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Temporal lobe magnetic resonance imaging can differentiate Alzheimer's disease from normal ageing, depression, vascular dementia and other causes of cognitive impairment

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ABSTRACT

Background. Previous work suggests that temporal lobe magnetic resonance imaging (MRI) can distinguish those with dementia of the Alzheimer type (DAT) from healthy age-matched controls. However, its specificity with regard to conditions such as vascular dementia, depression and other disorders associated with cognitive impairment has not been determined.

Methods. We studied 222 subjects using T1 weighted MRI with 5·1 mm coronal slices throughout the temporal lobe. Subjects included: healthy controls ($N = 40$); DSM-III-R major depression ($N = 61$); NINCDS/ADRDA DAT ($N = 77$) and OTHER ($N = 44$, comprising subjects with vascular dementia, Huntington's disease, schizophrenia, alcohol related cognitive impairment and a group of 'memory complainers'). Hippocampus, amygdala, entorhinal cortex, parahippocampal gyrus and cerebral cortex were rated visually on a 0–3 scale by two experienced neuroradiologists blind to clinical diagnosis.

Results. Ratings of temporal lobe atrophy provided good separation between those with AD and all other groups. For example, anterior hippocampal atrophy had a sensitivity of 83% for detecting DAT, a specificity of 80% for controls, 87% for depressed subjects and 89% for OTHER. Other regions were less sensitive, but more specific for the diagnosis of DAT. In particular parahippocampal gyrus and entorhinal cortex had high specificity (97% for depressed subjects and 98% for OTHER). Because of an age-related increase in atrophy, sensitivity was highest for those over the age of 75, while specificity was highest for younger subjects. Significant correlations were observed between atrophy ratings of hippocampus, amygdala, entorhinal cortex and parahippocampal gyrus and CAMCOG memory score and length of history.

Conclusions. Temporal lobe MRI may have an important role in assisting with the clinical diagnosis of DAT, particularly its differentiation from depression and other disorders that may cause diagnostic difficulties in clinical practice.

INTRODUCTION

Definitive diagnosis of dementia of the Alzheimer type (DAT) and other dementias currently requires pathological examination of brain tissue obtained from biopsy or at autopsy (Byrne *et al.* 1991). There is much interest in trying to improve the accuracy of clinical diagnosis. Several groups, including our own, have suggested that temporal lobe changes visualized on magnetic resonance imaging (MRI), in particular hippocampal and amydala atrophy, may be early and sensitive markers for detecting those with Alzheimer's disease (AD)

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(Seab *et al*. 1988; Kesslak *et al*. 1991; Jack *et al*. 1992; Scheltens *et al*. 1992; Erkinjuntti *et al*. 1993; Desmond *et al*. 1994; Lehericy *et al*. 1994; O'Brien *et al*. 1994; O'Brien, 1995).

Although most previous studies have used healthy age-matched controls as the comparison group, if hippocampal atrophy is to be clinically useful in diagnosis its specificity, with regard to other conditions associated with cognitive deficits, needs to be demonstrated. In an earlier study (O'Brien *et al*. 1994) we found that visual ratings of hippocampal atrophy provided good discrimination between subjects with DAT and those with depression (sensitivity 93%; specificity 84%; 89% of the 75 cases correctly grouped). The aim of the current study was to assess further the ability of temporal lobe MRI to differentiate DAT from other disorders. We applied the ratings determined from that study to a larger group of subjects (which included the 75 previously reported by O'Brien *et al*. 1994) with DAT, healthy controls, depressed subjects, those with vascular dementia, Huntington's disease, schizophrenia, alcohol-related cognitive impairments and subjects presenting to a memory clinic with subjective complaints of poor memory, but for whom no objective psychological deficits could be demonstrated (hereafter termed 'memory complainers').

METHOD

Subjects

Forty control subjects (CON) over the age of 55 were recruited from among spouses of subjects seen in a hospital Memory Clinic ($N = 12$), from a register of normal volunteer subjects (not staff) kept for research purposes ($N = 21$) and from among residents of a retirement hostel ($N = 7$). A detailed history was taken from each subject regarding current physical health, education level, past medical history and current medication. The Cambridge Cognitive Examination for the Elderly (CAMCOG; Roth *et al*. 1986), which includes the Mini-Mental State Examination (MMSE; Folstein *et al*. 1975), and the Hamilton Depression Rating Scale (HDRS; Hamilton, 1967) were administered. Exclusion criteria included: evidence of depression (on clinical interview or score > 5 on the HDRS); dementia (from history or score < 80 on the CAMCOG) or evidence of any other neurological disorder (including history of stroke or transient ischaemic attack, epilepsy, Parkinson's disease, etc.); history of alcohol or drug abuse; presence of any major physical illnesses such as carcinoma, insulin dependent diabetes mellitus, renal or hepatic failure, sepsis or untreated hypothyroidism.

Sixty-one depressed subjects (DEP) over the age of 55 were recruited over an 18 month period from among in-patients of two Old Age Psychiatry Units and two General Psychiatry Units. All subjects suffered from major depression according DSM-III-R criteria (APA, 1987). Eighteen subjects had first onset of depression in old age (over 65), 49 fulfilled criteria for melancholic subtype (DSM-III-R), 22 had psychotic symptoms and five were bipolar. All underwent a standard psychiatric history and mental state examination and subjects were screened by history and physical examination to ensure they had no evidence of neurological disorder, alcohol or drug abuse or major physical illnesses such as carcinoma, insulin dependent diabetes mellitus, renal or hepatic failure, sepsis or untreated hypothyroidism. Routine haematology and biochemistry screening tests were performed (including thyroid function) to exclude an organic cause for depression. Cognitive function was assessed in all subjects by the MMSE and, if subjects could speak sufficient English, the CAMCOG (completed for 51 depressed subjects, the remaining being of Italian origin). Depression was rated using the HDRS. Because we aimed to include some depressed subjects with cognitive impairment or 'pseudo-dementia' no lower cut-off on the MMSE was chosen for the depressed group. Seventeen subjects scored below the conventional cut-off score denoting cognitive impairment ($\leqslant 23$).

Seventy-seven subjects with dementia of the Alzheimer type (DAT) were recruited from a hospital out-patient Memory Clinic (Ames *et al*. 1992). Twenty-eight subjects had early onset DAT (onset of dementia before age 65), 49 had late onset disease and 14 had associated psychotic features. Patients were assessed with the CAMDEX (Roth *et al*. 1986), which includes the CAMCOG; depression was assessed with the HDRS. All patients underwent a standard

dementia screen to exclude reversible cause for their dementia which included thyroid function tests, B12 and folate levels and syphilis serology. Diagnosis of Alzheimer's disease was made in accordance with NINCDS/ADRDA criteria (McKhann *et al*. 1984). Fifty-one patients fulfilled criteria for probable DAT, 22 for possible DAT and four for definite DAT (i.e. post-mortem confirmed). Reasons for the diagnosis of possible rather than probable DAT were as follows: the presence of mild B12 deficiency (two cases), maturity onset diabetes mellitus (two cases), a past history of carcinoma (three cases), minor vascular changes on CT scan (two cases), the predominance of frontal lobe features consistent with a diagnosis of frontal lobe dementia (nine cases) or the presence of some other atypical clinical features or course (four cases).

Other subjects were recruited from consecutive referrals to the same hospital Memory Clinic, thus representing a clinically relevant group. They were assessed with the CAMDEX and consisted of those who fulfilled DSM-III-R criteria for multi-infarct dementia dementia ($N = 7$) or a vascular amnestic syndrome ($N = 3$); those suffering from alcohol related cognitive impaired ($N = 5$), only one of whom fulfilled DSM-III-R criteria for dementia; those suffering from schizophrenia ($N = 4$) and a group of subjects presenting to the Memory Clinic with subjective complaints of poor memory but for whom no objective impairment was established ($N = 16$; 'memory complainers'). All of the latter scored above 80 on the CAMCOG, were felt to be cognitively normal after independent neuropsychological testing and none were felt to suffer from any depressive or other psychiatric disorder. In addition, a group of nine patients was recruited from the department's ambulatory Huntington's disease clinic. All fulfilled clinical criteria for Huntington's disease and all had a positive family history of Huntington's and/or diagnostic trinucleotide repeats testing (Huntington's Disease Collaborate Research Group, 1993). Of these, one was severely impaired (CAMCOG score 17), two mildly impaired (CAMCOG scores 51 and 62) while six scored above 80 on the CAMCOG and did not fulfil criteria for dementia. The study was approved by the relevant ethics committees.

Neuro-imaging technique

Full details of this have been previously given (O'Brien *et al*. 1994). A 0.3 Tesla MRI scanner was used with an inversion recovery (IR) sequence (30/500/1500 TE/TI/TR) and 5·1 mm coronal slices with a slice interval of 0·5 mm. As previously described regions of interest were selected as right anterior hippocampus (RAH), right posterior hippocampus (RPH), left anterior hippocampus (LAH), left posterior hippocampus (LPH), parahippocampal gyrus (PG), amygdala (A), hippocampus and amygdala (H + A), entorhinal cortex (EC) and generalized cerebral cortex (GEN). All regions were rated blind by two raters for atrophy (0 = normal, 1 = mild atrophy, 2 = moderate atrophy, 3 = severe atrophy; O'Brien *et al*. 1994). When there was disagreement between raters, the score of one rater (P.D.) was consistently chosen for analysis.

Statistical analysis

Inter-rater reliability for visual ratings of scans was assessed using weighted kappa that controls for chance agreement between raters (Hall, 1974; Cicchetti, 1976). Sensitivity and specificity values were obtained from the visual rating cut-offs. Receiver operator characteristic (ROC) curves (Metz, 1986) were constructed to examine sensitivity and specificities for all combinations of atrophy rating cut-off scores. Analysis of variance (ANOVA) with *post-hoc* Scheffé tests was used for comparisons between groups on continuous variables. As visual ratings of atrophy represent non-parametric data, comparisons between groups on these measures was determined using the Kruskal–Wallis analysis of variance and Mann–Whitney *U* test. Correlations between neuroimaging and cognitive variables of both groups were assessed using Spearman's rho. All statistical tests were 2-tailed and were regarded as significant at $P < 0{\cdot}01$ for correlations and $P < 0{\cdot}05$ for all other tests.

RESULTS

For the purposes of analysis and to facilitate presentation of results, subjects can be divided into four groups: CON ($N = 40$); DAT ($N = 77$); DEP ($N = 61$) and OTHER ($N = 44$). The OTHER group included those with vascular

Table 1. *Subject characteristics* (*mean* ± *S.D.*)

	CON ($N = 40$)	AD ($N = 77$)	DEP ($N = 61$)	OTHER ($N = 44$)	*P*
Age	71·6 ± 11·0	71·0 ± 8·3	71·2 ± 7·8	68·8 ± 11·6	NS
Sex (M : F)	20 : 20	36 : 41	18 : 43	21 : 23	NS
ED (years)	11·9 ± 2·7	10·8 ± 3·4	10·0 ± 2·6	10·6 ± 2·5	0·015[a]
MMSE (max 30)	28·5 ± 1·9	17·0 ± 6·1	25·1 ± 3·5	23·8 ± 4·7	< 0·001[b]
CAMCOG (max 107)	96·3 ± 5·5	58·0 ± 18·6	82·0 ± 10·2	79·6 ± 17·9	< 0·001[b]
HDRS	1·4 ± 1·8	3·0 ± 3·1	24·9 ± 6·0	6·0 ± 5·5	< 0·001[c]
Length of history (months)	N/A	46·4 ± 26·0	9·2 ± 14·4	55·4 ± 67·5	< 0·001[d]

ED, Number of years full time education; MMSE, Mini-Mental State Examination; CAMCOG, Cambridge Cognitive Examination; HDRS, Hamilton Depression Rating Scale.

[a] Significant difference between DEP and CON.

[b] Significant differences between CON and OTHER; CON and DEP; AD and all other groups.

[c] Significant differences between CON and DEP; CON and OTHER; DEP and AD; DEP and OTHER.

[d] Significant differences between DEP and AD: DEP and OTHER.

dementia/amnestic syndrome; alcoholic related cognitive impairment; functional psychiatric illness; Huntington's disease and the 'memory complainers'. Subject characteristics are shown in Table 1. Groups were well matched for age and sex, although the DEP Group had significantly fewer years education than the other groups. As expected, MMSE and CAMCOG scores were significantly lower in the DAT group compared to other groups and HDRS scores were significantly higher in DEP subjects, who also had a shorter duration of history (see Table 1). The HDRS scores in the OTHER group were significantly higher than in the control subjects but mean scores were still low (6·0 ± 5·4 compared with 1·4 ± 1·8). Further analysis of subject groups making up the OTHER category revealed that this increase in the HDRS scores was due to higher scores within the vascular dementia/amnestic group (mean score in this group 9·7 ± 9·8).

Inter-rater reliability is generally considered to be good if kappa $\geqslant$ 0·6 and excellent if kappa $\geqslant$ 0·8. Weighted kappa values for visual ratings of atrophy were as follows: right anterior hippocampus 0·78; right posterior hippocampus 0·74; left anterior hippocampus 0·80; left posterior hippocampus 0·73; amygdala 0·77; hippocampus + amygdala 0·80; entorhinal cortex 0·73; parahippocampal gyrus 0·63; generalized cerebral cortex 0·60. Anterior and posterior hippocampal atrophy scores were obtained as previously described (O'Brien *et al.* 1994) by summing the appropriate ratings and so had a score from 0 to 6 (anterior score = right anterior hippocampus plus left anterior hippocampus; posterior score = right posterior hippocampus plus left posterior hippocampus). There were significant differences in atrophy ratings between DAT subjects and all three other groups ($P < 0{\cdot}001$ for all areas), but no differences between controls and depressed subjects. There were no significant differences in atrophy ratings between those with probable and possible AD.

Using the same cut-off ratings defined in our previous paper (O'Brien *et al.* 1994), sensitivity and specificity values for distinguishing between DAT subjects and the all the other groups are shown in Table 2. Anterior hippocampus was the most sensitive region for detecting DAT subjects and 83% of subjects showed hippocampal atrophy. However, specificity was highest for other areas, in particular parahippocampal gyrus and entorhinal cortex. For example, using parahippocampal gyrus atrophy, although sensitivity for detecting DAT was only 61%, specificity for excluding DEP subjects was 97% and for excluding OTHER subjects was 98%. The rating of general cortical atrophy provided reasonable sensitivity for detecting DAT (77%) but lower specificity than using ratings of temporal lobe structures (see Table 2). Positive and negative predictive values, arguably of more interest to clinicians faced with a diagnostic problem in an individual patient, are also shown in the table. Positive predictive value was highest for parahippocampal gyrus (85%) while negative predictive value was highest for anterior hippocampus (91%).

Controls with anterior hippocampal atrophy were significantly older than those without

Table 2. *Sensitivity and specificity values for distinguishing between AD and other groups*

	Sensitivity for AD ($N = 77$)	Specificity for excluding							Positive Predictive Value (AD *v.* all OTHERS)	Negative Predictive Value (AD *v.* all OTHERS
		CON ($N = 40$)	DEP ($N = 61$)	MID ($N = 10$)	ALC ($N = 5$)	SHZ ($N = 4$)	HC ($N = 9$)	MC ($N = 16$)		
Anterior hippocampus	64/77 83%	32/40 80%	53/61 87%	7/10 70%	5/5 100%	4/4 100%	8/9 89%	15/16 94%	64/85 75%	124/137 91%
Posterior hippocampus	58/77 75%	33/40 83%	55/61 90%	8/10 80%	5/5 100%	4/4 100%	9/9 100%	14/16 89%	58/75 77%	128/147 87%
Amygdala	53/77 69%	35/40 88%	58/61 95%	8/10 80%	5/5 100%	4/4 100%	9/9 100%	15/16 94%	53/64 83%	134/158 85%
Hippocampus + Amygdala	61/77 81%	33/40 83%	57/61 93%	7/10 70%	5/5 100%	4/4 100%	9/9 100%	14/16 89%	61/77 79%	129/145 89%
Parahippocampal gyrus	47/77 61%	35/40 88%	59/61 97%	10/10 100%	4/5 80%	4/4 100%	9/9 100%	16/16 100%	47/55 85%	137/167 82%
Entorhinal cortex	56/77 73%	34/40 85%	58/61 95%	9/10 90%	4/5 80%	4/4 100%	9/9 100%	16/16 100%	56/67 84%	134/155 86%
Cerebral cortex	59/77 77%	27/40 68%	52/61 85%	7/10 70%	4/5 80%	4/4 100%	9/9 100%	11/16 69%	59/94 63%	110/128 86%

Cut-off score used was as previously defined (O'Brien *et al.* 1994), an atrophy rating of 0/1 for all regions except anterior and posterior hippocampal when the cut-off was a combined atrophy rating of score 1/2.

atrophy (mean age $82{\cdot}9 \pm 6{\cdot}8$ *v.* $68{\cdot}8 \pm 10{\cdot}0$, $P = 0{\cdot}001$) and had significantly lower MMSE and CAMCOG scores (MMSE scores: $26{\cdot}5 \pm 2{\cdot}9$ *v.* $29{\cdot}0 \pm 1{\cdot}2$, $P = 0{\cdot}047$; CAMCOG: $90{\cdot}8 \pm 6{\cdot}2$ *v.* $97{\cdot}7 \pm 4{\cdot}5$, $P = 0{\cdot}016$). DEP subjects with hippocampal atrophy were not significantly older than those without atrophy (mean age $74{\cdot}5 \pm 9{\cdot}0$ *v.* $70{\cdot}7 \pm 7{\cdot}6$, $P = 0{\cdot}21$) neither were they significantly different in MMSE or CAMCOG scores (MMSE score $23{\cdot}0 \pm 4{\cdot}9$ *v.* $25{\cdot}4 \pm 3{\cdot}2$, $P = 0{\cdot}22$; CAMCOG score $76{\cdot}4 \pm 12{\cdot}2$ *v.* $83{\cdot}0 \pm 9{\cdot}5$, $P = 0{\cdot}09$). DAT subjects without hippocampal atrophy were not significantly different from those with atrophy in terms of age ($67{\cdot}2 \pm 9{\cdot}6$ *v.* $71{\cdot}8 \pm 7{\cdot}9$, $P = 0{\cdot}065$), MMSE ($18{\cdot}5 \pm 6{\cdot}1$ *v.* $16{\cdot}7 \pm 6{\cdot}1$, $P = 0{\cdot}325$) or CAMCOG score ($64{\cdot}9 \pm 14{\cdot}5$ *v.* $56{\cdot}5 \pm 19{\cdot}1$, $P = 0{\cdot}14$), but did have a significantly shorter length of history of cognitive decline as judged by an informant ($29{\cdot}8 \pm 20{\cdot}1$ *v.* $49{\cdot}8 \pm 26{\cdot}0$ months, $P = 0{\cdot}005$). There were no differences between probable and possible DAT in atrophy ratings. Advancing age was significantly correlated with anterior hippocampal atrophy for CON ($r = 0{\cdot}54$, $P < 0{\cdot}001$) and DAT subjects ($r = 0{\cdot}25$, $P = 0{\cdot}03$) but not for DEP ($r = 0{\cdot}21$, NS) or OTHER ($r = 0{\cdot}28$, $P = 0{\cdot}064$).

As the selection of any given cut-off to discriminate groups, although based on our previous work may be criticized as being somewhat arbitrary, we constructed receiver operator curves (ROC) for ratings of anterior hippocampal atrophy to demonstrate discrimination across the whole range of possible cut-offs (Metz, 1986). These are plotted in Figs. 1 and 2, subjects above and below the age of 75 are plotted separately as both this study and others (e.g. Scheltens *et al.* 1992) have demonstrated an age-related increase in hippocampal atrophy in those without dementia. As can be seen from Figs. 1 and 2, the sensitivity of hippocampal atrophy is greatest in those aged above 75, though specificity is lower, while in those under the age of 75 specificity is lower but sensitivity higher. Importantly, it can also be

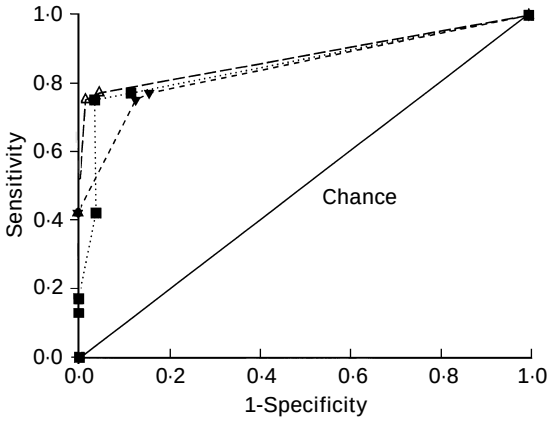

FIG. 1. Receiver Operator Characteristic (ROC) curve for ratings of anterior hippocampal atrophy in detecting Alzheimer's disease from other groups for subjects under the age of 75. (△, DEP; ■, CON; ▼, OTHER.)

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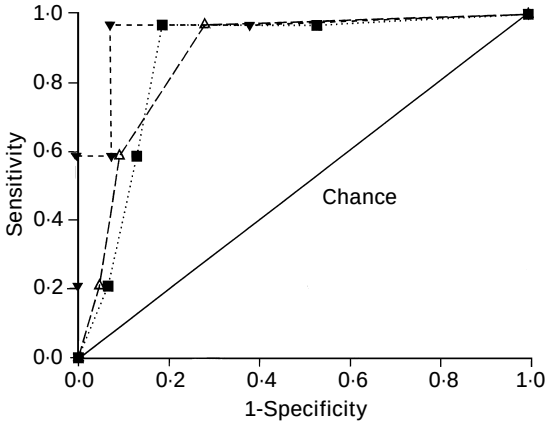

FIG. 2. Receiver Operator Characteristic (ROC) curves for ratings of anterior hippocampal atrophy in discriminating patients with Alzheimer's disease from other groups, aged over seventy-five. Note: that sensitivity is higher, but specificity is lower than for younger subjects. (△, DEP; ■, CON; ▼, OTHER.)

seen that the discriminating ability of anterior hippocampal atrophy in separating DAT subjects from DEP and OTHER groups is at least as good as in separating DAT subjects from CON.

For DAT subjects correlations were examined between ratings of atrophy and lengths of history and CAMCOG subscale scores. These are shown in Table 3. There were highly significant correlations between length of history and temporal lobe atrophy ratings and significant correlations between memory and orientation subscales of the CAMCOG and atrophy ratings of the hippocampus and parahippocampal gyrus. No significant correlations were found between other CAMCOG subscales or total CAMCOG or MMSE scores and atrophy ratings.

DISCUSSION

This study has demonstrated significantly greater cortical and medial temporal lobe atrophy in subjects with DAT compared to elderly controls, depressed subjects, those with vascular dementia and vascular amnestic disorder, Huntington's disease and those with a variety of other causes of cognitive impairment or complaints of poor memory. Ratings of medial temporal lobe atrophy had high sensitivity and specificity for detecting those with DAT, not only from controls but from all other groups. A number of studies have investigated the usefulness of temporal lobe changes on MRI as an early diagnostic marker for DAT. Four small studies (Seab *et al.* 1988; Kesslak *et al.* 1991; Killany *et al.* 1993; Lehericy *et al.* 1994) reported no overlap between those with dementia and age-matched controls on temporal lobe measures, suggesting that temporal lobe atrophy may be an absolute diagnostic test for DAT. However, other studies (reviewed by O'Brien, 1995), including all larger studies such as the current one, has found that some overlap does occur.

We found that anterior hippocampus was the most sensitive region for detecting Alzheimer's disease and 83% of our 77 subjects had evidence of anterior hippocampal atrophy. Other regions, such as parahippocampal gyrus and entorhinal cortex, appeared less sensitive for identifying those with DAT but had higher specificity; specificity for parahippocampal gyrus being 88% for control subjects, 97% for those with depression and 98% for OTHER subjects. Our findings are in agreement with the study by Erkinjuntii *et al.* (1993) who also used visual atrophy ratings and found high specificity (96%)

Table 3. *Correlations for AD subjects* (N = 77) *between clinical variables and atrophy ratings*

	AH	PH	Amygdala	EC	PG	GEN
Length of history	0·36 $P = 0·001$	NS	0·43 $P = 0·001$	0·46 $P < 0·001$	0·31 $P = 0·007$	0·46 $P = 0·001$
CAMCOG (total)	NS	NS	NS	NS	NS	NS
Memory	−0·34 $P = 0·003$	−0·30 $P = 0·009$	−0·39 $P = 0·001$	−0·31 $P = 0·007$	−0·33 $P = 0·004$	NS
Language	NS	NS	NS	NS	NS	NS
Orientation	NS	NS	NS	NS	NS	NS
Praxis	NS	NS	NS	NS	NS	NS
Abstraction	NS	NS	NS	NS	NS	NS

Spearman's correlations, only those signicant at or below $P = 0·01$ are reported.
AH, anterior hippocampus; PH, posterior hippocampus; EC, entorhinal cortex; PG, parahippocampal gyrus; GEN, generalized cortex.

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for entorhinal cortex. As such, atrophy of the entorhinal and parahippocampal cortex appears to be a highly specific marker for the presence of DAT which fits with pathological work suggesting that the disease process in Alzheimer's disease may start in this area entorhinal cortex (Braak & Braak, 1991) and our finding of a correlation between length of history and atrophy of the entorhinal cortex (Spearman's rho = 0·46, $P < 0·001$).

Few studies have investigated the usefulness of MRI in distinguishing DAT from groups other than healthy elderly controls. While relatively non-specific measurements such as ventricular enlargement and cortical atrophy may not be helpful in separating DAT subjects from depressed subjects (Rabins *et al*. 1991), we previously reported good separation between DAT and depression, based on 75 cases (O'Brien *et al*. 1994). The current study extends our previous report and also includes comparisons with other clinically important subject groups. Importantly, we found MRI was able to separate DAT subjects from those with other causes of cognitive impairment and, while not an absolute diagnostic test, we believe accuracy is high enough to be helpful as an adjunct to clinical diagnosis. Strikingly, specificity was 100% for all cases of Huntington's disease, alcoholic related cognitive impairment and schizophrenia, though numbers were admittedly small. Based on the 10 cases of vascular related cognitive impairment, temporal lobe MRI showed an impressive ability to distinguish such cases from DAT.

The main strengths of the current study are the inclusion of a large number of subjects with a wide variety of diagnoses assessed with a standardized schedule and the prospective application of a rating scale developed and published previously. However, our study also has its limitations. We were only able to obtain post-mortem confirmation of diagnosis in four subjects and clearly longer follow-up of all subjects will be needed to determine whether apparently cognitively normal subjects who showed medial temporal lobe atrophy subsequently develop dementia. We were only able to study 11 subjects in the OTHER group who fulfilled DSM-III-R criteria for dementia. However, temporal lobe MRI was able to separate these eleven from DAT subjects with high accuracy. Seven subjects did have a multi-infarct dementia and a further three a vascular amnestic syndrome. While these numbers are small, our data indicates that temporal lobe MRI may be useful in differentiating AD from vascular dementia. Our results conflict with those reported by Laakso *et al*. (1996) who studied hippocampal volumes on MRI in nine subjects with vascular dementia. They found that four had bilateral atrophy, three unilateral atrophy and two no atrophy. A groups of patients with Parkinson's disease with dementia had even more pronounced hippocampal atrophy that those with DAT. We did not study subjects with Parkinson's disease and both our study and that of Laakso *et al*. (1996) involved too few subjects with vascular dementia to draw firm conclusions. It may be that differences between our results are explained by differences in the location of vascular pathology between studies (only one subject in our study had an infarct involving the hippocampus). Clearly, further study of temporal lobe MRI in different dementias is required with neuropathological confirmation of diagnosis.

As well as cross-sectional measurments, longitudinal changes both on CT and MRI may be more useful in identifying those with DAT (Jobst *et al*. 1994; Fox *et al*. 1996), possible even at a 'preclinical' stage (De Leon *et al*. 1993; Fox *et al*. 1996). There is a need to study further potential markers both on structural and functional imaging that may assist with the early diagnosis of DAT and its differentiation from other dementias.

A strong correlation between age and temporal lobe atrophy was seen in control subjects and, to a lesser extent, in those with DAT with a similar non-significant trend seen in other subjects. An age-related increase in hippocampal atrophy has also been found by others (Jobst *et al*. 1992, 1994; Scheltens *et al*. 1992; Erkinjuntti *et al*. 1993). As such, the sensitivity and specificity for hippocampal atrophy in distinguishing DAT from other groups varied according to the age of the patient. This is illustrated in Figs. 1 and 2. At older ages sensitivity was high (over 90%), though with low specificity, while at younger ages sensitivity was lower (below 80%) while specificity was much higher. In practice, this will mean that atrophy will need to be interpreted in light of the subject's age, with a greater degree of

atrophy in older subjects being necessary before appearances can be interpreted as suggestive of DAT. The age-related increase in hippocampal atrophy in controls may be related to the increase in Alzheimer-type pathology known to occur with normal ageing, as hippocampal atrophy on MRI correlates with hippocampal tangle count at post-mortem (Huesgen *et al*. 1993).

In conclusion, this study has shown that temporal lobe MRI may be a useful diagnostic aid in distinguishing those with DAT from age-matched controls, depressed subjects and those with other causes of cognitive impairment. In particular, we found atrophy of the entorhinal cortex and parahippocampal gyrus to be highly specific for DAT. Future work should examine the progression of hippocampal atrophy over time by serial scanning (Fox *et al*. 1996). The long-term follow-up of subjects who have shown hippocampal atrophy should be undertaken to determine whether they are at an increased risk of developing dementia as has been suggested for those with CT evidence of temporal atrophy (De Leon *et al*. 1993).

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