Single photon emission tomography using ^{99m}Tc -HM-PAO in the investigation of dementia

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SUMMARY Single photon emission tomographic imaging of the brain using ^{99m}Tc HM-PAO was carried out in patients with a clinical diagnosis of Alzheimer's disease, non-Alzheimer frontal-lobe dementia, and progressive supranuclear palsy. Independent assessment of reductions in uptake revealed posterior hemisphere abnormalities in the majority of the Alzheimer group, and selective anterior hemisphere abnormalities in both other groups. The findings were consistent with observed patterns of mental impairment. The imaging technique has potential value in the differential diagnosis of primary cerebral atrophy.

Dementia, associated with cerebral atrophy, may result from a wide variety of neurological conditions, which include Alzheimer's disease, Pick's disease and Pick-like degeneration,¹ and progressive supranuclear palsy. While the differentiation between forms of dementia on clinical grounds remains imprecise,^{2,3} it is increasingly recognised that different dementing diseases are associated with distinct patterns of neuropsychological breakdown. Amnesia, language disorder and perceptuo-spatial deficits in the presence of preserved social behaviour is characteristic of Alzheimer's disease.³⁻⁵ Conversely, disordered social competence and personality change, with relative sparing of "instrumental" functions, is suggestive of a non-Alzheimer dementing process.^{1,3} Progressive supranuclear palsy (Steele-Richardson syndrome) is a subcortical disease which results in mental changes similar to those seen with frontal cortical lesions.^{6,7}

X-ray computed tomography fails to distinguish between forms of cerebral atrophy, and perpetuates the notion of dementia as a generalised and undifferentiated impairment of intellect. By contrast, positron emission tomography (PET) has demonstrated reduced energy metabolism in the posterior

cerebral hemispheres of patients with clinically presumed Alzheimer's disease⁸ and in the anterior hemispheres of patients with progressive supranuclear palsy,⁹ highlighting regional functional differences between the two conditions. Despite its potential value in the investigation of dementia, however, PET is an expensive technique which is available in only few neurological centres.

Single photon emission tomography (SPET) using the rotating gamma camera has recently become widely available, and there has been concurrent development of gamma-emitting radiopharmaceuticals which are taken up by brain tissue. For some years the most promising radiopharmaceutical agents for demonstration of regional cerebral perfusion were ^{123}I -labelled derivatives of amphetamine.¹⁰⁻¹² ^{123}I -isopropylamphetamine (IMP) was found to indicate reduced perfusion in the parieto-occipital regions in patients with presumed Alzheimer's disease.¹³ These compounds have, however, chemical, physical and practical drawbacks; for single-photon imaging, technetium-99m labelled materials offer significant advantages, and recent research effort has been directed at developing such a material which, like the amphetamines, will cross the intact blood brain barrier and be accumulated within functioning cells.¹⁴

A new radiopharmaceutical ^{99m}Tc -hexamethyl propyleneamine oxime (HM-PAO)¹⁵ has been shown to give images of cerebral perfusion comparable to those obtained with ^{123}I -IMP.¹⁶ Bio-distribution

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studies in eight normal volunteers showed that, ten minutes after intravenous injection, uptake in the brain was 4.4% of the injected dose, remaining effectively constant for up to 24 hours.¹⁷ Tomographic brain images indicated that the distribution of the compound was related to regional cerebral perfusion.

The purpose of the present study was to examine the diagnostic potential of ^{99m}Tc HM-PAO in the evaluation of patients with cerebral atrophy, and in particular to determine whether the dementia of Alzheimer's disease could be distinguished from presumed non-Alzheimer frontal-lobe dementia and from progressive supranuclear palsy on the basis of the SPET images.

Patients

The study group consisted of 41 patients, 17 male and 24 female, referred to a neurology department, with a history of at least one year duration of progressive intellectual deterioration and decreased social independence. Criteria for inclusion in the study were: (1) absence of a history of vascular disease, alcohol abuse and major head trauma; (2) absence on examination of clinical evidence of cerebro-vascular or systemic disease; (3) conformity, on the basis of history and neurological and neuropsychological examination, to one of the three clinical groups described below.

In all patients, ratings using the Hachinski scale¹⁸ yielded an ischaemic score of less than four. Computed tomography revealed the presence of cerebral atrophy, in the absence of vascular lesions.

(a) Presumed and proven Alzheimer's disease

These patients presented with a progressive decline in memory and in the majority language and perceptuo-spatial difficulties, in the presence of relatively preserved social competence, and physical well-being. Mental examination³ revealed amnesia, together with aphasia and/or visuo-spatial and constructional difficulties. Neurological findings were limited to mild extrapyramidal features, and electroencephalography characteristically revealed slowing of wave forms. The patients fulfilled NINCDS-ADRDA¹⁹ criteria for probable Alzheimer's disease, and in four cases the diagnosis had been confirmed at cerebral biopsy.^{3 20}

(b) Presumed and proven non-Alzheimer dementia of frontal-lobe type

These patients presented with disordered social conduct,

personality change, loss of initiative and forgetfulness, in the absence of notable physical symptoms. Mental examination showed the patients to be disinhibited and inattentive, with impaired abstraction, planning and problem solving abilities, as measured by performance on the modified Wisconsin card sorting test,²¹ Weigl's block test,²² a test of similarities²³ and a picture sequencing task. Language disorder was limited to anomia and there was no evidence of perceptuo-spatial deficits. Neurological signs were absent or limited to frontal release phenomena. Electroencephalography was normal. The clinical picture is of a frontal lobe syndrome, and is consistent with a possible diagnosis of Pick's disease,²⁴ although cerebral biopsy of the temporal lobe in one patient and of the frontal lobe in a second patient had not revealed the classical morphological characteristics of that disease. In those two cases tissue examination had confirmed the absence of the histological features of Alzheimer's disease, and revealed no reduction in choline acetyltransferase activity or in acetylcholine synthesis.³ The patients were clinically similar to those described by others,¹ in whom necropsy has revealed a fronto-temporal atrophy and an absence of the pathology of Alzheimer's disease.

(c) Progressive supranuclear palsy

These patients presented with a history of mental slowing and forgetfulness, against a background of falls and "visual" disturbances. Mental examination revealed slowing, particularly in response initiation, concreteness of thinking and difficulty in shifting mental set, characteristic of a "subcortical dementia".^{6 25} Performance was poor on tests of abstraction, problem solving and mental flexibility,²¹⁻²³ believed to be sensitive to "frontal lobe" functioning. There was no evidence of an aphasic disorder, visual agnosia or spatial disorientation. Neurological examination revealed the presence of gaze palsy, nuchal and limb rigidity, pseudo-bulbar palsy and imbalance, indicating a diagnosis of progressive supranuclear palsy.

Patient details are summarised in table 1. The three groups did not differ significantly in terms of age, nor in terms of duration of illness at the time of scanning (unpaired *t* tests).

The study sample constituted consecutive referrals to a neurological department who met the clinical criteria for the three diagnostic categories described. Some selection bias may however exist: atypical patients in whom a clinical diagnosis could not be made with any degree of certainty were excluded from the series.

The eight normal volunteers who had participated in the earlier biodistribution studies¹⁷ served as a reference group.

Table 1 Summary of patient groups

Diagnostic group	No in group	No of males:females	Age (years)		Duration of illness (years)	
			Mean	Range	Mean	Range
Alzheimer's disease	23	11:12	63	55-73	5	1-12
Frontal lobe dementia	9	3: 6	61	49-69	5	2- 9
Progressive supranuclear palsy	9	3: 6	66	48-75	6	2-12

Methods and procedure

The hexamethyl propyleneamine oxime was supplied by Amersham International as a freeze-dried kit (now known as "Ceretek"). It was reconstituted with ^{99m}Tc -pertechnetate solution, and a dose of 550MBq was administered to the patient intravenously within 30 minutes of preparation (usually within 10 minutes). The patient was subsequently positioned supine on a cantilevered tomography table with the patient's head supported in a low-attenuation carbon fibre head-rest attachment so that the orbito-meatal line was vertical. Imaging was carried out with a rotating gamma camera (International General Electric 400 A/T) in conjunction with motorised table motion (the programmable body contour option) so that minimum camera-patient distance was ensured during the acquisition of a set of projection images covering a full 360° rotation about the long axis of the patient.

The set comprised 64 images, each of 20 seconds duration, typically yielding four million counts per acquisition. The data were stored in a Medical Data Systems A-cubed computer system using a 64 × 64 matrix with a zoom factor of 1.48. This corresponded to a pixel size of 4.2 mm.

Each projection image was corrected for non-uniformity and pre-processed with an 11-point two-dimensional smoothing filter. Transaxial sections of 2-pixel thickness (8.4 mm) were reconstructed using the Medical Data Systems tomography software (Butterworth filter of order 4 with a cut-off of 0.76 cycles/cm). Attenuation correction was performed based on Sorenson's method.²⁶ An attenuation ellipse was applied by defining four points at the periphery of the head as visualised on the anterior and lateral views.

Images of the set of sections from the orbito-meatal level to the top of the head were displayed with a 20% cut-off and photographed. Each transverse section image was shown alongside the anterior projection with a superimposed line indicating the level of the section for the purpose of reporting. The resolution of this imaging system has been measured to be 15 mm FWHM in the plane of the reconstructed transverse section.

The reconstructed brain images were evaluated independently by two individuals, who were unaware of the clinical findings, and had no contact with the patients. The raters identified regions of reduced uptake in the cerebral hemispheres, which were classified simply as anterior or posterior, and left or right hemisphere abnormalities. The classifications were then compared with the clinical groupings.

For the purpose of statistical comparison patients were rated clinically in terms of relative severity of dementia: mild, moderate or severe, and in the Alzheimer group the presence or absence of perceptuo-spatial deficits was recorded, as measured by performance on visuo-constructional tasks.³

Ethical approval for the study had been obtained from the Manchester Central District Ethical Committee, and use of the agent HM-PAO was approved by the Administration of Radioactive Substances Advisory Committee of the DHSS. The nature of the investigation and its purpose was explained to patients' relatives and written consent was obtained from next of kin.

Analysis of results involved non-parametric statistical techniques.²⁷

Fig 1 Normal volunteer. The transaxial section images from the ^{99m}Tc -HM-PAO scan show reasonably uniform activity in the cortex with the ventricles and white matter as regions of lower activity (left side of image = right hemisphere; right side = left hemisphere).

Fig 2 *Alzheimer's disease. This 59 year old female demonstrated marked impairment of memory, language and spatial orientation, while retaining a normal social facade. The ^{99m}Tc -HM-PAO scan clearly shows a bilateral posterior defect.*

Fig 3 *Non-Alzheimer "frontal" dementia. This 55 year old female displayed disinhibition, social misconduct and reduction in self-care and personal hygiene, in the absence of language or perceptuo-spatial disorder. Perseveration was a prominent feature. The ^{99m}Tc -HM-PAO scan shows a clear perfusion defect in the frontal region, rather more pronounced on the left, extending through the cortical rim.*

Fig 4 Progressive supranuclear palsy. This 64 year old male exhibited impaired powers of abstraction and mental flexibility, in the absence of perceptual, spatial or linguistic disorder. The ^{99m}Tc -HM-PAO scan shows a marked perfusion defect in the frontal region but an intact cortical rim suggesting that the underperfused region may be sub-cortical.

Results

There was no adverse reaction to the radiopharmaceutical. In three patients (two with presumed Alzheimer's disease and one with progressive supranuclear palsy) adequate images were not achieved owing to lack of patient cooperation in the procedure. The results are based therefore on the tomographic images of 38 patients: 21 with presumed or proven Alzheimer's disease, nine with presumed or proven non-Alzheimer dementia of frontal-lobe type, and eight with progressive supranuclear palsy. In classifying brain images there was good concordance between the two raters (93%).

Differences in distribution of uptake were noted in the three patient groups, and are illustrated by figs 1–4. Each figure shows a set of four sections, taken from the orbitomeatal line as a base.

Figure 1 shows, for reference, transaxial section images from the scan of a normal volunteer. The ventricles and surrounding white matter are seen as regions of low activity surrounded by reasonably uniform activity in the cerebral cortex. In this and other scans from normal volunteers there was no notable decrease of activity in either anterior or posterior cortex.

Figure 2 shows transaxial section images obtained from a 59 year old female, with a clinical diagnosis of Alzheimer's disease. The scan clearly shows a bilateral posterior defect.

Figure 3 shows images, obtained from a 55 year old female, with a clinical diagnosis of non-Alzheimer frontal lobe dementia. The scan shows a clear perfusion defect in the frontal region, rather more pronounced on the left, extending through the cortical rim.

Figure 4 shows images obtained from a 64 year old male, with progressive supranuclear palsy. The scan shows a marked perfusion defect in the frontal region, but an intact cortical rim consistent with the suggestion that the under-perfused region may be sub-cortical.

The figures illustrate distributions of uptake which appear characteristic of the clinical groups. Nevertheless, there was not total uniformity of findings and variation did occur within each group. The tomographic findings for each clinical group are summarised in table 2, and indicate the number of patients showing respectively, selective posterior, combined posterior and anterior, selective anterior, and no hemisphere abnormalities.

Reduced uptake in the posterior cerebral hemi-

Table 2 Locus of uptake defects in the cerebral hemispheres

Clinical diagnosis		Posterior	Posterior + anterior	Anterior	None
Alzheimer's disease	(n = 21)	7 (33%)	7 (33%)	3 (14%)	4 (19%)
Frontal lobe dementia	(n = 9)	1 (11%)	1 (11%)	7 (78%)	0
Progressive supranuclear palsy	(n = 8)	0	0	7 (88%)	1 (12%)

spheres was present in 14 (67%) Alzheimer patients, in two patients classified as non-Alzheimer frontal-lobe dementia (22%), and in no patients with progressive supranuclear palsy. A chi-squared test, employing Yates' correction factor, revealed the difference in frequency of occurrence of posterior hemisphere abnormalities in the Alzheimer group compared with the other two groups combined to be statistically significant ($\chi^2 = 9.47$, $df = 1$, $p < 0.01$). Individual group comparisons with respect to presence of posterior defects revealed significant differences between the Alzheimer group and both the frontal-type dementia and progressive supranuclear palsy groups (Fisher's exact test, $p < 0.05$ and $p < 0.002$ respectively) but no difference between the two non-Alzheimer groups.

A selective reduction in uptake in the anterior hemispheres occurred in seven (78%) of the non-Alzheimer frontal-lobe dementia group, and in seven (88%) of patients with progressive supranuclear palsy, but in only three (14%) of the Alzheimer group. This difference in frequency of selective anterior hemisphere abnormalities between Alzheimer and the two non-Alzheimer groups was highly significant ($\chi^2 = 14.96$, $df = 1$, $p < 0.001$). Individual group comparisons with respect to presence of selective anterior defects revealed highly significant differences between the Alzheimer group and both the frontal-lobe dementia and progressive supranuclear palsy groups (Fisher's exact test, $p < 0.002$ and $p < 0.001$ respectively), but no difference between the two non-Alzheimer groups.

The presence of posterior hemisphere abnormalities in the Alzheimer group was significantly related to the presence of perceptuo-spatial deficits found on clinical testing (Fisher's exact test $p < 0.001$): table 3 shows the frequency of occurrence of visuo-spatial defects in relation to presence of posterior hemisphere reductions in uptake. Normal scans in the Alzheimer group occurred in those patients with a relatively mild dementia in whom the prominent feature was a progressive amnesia and in whom spatial and visuo-constructional difficulties were absent.

Of the 14 patients in the Alzheimer group showing posterior hemisphere reductions in uptake (table 2), this was reported as bilateral in 11 patients, and unilateral in three. Unilateral defects were not evidently associated with a corresponding prominence of

language or perceptuo-spatial disability in those patients.

Posterior hemisphere abnormalities in the Alzheimer group represented either a selective abnormality, or were accompanied by reductions in uptake in the anterior hemispheres also (table 2). Of this latter group, anterior abnormalities were reported to be unilateral in four cases and bilateral in three. The difference between circumscribed posterior defects and a more widespread distribution of abnormalities could not be explained in terms of overall clinical severity of the patients (Kendal rank correlation coefficient $T = 0.09$, $z = 0.46$, $p > 0.1$), nor in terms of duration of disease (Mann-Whitney U test: $U = 16.5$, $p > 0.1$). However, in those three patients in whom the accompanying anterior changes were bilateral, personal and social conduct had deteriorated out of proportion to their neuropsychological deficits and that of the other patients with Alzheimer's disease.

Selective anterior hemisphere scan defects characterised both patients with non-Alzheimer frontal-lobe dementia, and those with progressive supranuclear palsy. A comparison of figs 3 and 4 suggests, however, that the pattern of abnormality in those two groups may not be identical. In order to assess the degree to which the two "anterior" groups could be distinguished on the basis of scan appearances, the scans from the 17 patients in these two groups were re-examined retrospectively, and without knowledge of clinical diagnosis. In three of these scans the images were obscured by movement artifact, precluding further analysis; the remaining 14 were designated as conforming to the pattern depicted in fig 3, to that of fig 4, or deemed equivocal. Of eight patients with non-Alzheimer frontal-lobe dementia seven (88%) were classified as having a scan appearance similar to that of fig 3. Conversely, the pattern depicted in fig 4 was identified in five (83%) of six patients with

Table 3 Alzheimer's disease: relationship between visuo-spatial deficits and posterior hemisphere reductions in uptake

		Posterior defect	
		Present	Absent
Visuo-spatial disorder	Present	14 (67%)	2 (9%)
	Absent	0	5 (24%)

progressive supranuclear palsy. In remaining cases the appearances were equivocal.

Discussion

Cerebral imaging by single photon emission tomography, using ^{99m}Tc HM-PAO, indicated regional differences in uptake of tracer in patients with different forms of cerebral atrophy. Posterior hemisphere abnormalities were common in the Alzheimer group, rare in patients classified as suffering from non-Alzheimer dementia of frontal-lobe type, and did not occur in patients with progressive supranuclear palsy. Conversely, selective abnormalities in the anterior hemispheres were characteristic of both patients with non-Alzheimer frontal-lobe dementia and with progressive supranuclear palsy, but occurred only rarely in patients with Alzheimer's disease. The pattern of findings is consistent with reports from positron emission tomography,^{8 9 28} and accords with the predictions regarding regional functional differences based on the patients' clinical pattern of performance. Patients in the non-Alzheimer dementia and progressive supranuclear palsy groups had shown a pattern of deficits suggestive of frontal lobe dysfunction, while in the Alzheimer group patients displayed language and visuo-spatial abnormalities, suggestive of posterior hemisphere dysfunction. Indeed, in the Alzheimer group reduction in uptake of tracer in the posterior hemispheres was strongly associated with the presence of clinically evident visuo-spatial deficits. The findings emphasise recent reports^{8 29 30} that Alzheimer's disease may not be the uniformly diffuse disorder that has previously been supposed.

The finding in this study of selective anterior hemisphere abnormalities in those patients with a diagnosis of non-Alzheimer frontal-lobe dementia is particularly important, since it provides an independent marker of a clinical syndrome, different, yet frequently undifferentiated from that of Alzheimer's disease. That this syndrome has an underlying pathophysiology distinct from that of Alzheimer's disease is strongly indicated by recent studies of such patients who have undergone cerebral cortical biopsy,³ and by clinical similarities to patients in whom absence of Alzheimer pathology has been confirmed at autopsy.^{1 31}

While characteristic image patterns emerged in the three groups, there was nevertheless not a 100% concordance between diagnostic category and tomographic findings. Several contributory factors might account for this observation. First, the patients in all groups cover a broad spectrum of disease severity, their dementia ranging from mild to advanced. Patterns of abnormality striking in patients with mod-

erate or advanced dementia may not be apparent in early cases. In the Alzheimer group "early" patients were those whose prominent abnormality was a progressive amnesia, in whom perceptuo-spatial deficits were minimal or absent. In such relatively early cases tomographic images revealed no unequivocal evidence of abnormality, and these were reported as normal. Second, functional heterogeneity may exist within a diagnostic group. Indeed, the possibility of clinical sub-groups of Alzheimer's disease has been recognised.³²⁻³⁴ Third, the allocation to diagnostic group on the basis of clinical features may itself be imprecise. Histological confirmation of disease aetiology was present in only a minority of patients, and although extensive clinical assessment was likely to ensure a high degree of diagnostic accuracy the possibility of misclassifications cannot be overlooked. It is recognised, for example, that some patients with a clinical picture of Alzheimer's disease may not have that condition.³

The presence of "frontal" changes in Alzheimer's disease is well documented.^{24 35} However, such reports tend to be based on histopathological examination of end stage disease, and it has been suggested that the anterior hemisphere changes observed in Alzheimer's disease may reflect a relatively late development in the disease's course.⁸ This suggestion is supported clinically by the observation of well-preserved social graces in cognitively impaired Alzheimer patients.²⁻⁴ It is borne out also by studies of cerebral oxygen utilisation which showed that profound depression in the frontal regions characterised patients with severe but not moderate dementia.³⁶ In the present study, bilateral anterior hemisphere defects coincided with bilateral posterior changes in three cases. These patients exhibited a relatively advanced dementia, and more importantly, demonstrated, on clinical examination, greater apathy and behavioural disinhibition than generally encountered in the Alzheimer group. However, where unilateral anterior hemisphere defects were reported in the Alzheimer group, these were not evidently associated with specific behavioural characteristics, nor with a more advanced disease state than other Alzheimer patients. Indeed, it is of some interest that two patients, who were profoundly demented, and exhibited the rapid weight loss characteristic of terminal disease,³⁵ nevertheless maintained a selective bilateral posterior hemisphere defect. Thus, while it may be the case that anterior hemisphere involvement typically occurs in relatively late stage disease, the present findings raise the possibility of some heterogeneity within the Alzheimer population, with some patients retaining a regionally more circumscribed distribution of abnormality than others.

In evaluating the potential of this imaging tech-

nique as a diagnostic instrument in distinguishing forms of dementia it should be borne in mind that selection of patients in the present study was not entirely unbiased: those patients in whom the clinical profile was not well-defined were excluded. Moreover, patients with Alzheimer's disease were compared with patients with a distinct clinical profile, suggesting, a priori, differences in regional distribution of functional abnormality. The technique's diagnostic efficiency would be heightened if it were able to discriminate clinically similar patterns of dementia, such as that of Alzheimer's disease and cerebrovascular disease in which "focal cortical features" of aphasia, agnosia and spatial disorientation may be present.

Differentiation between Alzheimer's disease and dementia due to cerebrovascular disease might be expected to lie in the degree of uniformity of perfusion defects, with less uniform abnormalities occurring in the latter.¹³ However, the finding of some unilateral abnormalities in the present Alzheimer group, together with reports of hemispheric asymmetries in Alzheimer patients in studies using positron emission tomography³⁷⁻³⁹ indicate that differentiation may not be straightforward. Clinical reports^{40,41} suggest that Alzheimer's disease may present with a relatively "focal" clinical picture, supporting the possibility of a unilateral or asymmetric distribution of functional abnormality, which may be difficult to distinguish from that resulting from cerebrovascular disease. Future imaging studies comparing patients with Alzheimer's disease and dementia due to cerebrovascular disease who share a similar pattern of psychological disability would address these issues more directly.

The indication in the present study of differences in pattern of perfusion defects in the two "anterior" groups: non-Alzheimer frontal-lobe dementia and progressive supranuclear palsy, does, however, provide some optimism that this imaging technique may indeed assist in discriminating between diseases associated with similar patterns of mental change.

The classification of images using ^{99m}Tc HM-PAO is qualitative, and hence subject to problems of establishing appropriate norms. Nevertheless, the agreement in classification of images by the two raters in this study was high, suggesting that the findings are robust. Moreover, the double dissociation in patterns of abnormality revealed in comparing clinical groups, suggests that the observed perfusion defects are indeed disease-related and not attributable to non-specific effects of age or individual variation, or indeed to artefacts associated with the imaging technique itself. Further studies involving "normal" elderly would serve to refine the technique as a diagnostic tool.

In assessing the viability of an investigative pro-

cedure in a dementing population, practical considerations are paramount. The present patient series included a wide range of dementia severity, and a spectrum of disability, including visuo-spatial disorientation, amnesia, and physical inco-ordination and imbalance, all features which may hinder patient co-operation. Nevertheless, few problems were encountered and the procedure was successfully executed in 38 of the 41 patients initially entered into the study. The procedure appears to be relatively unstressful, making few demands on the demented patient, and for the majority of patients is a viable clinical procedure. Moreover, the technique is relatively inexpensive and widely available.

The present study points to the value of single photon emission tomography, using ^{99m}Tc HM-PAO, in the investigation of dementing illnesses, and this technique may ultimately help to refine the clinical distinctions between this heterogeneous group of conditions and increase understanding of dementia. The regional selectivity of abnormalities which appear accurately to reflect major psychological areas of dysfunction make it necessary to question the traditional notion of dementia as a generalised and undifferentiated impairment of intellect, and provides optimism for more precise classifications of dementia in the future.

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