Brain (1996), **119**, 2001–2007

Presymptomatic hippocampal atrophy in Alzheimer's disease
A longitudinal MRI study

N. C. Fox,[1,2] E. K. Warrington, [1] P. A. Freeborough,[1,2] P. Hartikainen,[1,2] A. M. Kennedy,[1,2] J. M. Stevens[1,2] and M. N. Rossor[1,2]

[1]*The National Hospital for Neurology and Neurosurgery and* [2]*St Mary's Hospital, London, UK*

Correspondence to: Dr Martin Rossor, Dementia Research Group, The National Hospital for Neurology and Neurosurgery, Queen Square, London WC1N 3BG, UK

Summary
The hippocampal formation (HF) is known from pathological and MRI studies to be severely atrophied in established Alzheimer's disease. However, it is unclear when the earliest changes in the HF occur. We performed a longitudinal study of asymptomatic individuals at risk of autosomal dominant familial Alzheimer's disease in order to assess presymptomatic changes in the HF. Seven at risk members of a familial Alzheimer's disease pedigree associated with the amyloid precursor protein 717 valine to glycine mutation underwent serial MR scanning and neuropsychological assessments over 3 years. These assessments were compared with results from 38 normal controls. During the study three at risk subjects became clinically affected. Volumetric measurement of the HF showed that asymmetrical atrophy developed in these subjects before the appearance of symptoms. Verbal and visual memory measures declined in parallel with hippocampal loss. A loss of up to 8% per annum of the volume of the HF occurred in the 2 years over which symptoms first appeared. These findings may have implications for early diagnosis of Alzheimer's disease.

Keywords: Alzheimer's disease; MRI; hippocampus; memory; amyloid precursor protein

Abbreviations: CDR = Clinical Dementia Rating; HF = hippocampal formation; MMSE = Mini Mental State Examination; nHF = hippocampal formation normalized for intracranial volume

Introduction
The HF is invariably involved in severe cases of Alzheimer's disease, so much so that Alzheimer's disease has been called a 'hippocampal dementia' (Hyman *et al.*, 1984; Ball *et al.*, 1985). The histopathological hallmarks of the disease, neurofibrillary tangles and amyloid plaques, are found in large numbers in the hippocampus. Macroscopically these are accompanied by gross atrophy of the HF and concomitant enlargement of surrounding CSF spaces (West *et al.*, 1994). Post-mortem studies of elderly mildly affected individuals have suggested that these pathological changes start in the entorhinal cortex and hippocampus before progressing to the association cortices (Braak *et al.*, 1993). The hippocampus is known to be closely involved in memory function (Squire, 1986). These findings accord with the clinical observation that memory impairment is one of the earliest manifestations of Alzheimer's disease (Newman *et al.*, 1994; Soininen *et al.*, 1994; Hodges and Patterson, 1995).

Support *in vivo* for the involvement of the HF in Alzheimer's disease comes from MRI. Reproducible MRI-based volumetric measurement of the HF is well established with contiguous thin slice acquisition allowing accurate quantification of atrophy (Jack *et al.*, 1992). Hippocampal volumes have consistently been shown to be reduced by as much as 40% in patients with clinically diagnosed Alzheimer's disease of moderate severity (Seab *et al.*, 1988; Kesslak *et al.*, 1991; Jack *et al.*, 1992). The extent of hippocampal atrophy correlates with overall severity and memory impairment (Kesslak *et al.*, 1991; Deweer *et al.*, 1995; Laakso *et al.*, 1995). Studies of patients described as mildly affected, e.g. Mini Mental State Examination (MMSE) score >21, have shown that on average the HF has already lost 25% or more of its volume at this stage of Alzheimer's disease when compared with normal controls (Killiany *et al.*, 1993; Lehericy *et al.*, 1994; Laakso *et al.*, 1995). However,

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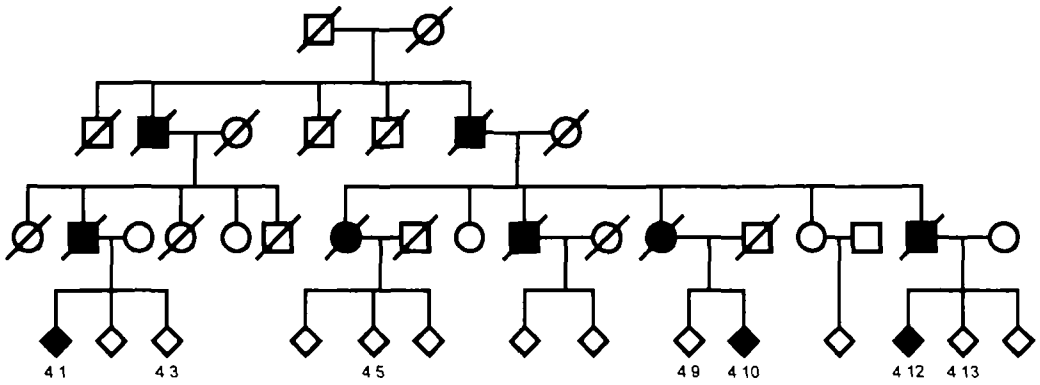

Fig. 1 Family tree. Squares = males; circles = females; filled symbols = affected; diagonal line = deceased subject. At risk individuals are shown with a diamond to preserve anonymity; those who took part in the study have subject numbers underneath the symbol.

even such mildly affected patients have had symptoms for some months or years. Studies of patients with clinically diagnosed Alzheimer's disease will inevitably miss any pre-symptomatic changes.

To test the hypothesis that structural changes in the HF are measurable by MRI before the development of overt symptoms, we conducted a prospective study of subjects at risk of familial Alzheimer's disease. Individuals carrying a mutation in the amyloid precursor protein gene develop familial Alzheimer's disease with an early and relatively predictable age at onset (Rossor *et al.*, 1993). This study recruited subjects who were within 5 years of the historical age at onset for that family. In this way early symptomatic or pre-symptomatic cerebral changes may be detected in individuals who later become clinically affected. Longitudinal scanning allows small volume changes to be detected as the initial scan for each subject can be used as a within-subject control. Over a 3-year period serial MRI-based volumetric measurement of the HF and detailed neuropsychological assessments of seven initially asymptomatic, at risk individuals from a familial Alzheimer's disease pedigree associated with the amyloid precursor protein 717 valine to glycine mutation were performed (Chartier-Harlin *et al.*, 1991). The results in the three subsequently symptomatic cases and in the four asymptomatic siblings were each compared with neuropsychological and HF measurements of 38 normal controls.

Methods

Subjects

Seven (six male and one female) at risk members of a large familial Alzheimer's disease amyloid precursor protein $717_{Val\text{-}Gly}$ pedigree who were within 5 years of the historical age at onset (45–55 years) of the disease within the family were recruited to a longitudinal study. The family tree is shown in Fig. 1; subject numbers refer to individuals who participated in the study. Details of this pedigree have previously been described (Kennedy *et al.*, 1993). Thirty-eight (19 male and 19 female) normal control subjects without a family history of dementia were recruited from volunteers and from the spouses of individuals with familial Alzheimer's disease. Informed written consent was obtained from all subjects. The study received ethical approval from participating centres.

Each assessment included clinical examination, neuropsychometry and an MRI volumetric scan. On each visit a careful history for the presence of symptoms was taken from the subject and from the subject's spouse or other close family member. All subjects were assessed with the MMSE and the Clinical Dementia Rating (CDR) (Folstein *et al.*, 1975; Hughes *et al.*, 1982).

Neuropsychology

Comprehensive neuropsychological assessments were carried out at approximately the same time as the MRI scan. The test battery included measures of current intelligence, verbal and visual memory, naming, perception and arithmetic. The tests administered were the Wechsler Adult Inventory Scale—Revised, short version of four verbal subtests and three performance subtests (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) and the Graded Difficulty Arithmetic Test (Jackson and Warrington, 1986). The National Adult Reading Test (Nelson, 1991) was administered to obtain a measure (reading IQ equivalent) of optimum level of intellectual function. Controls underwent the memory tests described above as well as the National Adult Reading Test.

Imaging

MRI was performed on a General Electric 1.5 Tesla Signa unit. All scans included a routine sagittal (T_1-weighted) scout sequence and an axial dual-echo sequence (T_2- and proton

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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 256×128 image matrix with acquisition parameters (35/5/1/35—TR/TE/NEX/FLIP).

MRI measurements

Digitized MR images were transferred to a Sun work station (Sun Microsystems Inc., Mountain View, Calif., USA) where measurements were performed retrospectively in a randomized and blinded fashion. All patient details were removed from the images and the studies were chosen at random from a larger group including normal controls. Measurements were made using the MIDAS image analysis program (Freeborough *et al.*, 1996). This program allows the viewing and defining of anatomical regions of interest in the coronal, axial or sagittal planes simultaneously. The HF was defined as including the dentate gyrus, the hippocampus proper, the subiculum and the alveus. The fornix and fimbria were excluded from the measurements. Standard neuroanatomical atlases were used to define the HF from its tail to its head (typically 25 to 30 slices in the coronal plane) (Duvernoy, 1988). T_1-weighted MRIs permit grey and white matter structures to be differentiated and the thin slices employed (1.5 mm) give a voxel size of 2.65 mm and increased accuracy to the volume estimates. The HF was first manually outlined in the sagittal plane and then edited in the coronal plane. The use of more than one plane of measurement, while time consuming, allows more accurate determination of anatomical boundaries. Change in hippocampal volume measurements for the same individual may be compared directly but in order to allow comparisons between individuals who have different total brain volumes the hippocampal volumes were normalized using the total intracranial volume as a measure of premorbid brain size. Total intracranial volumes were measured using the axial T_2-weighted scans. The external limit of the CSF (inner border of the calvarium) was outlined using a semi-automated interactive grey level thresholding technique. The inferior plane of the intracranial volume was arbitrarily taken to be the lowest slice which included cerebellar tissue. The volumes of the HF and the total intracranial volumes so defined were calculated automatically. The relationship between the HF volume and the total intracranial volume was calculated using a linear regression model ($r = 0.54$, $P < 0.001$): the HF volumes of all the individuals were then normalized for intracranial volumes according to the covariance method described by Jack *et al.* (1989). Intra-rater reproducibility was estimated by measuring 13 HFs twice without knowledge of the individual's identity or the previous measurement. This gave a mean (±SD) of the difference between measurements of 55 mm^3 (±106 mm^3), equivalent to a mean difference of 1.85% and a coefficient of variation of 3.6% (Altman, 1991). Similarly, interrater reproducibility was tested by two of us (N.C.F. and P.H.) separately measuring 16 HF volumes. This gave a mean (±SD) difference between measurements of 23 mm^3 (±114 mm^3), equivalent to a mean difference of 0.9% and a coefficient of variation of 4.3%.

Statistical analyses

The normalized volumes of the HFs of the at risk individuals who became affected and the at risk individuals who remained well were each compared with the controls using the Mann–Whitney *U* test (two-tailed) with MINITAB software (State College, Penn., USA).

Results

Subjects

The mean (±SD) age of the at risk subjects of 45 years (±5 years) did not differ significantly from the mean (±SD) age of the control subjects of 48 years (±8 years). At the initial assessments, all seven at risk family members were asymptomatic in that neither they, nor their families, had any complaints relating to their cognitive function. At entry into the study all subjects were working full-time. All had normal neurological assessments and all scored 29/30 or 30/30 on the MMSE and 0 on the CDR.

Clinical

There was no significant deterioration either clinically or in the neuropsychology test scores of four of the subjects. Three subjects, 4.1, 4.10 and 4.12, however, became clinically affected during the course of the study, with concerns about memory function appearing before their second assessments. Subject 4.1 became worried about his memory 2 years after his first scan and sought medical advice because of this 1 year later. At this stage he was still working and scored 27/30 on the MMSE and 0.5 on the CDR. He continued working full-time until 3 months after his third scan, 3.5 years after recruitment into the study. Subject 4.10 became worried about his memory in the year following his first scan and began to have difficulties route finding and coping at work during the next year. He went on sick leave 4 months before his second scan. At the time of his second scan he was still able to score 28/30 on the MMSE and had a CDR of 0.5–1.0. By the time of his third scan, a year later, he was significantly cognitively impaired with a CDR of 1.0–2.0. Subject 4.12 started having trouble coping with work 18 months after the first scan and her husband became concerned that her memory had deteriorated. She retired on sick leave 6 months later, a year before the last scan. At this stage her MMSE had fallen to 24/30 with a CDR of 0.5–1.0.

Neuropsychology

Full-scale Wechsler Adult Inventory Scale—Revised scores together with reading IQ equivalent scores for each subject

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Table 1A *Reading and intelligence tests*

	Reading IQ equivalent	Full scale WAIS IQ		
	Session/scan	Session/scan		
	1	1	2	3
4.3	105	109	118	109
4.13	94	101	100	
4.5	110	98	101	109
4.9	111	117	107	
4.1	96	101	101	95
4.12	116	93*	84†	
4.10	108	95*	83†	78†

Discrepancy score: *<5%; †<1%.

Table 1B *Recognition memory tests*

	Words (max. 50)			Faces (max. 50)		
	Session/scan			Session/scan		
	1	2	3	1	2	3
4.3	49	48	45	48	46	48
4.13	46	45		46	45	
4.5	49	49	47	45	47	45
4.9	37‡	48	47	47	46	44
4.1	40*	28‡	38*	49	31‡	36†
4.12	40*	27‡		42	37	
4.10	33‡	25‡	13‡, §	33‡	35‡	11†, §

Discrepancy score: *<25%; †<5%; ‡<1%. §Maximum 25.

at each assessment are given in Table 1A. A significant decrement between these scores at the fifth and first percentile is indicated. Similarly, verbal and visual memory scores are given in Table 1B and naming, arithmetic and perceptual scores are given in Table 1C.

At risk subjects who remained well

There was no deterioration in these four subjects' neuropsychological test scores. One individual, Subject 4.9, had a verbal memory score at the first assessment that suggested a selective impairment that was not present in subsequent assessments.

At risk subjects who became clinically affected

The memory assessments of these three subjects were initially all above the fifth percentile apart from those of verbal and visual memory in Subject 4.10. By the second assessment, Subject 4.1 had a global memory deficit and Subject 4.12's verbal memory test scores had fallen to below the first percentile. Subjects 4.10 and 4.12, at their initial assessments, had a significant discrepancy between their reading IQ equivalent score and their full scale score; these became more pronounced as they became clinically affected. Performance on the naming test was entirely normal in all individuals at all assessments. Arithmetic was impaired at the first assessment in one individual and had deteriorated in one individual by the second assessment. In all but one individual, perception was entirely normal at all assessments.

Hippocampal volumes

Tables 2 and 3 show the hippocampal formations normalized for intracranial volume (nHF), of the at risk individuals and control subjects. The volumes of the nHFs of the four at risk subjects who remained well, were not significantly different from the controls, at any stage of the study (*see* Fig. 2). All these subjects had <4% change in volume measurements (mean 1% loss) over the 3 years (See Fig. 3).

By contrast, the volumes of the left nHFs of the three subjects who became symptomatic were significantly different from the left nHFs of the normal controls even at the time of their initial scan ($P < 0.05$). The right nHFs were not significantly different from the controls at this stage. At the second scan (when the three subjects were already symptomatic, with MMSEs of 28/30, 27/30 and 24/30) both right and left hippocampi were significantly different from the normal controls ($P < 0.01$). The volumes of the HFs of two of these subjects changed markedly over this period with volume losses of 5–10% per annum (*see* Figs 2 and 3). Furthermore, there was already marked asymmetry in these subjects' hippocampi at the time of their initial scan. The volume of Subject 4.1's left HF was 9% smaller than his right, Subject 4.13's left HF was 6% smaller than her right, whereas Subject 4.10's right HF was 12% smaller than his left. None of the normal controls or the at risk subjects who remained well had asymmetry of >5%.

Discussion

This study shows that significant hippocampal atrophy in familial Alzheimer's disease is detectable at an early stage in the disease, and when subjects are apparently asymptomatic. At the time of their initial scans, all three subjects who subsequently became clinically affected had significant asymmetry in their hippocampal volumes implying that atrophy of the smaller HF had occurred over some period before the initial scan. In each subject, hippocampal atrophy appeared when the subject was still working full time and was scoring above 28/30 on the MMSE. This is 1–2 years earlier than these individuals would otherwise have presented clinically. The definition of pre-symptomatic was that neither the subject nor their family had any complaints about their cognitive function. The neuropsychological results show that even when these criteria were fulfilled, memory deficits were

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Table 1C *Naming, arithmetic and perception*

	Naming (max. 30)			Arithmetic (max. 24)			Perception (max. 30)		
	Session/scan			Session/scan			Session/scan		
	1	2	3	1	2	3	1	2	3
4.3	25	28		13	15		29	29	
4.13	22	22	22	11	11	12	28	27	29
4.5	20	21	22	20	21	23	20	21	21
4.9	28	27		11	12		27	27	
4.1	19	18	20	12	15	14	21	27	26
4.12	26	20		11	6*		16†	13*	
4.10	26	26	28	5*	2‡		26	23	24

Discrepancy score: *<25%; †<5%; ‡<1%. The results of the neuropsychological tests conducted at the time of each scan (*see* Fig. 1) are shown for the at risk individuals; subjects who became symptomatic are shown in the lower half.

Table 2 *Normalized hippocampal volumes for the at risk individuals*

		Scan 1 (nHF/mm^3)	Scan 2 (nHF/mm^3)	Scan 3 (nHF/mm^3)	Change (%/year)
4.3	L	2975	3041	2922	−0.6
	R	3021	3153	2971	−0.6
4.13	L	3151	3063		−0.9
	R	3199	3151		−0.5
4.5	L	3170	3203	3194	0.2
	R	3328	3187	3347	0.2
4.9	L	2880	2962	2956	1.1
	R	2991	3056	3012	0.3
4.1	L	2745	2648	2529	−2.7
	R	3018	2574	2475	−6.2
4.12	L	2176	2084		−1.4
	R	2305	2160		−2.1
4.10	L	2405	2249	1888	−8.6
	R	2113	1865	1699	−7.8

Those at risk individuals who became symptomatic are shown in the lower half of the table.

Table 3 *nHF volumes of the controls*

	Median/mm^3	Mean/mm^3	SD/mm^3
Left	3001	3021	280
Right	3025	3038	267

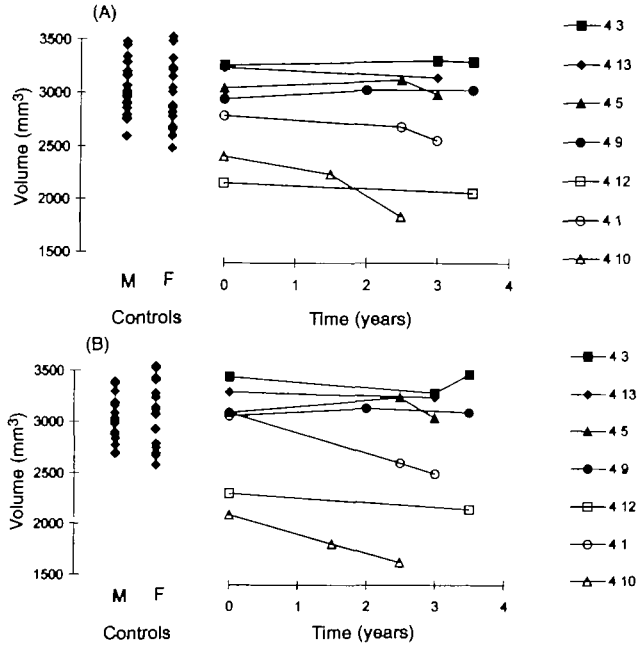

Fig. 2 Left (**A**) and right (**B**) hippocampal formation volumes, normalized for intracranial volume, showing atrophy in the three subjects who became affected (open symbols) while the hippocampal volumes of the four at risk individuals who remained well (closed symbols) stayed within the normal range of the controls. Values for the male (M) and female (F) controls are shown on the left of the graphs.

already measurable, with one individual having a global memory deficit and two other individuals having a selectively weak verbal memory.

This study of familial Alzheimer's disease, extends previous MRI findings in sporadic Alzheimer's disease which have shown that even mildly affected individuals have hippocampal volumes that are, on average, 25% smaller than normal controls (Killiany *et al.*, 1993; Lehericy *et al.*, 1994). Individuals classified as mildly demented on the basis of an MMSE score may have had symptoms for some considerable period, usually for at least 2 years (Laakso *et al.*, 1995), but in some cases the duration of symptoms was ≥6 years (Murphy *et al.*, 1993). Rates of atrophy in familial Alzheimer's disease at a presymptomatic or very early symptomatic stage have not been reported previously. Rates of atrophy in the hippocampus may vary widely between individuals and with disease progression (Jobst *et al.*, 1994). If the onset of hippocampal atrophy were to coincide with the onset of symptoms, then in order to have lost 25% of the volume of the hippocampus by the time the individuals were mildly affected, the mean rate of atrophy must have been between 5 and 10% per year if symptoms are assumed to have been present for between 2 and 5 years. The rate of hippocampal atrophy in this study was considerable and

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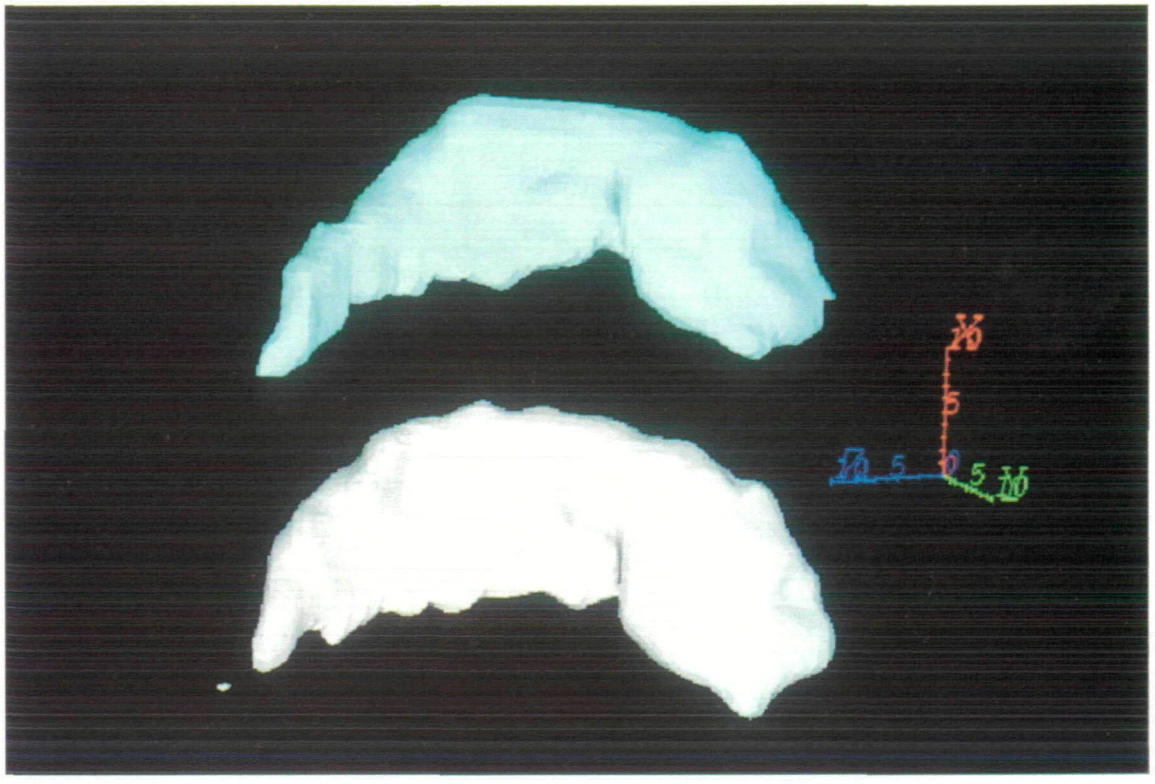

Fig. 3 Three-dimensional reconstruction showing atrophy of the left hippocampal formation of one at risk subject (4.10): the lower HF in grey is from the original scan (pre-symptomatic); by the time of his third scan (31 months later) his left HF (*above*, in blue) had lost 22% of its volume.

consistent with this estimate, at up to 8% per year, even at this very early clinical stage of the disease.

The wide variation in normal hippocampal size means that within-subject change in HF may discriminate cases of Alzheimer's disease from normal controls significantly earlier than absolute volumes. In addition, hippocampal asymmetry may be an early sign of the presence of a degenerative process. In much the same way the presence of a selective memory deficit may be a very early marker of cognitive deterioration and yet this deficit may not have produced any noticeable limitation in day to day functioning (Winters-Miner *et al.*, 1989; Newman *et al.*, 1994). This study does not answer the question of when or where cerebral changes in Alzheimer's disease are first detectable but it does indicate that the effects of the degenerative process, both in terms of neuropsychological deficits and rates of hippocampal atrophy in early onset familial Alzheimer's disease, may be significant at an earlier stage than has been shown previously. The consistency of the findings in these early onset familial cases needs to be confirmed by continued longitudinal scanning of other family members at risk of familial Alzheimer's disease and extended to sporadic cases of Alzheimer's disease. The combination of reliable hippocampal volumetry and neuropsychometry may have a role in the early diagnosis of Alzheimer's disease and in the measurement of early disease progression. Early diagnosis and objective measures of disease progression will be increasingly important in trials of therapies intended to slow or halt the disease process.

Acknowledgements

We wish to thank the staff of the MRI unit at St Mary's Hospital and the family members who helped with the study. N.C.F is an Alzheimer's Disease Society Research Fellow and this research was funded by this fellowship.

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Received June 3, 1996. Accepted July 19, 1996.

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