stages (Fox et al., 1996). It is perhaps worth commenting that the finding of early verbal memory deficits accords with imaging and autopsy reports of early hippocampal involvement in Alzheimer’s disease. By contrast, however, our observation of a deficit in the performance IQ argues that damage due to the disease may already be widespread even at this early stage, with involvement extending beyond the hippocampal formation.

There have been previous suggestions that presymptomatic cognitive deficits may predict a diagnosis of Alzheimer’s disease. Three longitudinal studies in sporadic elderly subjects suggested that cognitive decline may even precede dementia by several years. In the Framingham study a ‘preclinical phase’ of cognitive deficits preceded the clinical diagnosis of probable Alzheimer’s disease in some cases (mean age 76 years) by 6 years. Their study also found tests of verbal memory to be most significantly related to diagnostic outcome, however, their battery of tests was very limited taking only 20 min to administer and therefore they could not cover a wide range of cognitive domains (Linn et al., 1995). The most sensitive tests in their study were tests of verbal recall (the Percentage Retained of the Logical Memory test and Paired Associate Learning). In the Bronx Ageing Study, follow-up of individuals aged 75–85 years showed two tests of verbal memory (the Fuld Object Memory Evaluation and the Buske Selective Reminding Test) to be the most powerful predictors of subjects going on to receive a diagnosis of probable Alzheimer’s disease 6 months after the initial assessment (Masur et al., 1994). Howieson et al. (1997) followed a cohort of subjects aged >80 years who initially did not meet criteria for dementia; they found lower verbal memory scores in those individuals who developed clinical dementia on average 2.8 years later. However, there is recent evidence to suggest that in very elderly subjects who are apparently healthy, verbal memory declines ahead of non-verbal memory (Janowsky et al., 1996). By contrast, in our study all subjects were <65 years of age and they were carefully screened to exclude symptomatic individuals prior to entry.

The finding of presymptomatic neuropsychological deficits has not answered the question of when cognitive deficits are first detectable. Follow up of the unaffected at-risk cohort continues and may show that cognitive deficits are detectable even earlier than we report here. The ‘unaffected’ group is likely to include individuals who will subsequently become symptomatic, and that possibility would tend to blunt rather than increase any group differences. At this stage, we can only suggest that verbal memory loss is detectable some years before symptoms appear. This argues, at least in familial Alzheimer’s disease, against a catastrophic onset of the disease at the time of symptom appearance (Smith et al., 1996). It suggests that a gradual phase of neuronal degeneration and dysfunction precedes clinical diagnosis by many years. In familial Alzheimer’s disease the genetic defect is present from birth and yet the symptom onset is at least 30 years later. It is still unclear at what point the genetic defect starts to have an effect at a cellular level, although deposition of Aβ1–42 can be observed in Down’s syndrome (in which individuals carry an extra copy of the amyloid precursor protein gene) as early as the third decade (Teller et al., 1996).

This study demonstrates, in a population relatively free of the confounding effects of age-related cognitive decline or co-morbidity, that subtle cognitive deficits predate symptoms in familial Alzheimer’s disease by several years. This suggests that there exists a period of several years between detectable disease and clinical diagnosis; in theory this offers the
possibility of therapeutic intervention at a stage when most
cognitive function is still preserved. Furthermore, if
neuropsychological deficits are measurable then this must
reflect neuronal dysfunction or death which may be directly
detectable with improved imaging techniques or biochemical
markers. Our findings of presymptomatic cognitive
function accord with recent reports of hippocampal
atrophy on MRI and reduced cerebral glucose metabolism
on PET at a presymptomatic stage in elderly individuals
(Golomb et al., 1996) or those with a family history of
Alzheimer’s disease (Kennedy et al., 1995a; Fox et al.,
1996b; Reiman et al., 1996). Detailed comparison of the
predictive value of these investigations and neuropsychol-
ogical measurements is necessary to determine which com-
bination of tests are of greatest diagnostic use in an individual
case. However, it seems reasonable to suggest that sensitive,
and perhaps repeated, testing of verbal memory function
should form part of such diagnostic assessment. The detection
of these early changes may allow presymptomatic therapeutic
intervention in subjects at high risk of familial Alzheimer’s
disease.

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