THE VALUE OF IMAGING IN DEMENTIA RESEARCH

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CONTENTS

The value of imaging in dementia research

1 Introduction

Dementia affects at least 5% of people over 65 in the UK and USA, and incidence is increasing, partly due to an increase in lifespan but also possibly partly due to environmental factors (Pritchard *et al*., 2004). However, there is substantial disagreement in the diagnosis of dementia, with a study by Erkinjuntti *et al*. (1997) finding that only 20 of 1879 individuals assessed were deemed to be demented by all clinical protocols tested, whilst one protocol diagnosed almost 400 of the sample as demented. In diagnosing dementia *type*, two studies (Wetterling *et al*., 1996 and Pohjasvaara *et al*., 2000), found concordances of just 3% and 29% respectively for the diagnosis, via a range of protocols, of vascular dementia (**VaD**), generally considered to be one of the two commonest types, the other being Alzheimer's disease (**AD**). Even the latter assumption is disputed, with Charpentier *et al*. (2000) claiming that AD and frontotemporal dementia (**FTD**) are most common.

Some researchers consider that the commonly-used demarcations used for different dementias are spurious and unhelpful, as most aged brains show a range of pathologies (e.g. Perry *et al*., 1998) and the lesions deemed diagnostic for AD do not, in isolation, correlate well with dementia severity (Esiri *et al*., 1999). AD studies often exclude patients with vascular disease, yet most AD sufferers have cerebrovascular compromise as a contributory factor to their dementia, and the **CATCH** hypothesis proposes that AD is in fact consequent on cerebral **hypoperfusion** (impaired blood flow) (de la Torre, 2000).

Post-mortem diagnosis is widely regarded as the 'gold standard' for dementia diagnosis, yet even pathologists often do not agree on whether a brain came from a demented or non-demented person, or which kind of dementia s/he had (Ince, 2001).

Millions of dollars are spent annually on dementia research in the USA alone, but much of this involves often-crude animal models. *In vitro* models cannot represent the whole person or whole brain, and clinical trials still rely largely on clinical diagnostic protocols for selecting and classifying participants and analysing outcomes. As well as being inconsistent, these protocols cannot detect **prodromal** (preclinical) stages of dementia. Thus it is perhaps unsurprising that progress in finding causes and treatments is slow.

The main current treatments for AD are **acetylcholinesterase (AChE)** inhibitors, which can only provide modest, short-term symptomatic relief and do not work for all AD patients (e.g. *see* Nobili *et al*., 2002).

There is clearly an urgent need to develop and use more accurate, objective criteria for diagnosing dementia, and the disease processes need to be much better understood, separating causal factors from consequential ones and early triggers from later developments. Achieving these will facilitate earlier and more appropriate treatments which modify the disease itself rather than just relieving symptoms. Imaging normal and diseased human brains *in vivo* has great potential to provide insights into the development and progression of these devastating and costly diseases.

This review will take a holistic approach to examining aspects of that potential, linking ultrasound and angiographic imaging of vascular disease markers with X-ray computed tomography (**CT**), magnetic resonance imaging (**MRI)**, single-photon emission computed tomography (**SPECT**) and positron emission tomography (**PET**) brain findings, and briefly summarise some uses of additional imaging-related modalities. Clearly such an overview cannot be comprehensive, but an attempt will be made to reflect the relative prominence of emphasis on particular aspects of dementia, imaging and analytical methods found in the literature as a whole.

There is some inevitable overlap between section subject areas; where this occurs the reader will be directed to other relevant sections.

2 Fields of dementia research using imaging

Imaging has a variety of potential roles in dementia research. It can be used in epidemiological studies, comparing brain structure and physiology with lifestyle factors such as diet, smoking and use of medicines for other conditions (e.g. non-steroidal anti-inflammatory drugs - NSAIDs). Imaging studies can attempt to correlate cognitive deficits to specific **biomarkers** such as anatomical or physiological brain changes. Comparisons can be made between imaging and clinical diagnostic protocols for their respective effectiveness in predicting decline from mild cognitive impairment (**MCI**) to dementia (e.g. *see* de Leon *et al*., 2001; Huang *et al*., 2003).

The effects of treatment can be monitored, with regard both to gross changes (e.g. perfusion) and to specific molecular/structural correlates of dementia. Activation studies – imaging the brain during cognitive testing or other brain activity – may prove more useful for measuring brain function than studies performed under resting conditions. Radiopharmaceuticals can be used which bind to biological molecules such as **senile plaques** (**SPs**) and **neurofibrillary tangles** (**NFTs**), the lesions deemed to characterise AD. Imaging a range of such molecules and lesions holds promise for elucidating the chronological progress, and thus potentially chains of causation, of dementias.

Research can also aim to ascertain how well *in vivo* imaging findings correlate with post-mortem findings, with a view perhaps to revising 'gold standards' against which other studies are judged.

Whichever type of study is being undertaken, it is important to first exclude causes of dementia such as hydrocephalus and tumours, which is best achieved with CT or MRI.

3 Discriminating different types of brain abnormality through nuclear imaging

It is widely considered that AD is distinguishable from normal brains and those affected by VaD or frontal lobe dementia from images showing bilateral temporoparietal hypoperfusion or **hypometabolism** (impaired metabolism) (**Table 1**).

Due to overlaps in pathology it is not always possible to differentiate AD from Lewy body dementia, Creutzfeldt–Jakob disease, and dementia caused by Parkinson's disease, by nuclear imaging. Clinical manifestations can often distinguish these dementias.

Type of dementia	**Regional deficits identified by nuclear imaging**
Alzheimer's disease	Parietal, temporal and posterior cingulate cortices are affected early, with relative sparing of primary sensorimotor and primary visual cortices and sparing of striatum, thalamus and cerebellum. In early stages, deficits often appear asymmetric, but degeneration is eventually evident bilaterally.
Vascular dementia	Hypometabolism and hypoperfusion affect cortical, subcortical and cerebellar areas.
Frontotemporal dementia (e.g. Pick's disease)	Frontal cortex and anterior temporal and mesotemporal areas are affected earlier or with greater initial severity than are parietal and lateral temporal cortices, with relative sparing of primary sensorimotor and visual cortices.
Huntington's disease	Caudate and lentiform nuclei are affected early, with gradual development of diffuse cortical involvement.
Parkinson's dementia	Deficits are similar to those of AD, but with more sparing of mesotemporal area and less sparing of visual cortex.
Dementia with Lewy bodies	Deficits are similar to those of AD, but with less sparing of occipital cortex and possibly cerebellum.

Table 1 Imaging findings pertaining to differential diagnosis of dementias.
adapted from Silverman (2004)

Figures 1 & 2 show the location of some of the brain regions referred to in **Table 1**.

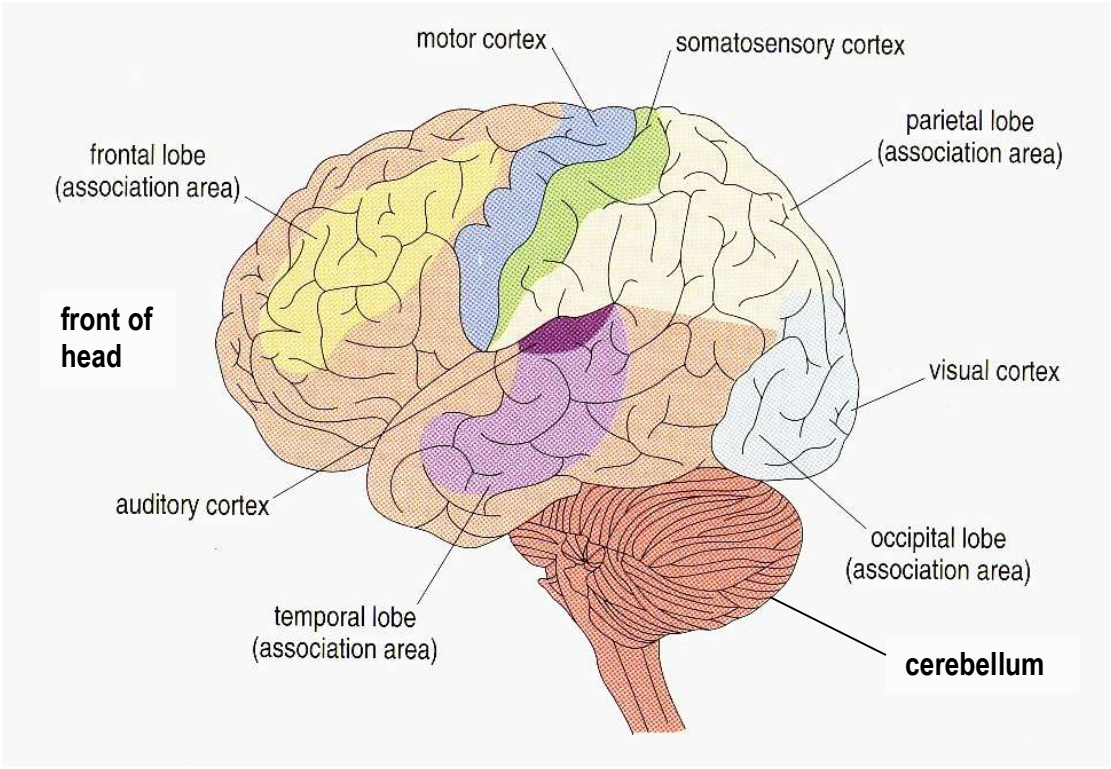


Figure 1

Diagram showing location of main cortical regions of brain plus cerebellum

adapted from Stewart (2000)

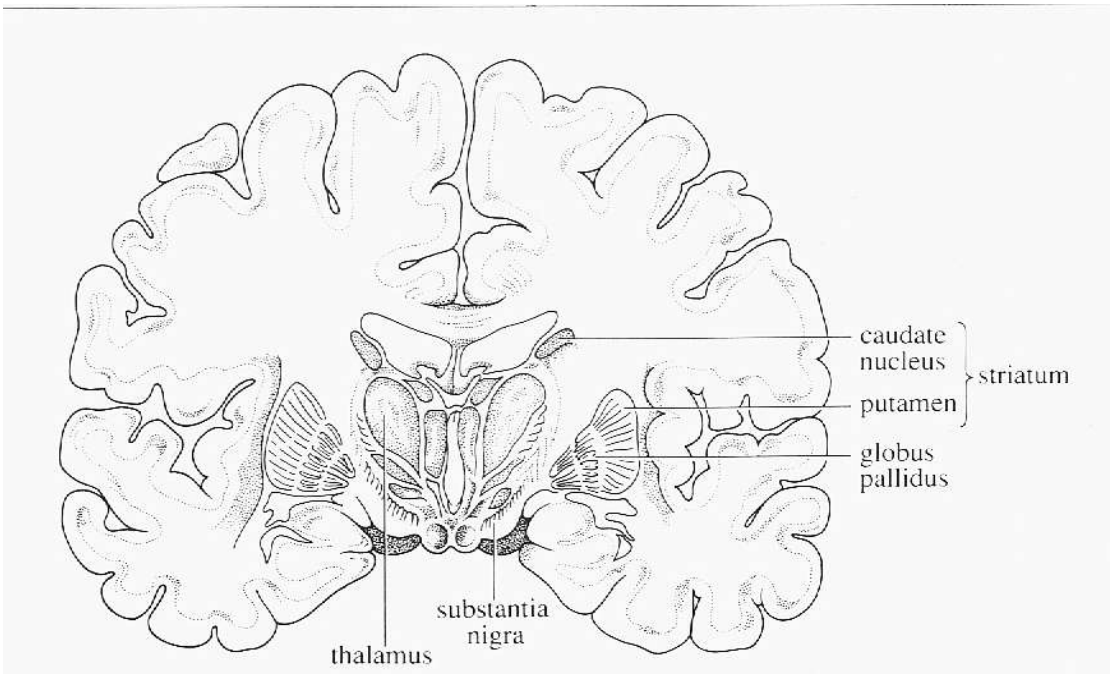


Figure 2

Coronal-slice diagram of brain showing some internal structures

Source: Metcalfe (2000)

Imaging can sometimes rule out conditions such as depression or hypothyroidism, but this is dependent on how images are interpreted, as illustrated in **Figure 3**, which shows PET images acquired using glucose analogue [^{18}F]2-fluoro-2-deoxy-*D*-glucose ([^{18}F]FDG). The brain on the left was initially interpreted as an AD brain, but the patient showed no cognitive decline over the subsequent two and a half years. The physician had failed to observe that the thalamus was isometabolic with the parietal

cortex, which is not normally seen in AD (also *see* Section 5). The patient had a history of depression and thyroid disease and was taking thyroid hormones.

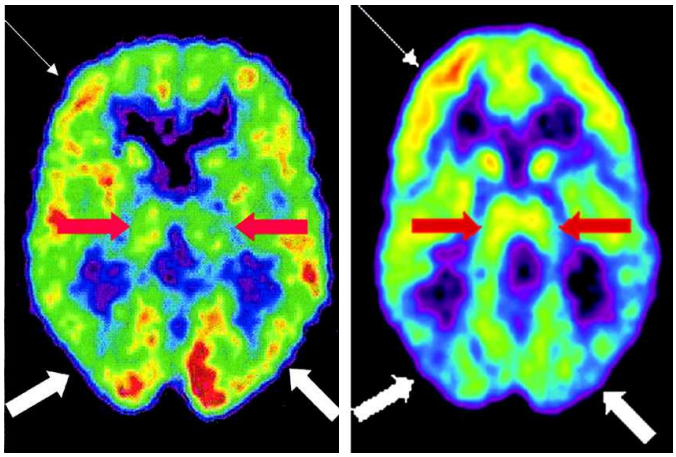


Figure 3

Axial [^{18}F]FDG PET scans of a patient with false-positive AD findings (left) and of one with AD (right). Misinterpretation could have been avoided if attention had been paid to the isometabolic status of the thalamus (enclosed by red arrows) with the parietal cortex (indicated by thick white arrows) in the first image. The AD brain also has the AD-typically hypometabolic parietal activity compared with the frontotemporal cortex (thin white arrows), which the non-AD brain has not. *adapted from Silverman (2004)*

Whilst impractical for routine clinical purposes due to its very short physical half-life (2.1 min.) and the lack of available cyclotrons for its production, PET radionuclide oxygen-15 (^{15}O) has some applications in dementia research. Using this radionuclide, Nagata *et al*. (2000) compared findings of cerebral blood flow (CBF), cerebral blood volume (CBV), cerebral metabolic rate of oxygen ($CMRO_2$), and oxygen extraction fraction (OEF) between patients with probable AD and those with vascular dementia. OEF is the fraction of oxygen transferred from capillaries to cells, and an increase is a compensatory response to ischaemia.

The team also calculated vascular reactivity (VR) and vascular transit time (VTT). VTT is the time taken for red blood cells to travel along blood vessels, and is determined as the ratio of CBV to CBF, while VR is estimated by comparing CBF during normal breathing with breathing during inhalation of 5% carbon dioxide.

Structural imaging with CT and MRI only revealed mild cortical atrophy in AD but numerous small infarcts in VaD. OEF, especially in the parietotemporal cortex, was found to be raised in probable AD but not in VaD, whereas VTT and VR were normal in AD but the VaD patient had prolonged VTT and decreased VR. CBF and $CMRO_2$ were most depleted in the temporal and parietal lobes in probable AD but in the frontal lobes in VaD, reflecting findings from SPECT perfusion studies and from [^{18}F] FDG PET glucose metabolism studies. **Figure 4** shows the different patterns observed.

Combined, these findings demonstrate that the AD patients had impaired cerebral metabolic reserves whilst the VaD patients had depleted vascular reserves, their blood vessels being unable to dilate further. The authors concluded that increased OEF plus normal vascular reserve indicates that vascular pathology in AD is confined to the capillaries and **blood-brain barrier** and that this pathology is likely to be a cause, not a consequence, of hypometabolism.

Weaknesses of this paper include the lack of reference to the size of the study sample, and the significantly different ages of the two patients for whom findings were

reported. However, findings were in good general agreement with those from other studies in this field.

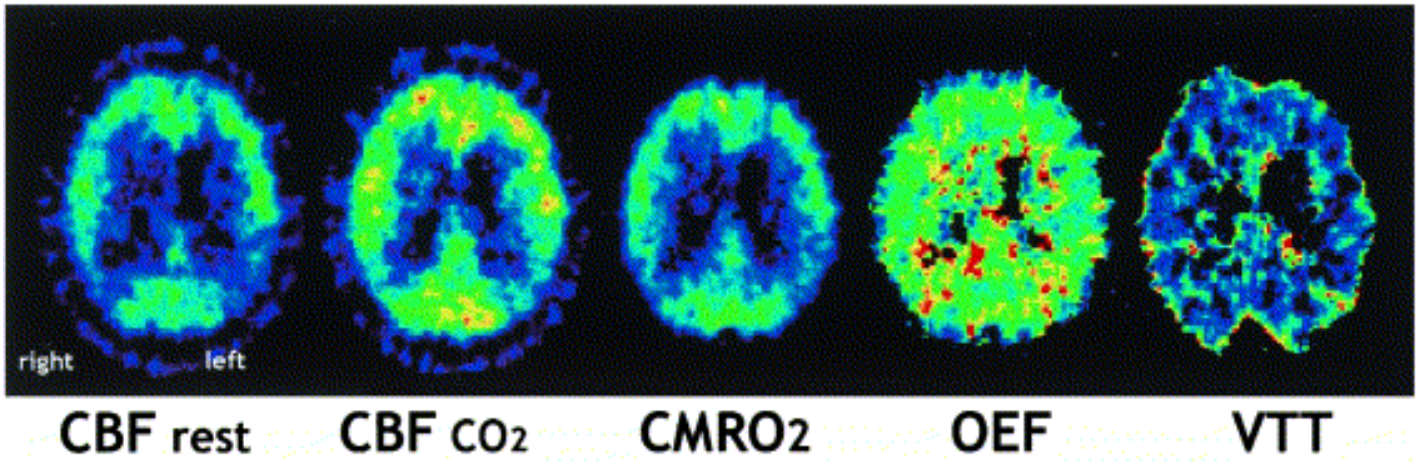
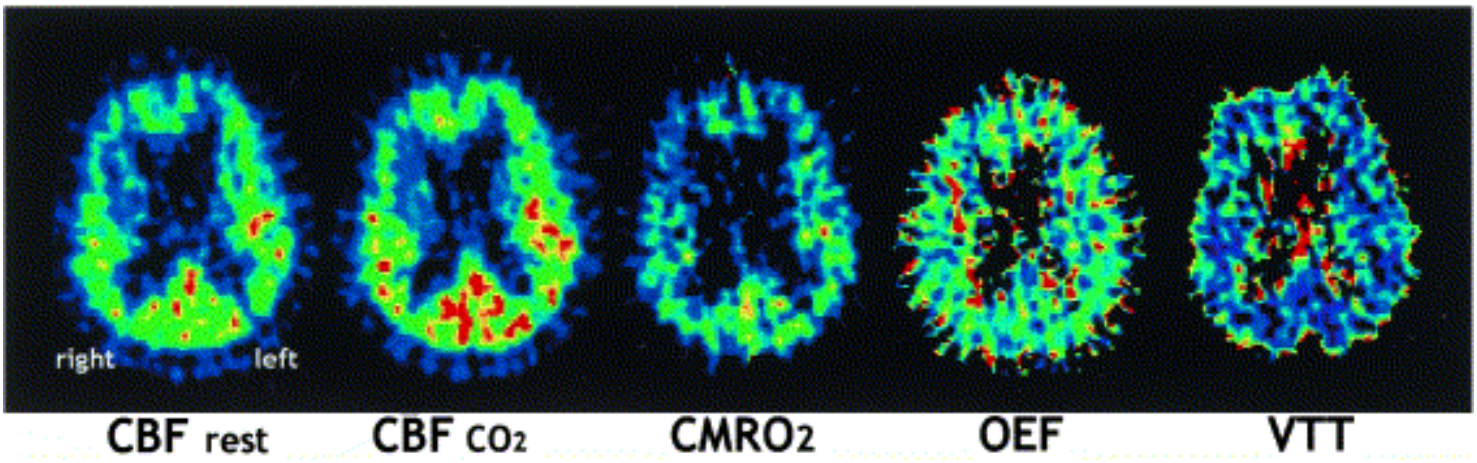


Figure 4

[^{15}O]PET images of brains of patients with probable AD (above) and VaD (below). Probable-AD case shows mainly temporoparietal CBF reduction during normal breathing (extreme left), significant CBF increase during CO_2 inhalation (second left), mainly temporoparietal $CMRO_2$ decrease (centre), diffusely increased OEF (second right), and no VTT prolongation.

VaD case shows mainly frontal CBF decrease during normal breathing (extreme left), poor CBF increase during CO_2 inhalation (second left), mainly frontal $CMRO_2$ decrease (centre), no significant OEF change (second right), diffuse bilateral VTT prolongation in both hemispheres (extreme right).

Abbreviations: CBF, cerebral blood flow; CMRO2, cerebral metabolic rate of oxygen; OEF, oxygen extraction fraction; VTT, vascular transit time. *Source: Nagata* et al. *(2000)*



4 Epidemiological/longitudinal studies

A 2000 review by Johnson and Albert notes conflicting findings in PET and SPECT studies on brain perfusion patterns in individuals with an **allele** (version of a gene) known to be a risk factor for AD: **apolipoprotein E-4** (**APOE-4)**. Some studies have found characteristic patterns of cortical hypoperfusion, whilst others have not, and the patterns reported have varied widely between studies. The authors point out that despite findings of early temporoparietal deficits, this brain region (a) is not associated with either memory or executive function, both of which are diminished in AD, and (b) does not show characteristic AD-type pathology in early AD. The finding is, however, consistent with the CATCH hypothesis for dementia, which postulates that the fundamental trigger for the pathology is the crossing of a threshold of cerebral hypoperfusion, arising from vascular compromise of one or more types. The APOE-4 gene is also a risk factor for vascular disease (e.g. *see* Humphries and Morgan, 2004).

Meyer *et al*. (2000) conducted a longitudinal study of 224 cognitively normal subjects to assess a number of risk factors for cognitive decline and for structural changes. CT imaging enhanced by xenon inhalation was used to assess atrophy, perfusion and tissue densities. A number of errors in the paper and a lack of clarity in tables make some of the associations hard to confirm.

The authors state that they found that hyperlipidaemia (high levels of blood fats), **transient ischaemic attacks** ('mini-strokes'), hypertension and smoking appeared to accelerate cerebral perfusional decline, leuko-araiosis (decreases in white-matter density) and cerebral atrophy and to contribute to mild cognitive decline and subsequent dementia. Hypertension was the strongest predictor of cognitive decline, and leuko-araiosis itself appeared to be a risk factor for such decline.

The Meyer team also found that leuko-araiosis and cerebral hypoperfusion preceded cerebral atrophy and were predictive of cognitive decline. They assert that their team has produced improvement in the cognitive performance of suspected early VaD dementia or a familial history of AD when risk factors were controlled, but it was not possible to verify this for the present review.

Many scientists have hypothesised that cerebral hypoperfusion is a consequence of reduced metabolic demand and thus would be expected to follow evidence of hypometabolism chronologically. Conversely, these findings, if confirmed, support the CATCH hypothesis, suggesting that the hypoperfusion is an earlier event in dementia aetiology and may be a causal factor in metabolic decline.

The contribution of vascular pathology to the various types of dementia can be investigated non-invasively using ultrasound.

Hofman *et al*. (1997) used this modality to assess the plaque load and vessel-wall thickness of the carotid arteries, as two indicators for atherosclerosis, in 284 dementia patients and 1698 controls.

As shown in **Table 2**, both measures were significantly associated with all types of dementia but especially with VaD.

This is consistent with the CATCH hypothesis of dementia. The importance of finding possible causal links between vascular disease and dementia is that there are already known and effective means of preventing and treating vascular disease, providing a potential way to prevent dementia from developing and perhaps to inhibit its progression. Also *see* Section 5.2.

Ultrasound measure	**Alzheimer's disease (*n* = 207)**	**Vascular dementia (*n* = 50)**	**Other dementia (*n* = 27)**	**All dementia (*n* = 284)**
Plaques in common carotid arteries	1.8 (1.2-2.7)	3.2 (1.6-6.8)	1.6 (0.6-4.3)	1.9 (1.3-2.7)
Wall thickness in common carotid arteries*	1.3 (1.0-1.6)	1.9 (1.3-2.8)	0.8 (0.4-1.5)	1.3 (1.1-1.6)

* Odds ratio of one SD (0.20 mm) increase in wall thickness

Table 2 Age-adjusted odds ratios of dementias (ranges in brackets) by ultrasound measures of carotid artery indicators of atherosclerosis

Source: Hofman et al. *(1997)*

Humphries and Morgan (2004) report findings of a clear relationship between the APOE-4 genotype and carotid artery atherosclerosis as ascertained with ultrasound artery wall measurement. However, the Hofman *et al*. study concluded that APOE-4 did not exert its dementia risk **via** vascular disease, and proposed rather that this genotype acted synergistically with vascular disease to increase risk.

APOE-4 may increase dementia risk via a reduction in binding sites on the brain's nicotinic receptors and low activity of the enzyme choline acetyltransferase, which deficits are seen in APOE-4-positive AD patients (Breteler, 2000), and the latter of which would result in lower levels of the central neurotransmitter **acetylcholine (ACh)**. This may account for an apparent protective effect of smoking against dementia in APOE-4 carriers. Specific **radioligands** (molecules with radioactive tracers attached, which bind to other specific molecules) for these receptors are now in development (*see* Section 7).

De Leon *et al*. (2001) found that hypometabolism in the **entorhinal cortex** (EC) of cognitively normal subjects, as measured with [^{18}F]FDG-PET, was predictive of decline to mild cognitive impairment (*see* **Table 3**).

Baseline EC hypometabolism was also predictive of neocortical hypometabolism, which is associated with cognitive impairment.

Chételat *et al*. (2003) found that hypometabolism in the right temporoparietal cortex, as measured by [^{18}F]FDG PET, predicted rapid decline from MCI to AD, whilst uptake in the posterior cingulate gyrus was not as reliably predictive. Like the previous study, this provides evidence as to which brain areas are involved in the pathology of AD at different stages.

	baseline			follow-up		
brain region	***non-declining subjects***	***declining subjects***	***statistical signifi-cance***	***non-declining subjects***	***declining subjects***	***statistical signifi-cance***
EC	91 ± 7	75 ± 7	$p \leq 0.01$	86 ± 5	71 ± 7	$p \leq 0.01$
Hip	90 ± 6	87 ± 5		86 ± 5	80 ± 11	$p \leq 0.05$
STG	105 ± 3	103 ± 4		103 ± 5	100 ± 9	
LTL	97 ± 7	91 ± 8		93 ± 4	86 ± 13	$p \leq 0.01$
OFL	101 ± 15	102 ± 8		105 ± 6	100 ± 12	
DFL	117 ± 9	109 ± 12		120 ± 7	113 ± 9	

Table 3 Correlations between glucose metabolism in different brain regions, as measured by [^{18}F]FDG PET, and cognitive decline. EC = entorhinal cortex; Hip = hippocampus; LTL = lateral temporal lobe; OFL = orbital frontal lobe; DFL = dorsolateral frontal lobe. *data source: de Leon* et al. *(2001)*

The ability to identify individuals likely to suffer cognitive decline – itself a predictor of dementia – could facilitate early intervention and aid epidemiological research looking at correlations with lifestyle factors, other medical conditions and drug use, as well as with the presence of specific lesions, improving the prospect of ascertaining primary causation.

5 Monitoring effects of treatment

5.1 AChE inhibitors

Consistent findings of significant decline in the cholinergic neurotransmission system in AD have led to the use of anticholinesterase drugs in its treatment. In AD there is a substantial decrease in the number of cholinergic neurons with axonal projections to the cerebral cortex, and this is thought to be the reason for a large reduction in levels of ACh (Nobili *et al*., 2002). ACh is broken down by AChE in the gaps (synapses) between neurons, so reducing AChE activity increases levels of ACh. Tune and colleagues conducted a study in 2003 on the efficacy of one of these, donepezil HCl (E2020), using [^{18}F]FDG-PET. They normalised the measurements of glucose metabolism to values for the **pons**, a brain region considered to be relatively unaffected by pharmacological intervention. The authors concluded that donepezil prevented brain metabolism from deteriorating in contrast to placebo. However, there are some apparent incongruities in the study. The images presented (**Figure 5**) do not resemble those of typical AD brains as presented in other metabolism and perfusion studies (cf. **Figures 3, 4 & 8**).

The deterioration in the 'placebo' brain appears unusually rapid for AD (claimed to be an average of 10.4% in six months relative to the pons) and also remarkably uniform. Such uniformity of decline is not typical in AD, in which the temporoparietal region usually declines significantly compared to the frontal regions, also largely sparing the thalamus, which appears to have become more hypometabolic than the temporoparietal cortex in the 'deteriorated' placebo brain in this study.

There are also clearly-visible differences between the two brains at baseline, and neither appears typical of AD although the images are described as 'representative'. This points up the importance of a human aspect of imaging: the need to process and interpret images and data skilfully.

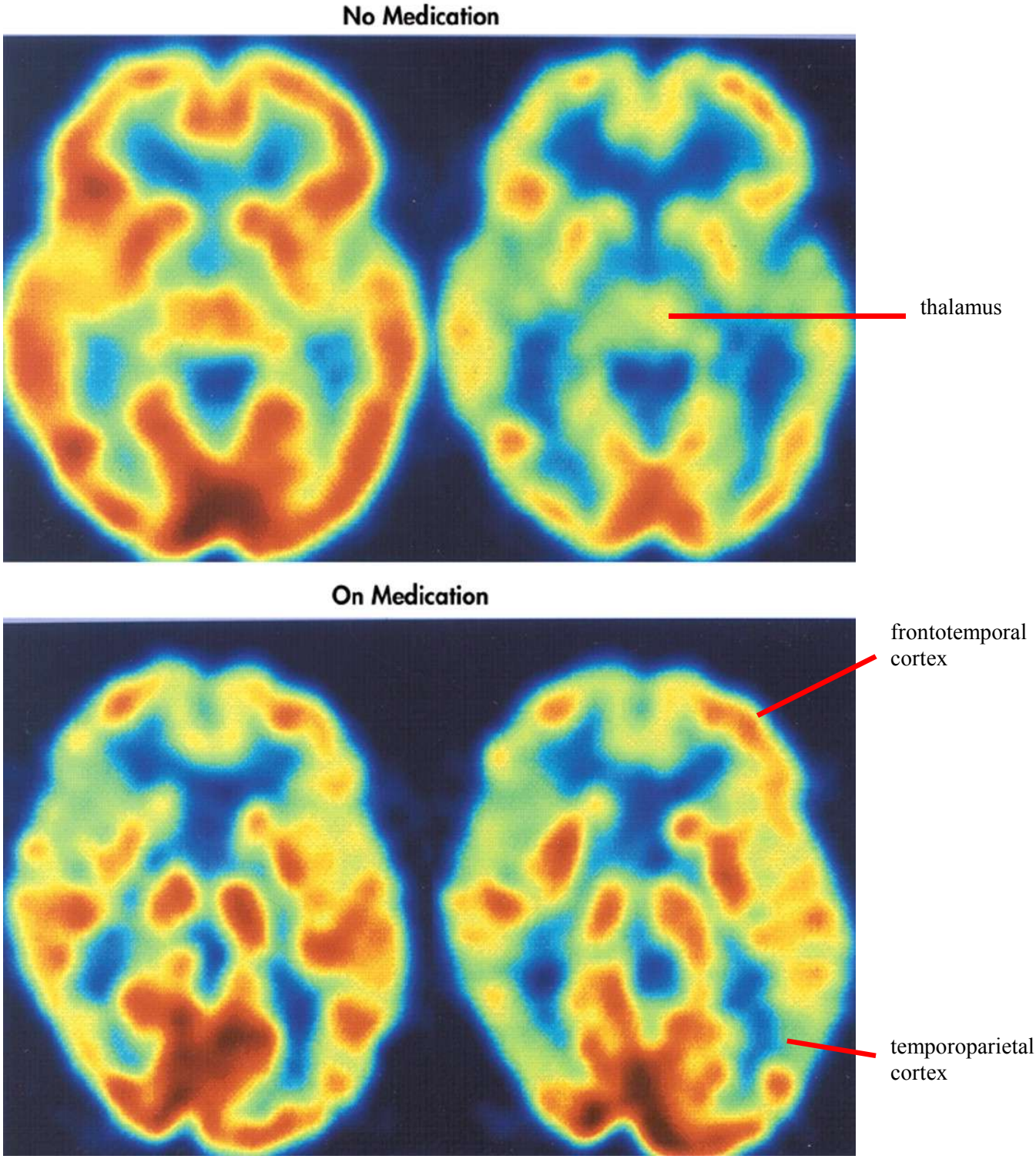


Figure 5 [^{18}F]FDG PET brain images from 'AD' patients given placebo or donepezil for six months. The left-hand images were taken at baseline and the right-hand images after 6 months of treatment.
Source: Tune et al. *(2003); labels added*

Although imaging is more objective than some clinical diagnostic criteria, it is not without elements of subjectivity and risk of bias or artefact (also *see* Section 10).

How useful was imaging in this study? The changes in glucose metabolism did not correspond to the patients' psychometric test findings yet, as acknowledged by the authors, donepezil has been shown by other studies to improve cognition in AD sufferers. However, a recent study found that donepezil produced no significant benefit for behavioural and psychological symptoms, formal care costs, unpaid caregiver time, adverse events or deaths (Courtney *et al*., 2004).

If Tune and colleagues' findings are valid, they show that the drug appears to have significantly improved brain metabolism in some regions affected in AD in one group of patients, whilst metabolism declined dramatically but non-AD-typically in another group. Imaging provided clear information, but the *meaning* of the information is unclear.

Another imaging study monitoring the effects of donepezil was reported by Nobili and colleagues in 2002. This team measured brain perfusion with radiopharmaceutical technetium-99m-hexamethyl-propylene amineoxime ([^{99m}Tc]HMPAO) and SPECT, and found a correlation between perfusion and cognitive response in patients treated with donepezil. However, the authors acknowledge that about half of the patients did not respond to treatment, and the lack of a control group meant that a placebo effect or a 'smoothed natural course of the disease' could not be ruled out as explanations for apparent treatment efficacy.

5.1.1 AChE radioligands

Another means of monitoring the effects of AChE inhibitors is by using radioligands for AChE. Iyo *et al*. (1997) estimated AChE distribution in 5 mild-AD patients and 8 controls with the PET radioligand [^{11}C]N-methyl-4-piperidyl acetate ([^{11}C]MP4A) which binds to the enzyme with good specificity. AChE levels appeared lower in AD than in controls in many cortical regions, most markedly in the parietotemporal cortex (*see* **Figure 6**). Post-mortem studies have found significant correlations between AChE depletion and both SP burden and cognitive decline.

Whilst this method is a potential tool for estimating the efficacy of AChE inhibitors, such findings perhaps call into question the wisdom of further inhibiting an enzyme which is already depleted.

Correlating AChE decreases with findings from other radiopharmaceuticals is likely to increase understanding of relationships between different aspects of dementia pathology and possible causal chains. Also *see* Section 7.

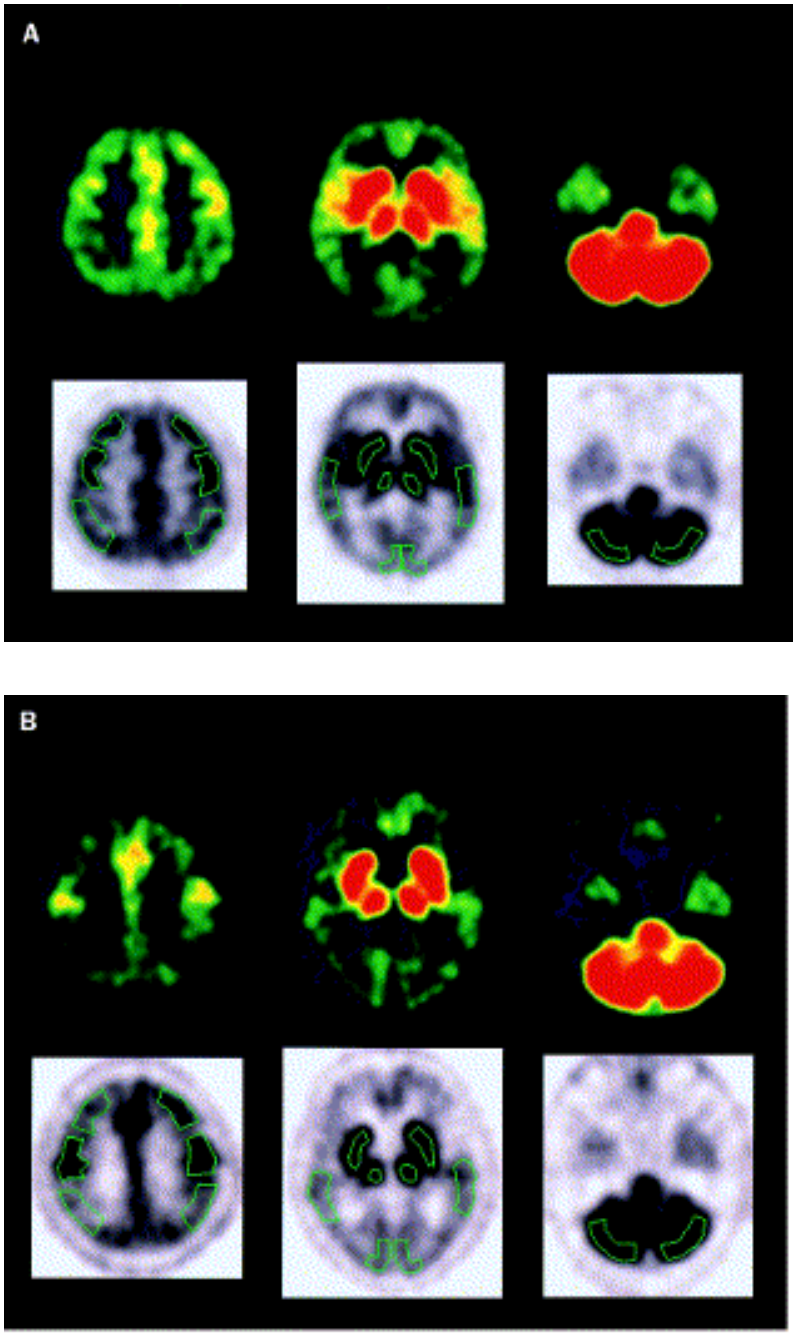


Figure 6

PET brain images of the radioactivity distribution in brains obtained 20–40 min after injection of [^{11}C]MP4A in a normal participant (upper three images in A) and in a patient with Alzheimer's disease (upper three images in B), with regions of interest outlined (lower images in A and B)

Source: Iyo et al. *(1997)*

5.2 Vitamins

Vitamin E supplementation has been found to delay AD patients' loss of ability to perform basic activities of daily living (Sano *et al*., 1997). Another vitamin found to be negatively associated with dementia (Breteler, 2000) and vascular compromise is folic acid. Title *et al*. (2000) used ultrasound to measure brachial flow-mediated dilation (FMD) in groups of patients with coronary artery disease given folic acid, folic acid plus Vitamins C and E, or placebo, and found significant improvement in the folic-acid-only group but not the folic-acid-plus group. Whilst this may appear to contradict studies finding benefit from Vitamin E on vascular health, the amount of Vitamin C given was very high – 2 g per day – which may have had adverse effects.

Folic acid produced a similar degree of FMD improvement to that achieved with synthetic statins and ACE inhibitors.

Pryor (2002) reports several studies using imaging to investigate associations between blood vitamin levels, dietary vitamin intake or vitamin supplementation, including Vitamin E, and aspects of vascular disease. The studies used ultrasound to measure carotid artery wall thickness or percutaneous transfemoral artery angiography to measure coronary artery stenosis (narrowing). On balance, Vitamin E in particular showed a negative association with vascular disease risk.

In view of the many findings of an apparent causal role for vascular disease in both vascular dementia and AD, and of the fact that dementia pathology takes many years – sometimes decades – to produce clinical symptoms, these findings present a potential means of early prevention and of long-term longitudinal study of the disease using various imaging modalities: ultrasound or angiography to assess vascular health alongside structural and functional brain imaging. Correlating the vascular and brain findings with vitamin intake and body vitamin levels may provide vital insights into dementia pathogenesis.

Zamrini *et al*. (2004) propose that imaging might facilitate reductions in participant numbers and duration in treatment trials. They cite trials currently lasting 5-7 years and requiring hundreds or thousands of participants, and suggest that imaging could reduce these to 6-12 months' duration and a few hundred participants.

6 Activation studies

Slosman *et al*. (2001) studied brain changes occurring during a verbal fluency test in patients deemed to have 'probable Alzheimer's disease' and healthy age-matched volunteers. 'Probable Alzheimer's disease' was diagnosed through detailed clinical examination including structural brain imaging with MRI or CT. Patients with a high **Hachinski ischemic score** were excluded from the study, so those with a significant vascular component to their cognitive impairment were not studied.

The researchers used [^{99m}Tc]HMPAO to image the subjects' brain perfusion by single photon emission computed tomography (SPECT). The baseline condition involved simple syllable repetition, during which 260 MBq of radiopharmaceutical was injected, and the activation condition involved the production of as many words as possible beginning with specific letters, while 1.04 GBq of the radiopharmaceutical was injected.

The imaging findings were analysed both visually and by statistical parametric mapping (**SPM**). Visual evaluation did not reveal clear differences between patients and controls, but SPM analysis showed dramatic differences between groups in specific brain areas when the activation condition was compared with baseline (*see* **Figure 7**).

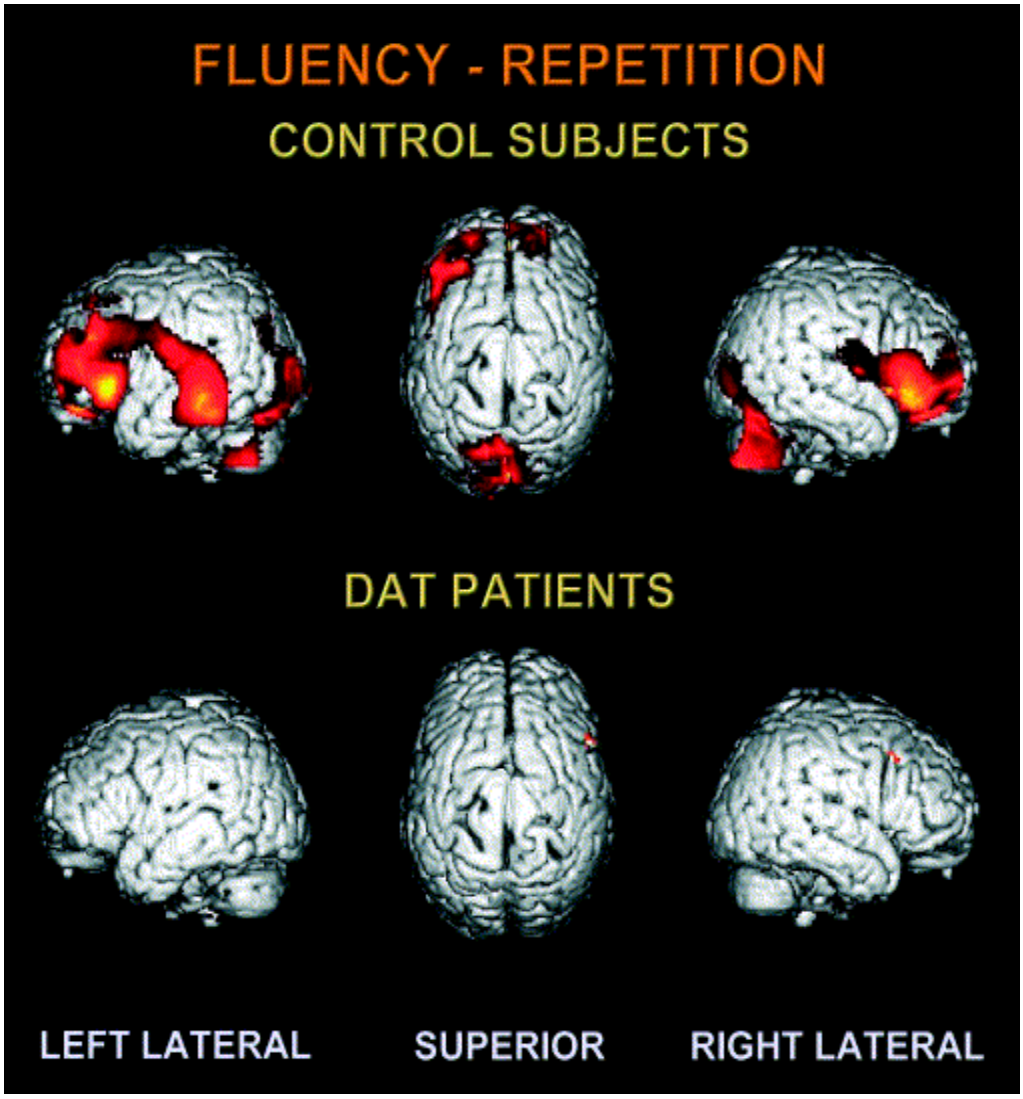


Figure 7

SPECT SPM of AD (designated 'DAT' here) and normal brains for verbal fluency activation minus baseline data (syllable repetition).

adapted from Slosman et al. (2001)

The AD patients were not severely demented and their baseline SPECT findings showed little evidence of hypoperfusion, but they appeared to be unable to increase regional perfusion in response to a cognitive task. The authors proposed a range of interpretations for this, including the possibility that the patients had high baseline perfusion due to AD pathology which involves inflammatory processes. The findings indicate that activation SPECT studies may be more useful than resting-state studies for detecting early-stage, and perhaps prodromal, dementia, and also provide information about regional brain function which resting studies cannot.

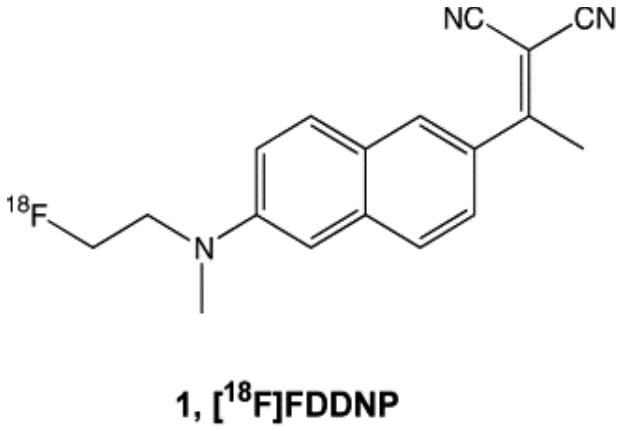
PET activation studies have also been carried out.

7 Imaging AD-characteristic lesions

7.1 Imaging amyloid

The main component of SPs is the abnormal protein beta-amyloid (**Aβ**). AD is generally considered to be diagnosable post-mortem by the presence of focal SPs in the **neocortex** and NFTs in the hippocampus, entorhinal cortex and neocortex. There has been a great deal of effort in recent years to develop radioligands which will bind to these. Some are already in clinical trials, whilst others have been found to bind successfully *in vitro*.

Agdeppa *et al*. (2003) have tested the SP- and NFT- binding PET radiopharmaceutical 2-(1{6-[(2-[^{18}F]fluoroethyl)(methyl)amino]-2-naphthyl} ethylidene)malononitrile ([^{18}F]FDDNP) (**Structure 1**) in humans with apparent success. [^{18}F]FDDNP crosses the blood-brain barrier readily due to its high hydrophobicity (log*P* = 3.92), and has greater retention in hypometabolic and atrophic regions of AD brains. It is more sensitive at early stages of AD than at later stages, and provides more specific information than does the more commonly-used [^{18}F]FDG. Comparison between *in vivo* findings and *in vitro* findings from post-mortem brain sections confirmed that the *in vivo* distribution of the radiopharmaceutical corresponded well with the presence of SPs and NFTs.



1, [^{18}F]FDDNP

Structure 1

PET imaging radiopharmaceutical 2-(1{6-[(2-[^{18}F]fluoroethyl)(methyl) amino]-2-naphthyl} ethylidene)malononitrile ([^{18}F]FDDNP)

Source: Agdeppa et al. *(2003)*

Figure 8 illustrates AD and normal brains imaged with [^{18}F]FDDNP and [^{18}F]FDG PET and with MRI. The PET images show the correspondence between hypometabolism, as demonstrated by low retention of [^{18}F]FDG, and the presence of SPs and NFTs, as demonstrated by high retention of [^{18}F]FDDNP. The atrophy seen in the AD MRI image corresponds to regions of hypometabolism and high NFT and SP concentration.

[^{18}F]FDDNP has also been found to bind *in vitro* to the characteristic lesions of two other forms of dementia: Pick's disease (a type of FTD) and dementia with Lewy bodies.

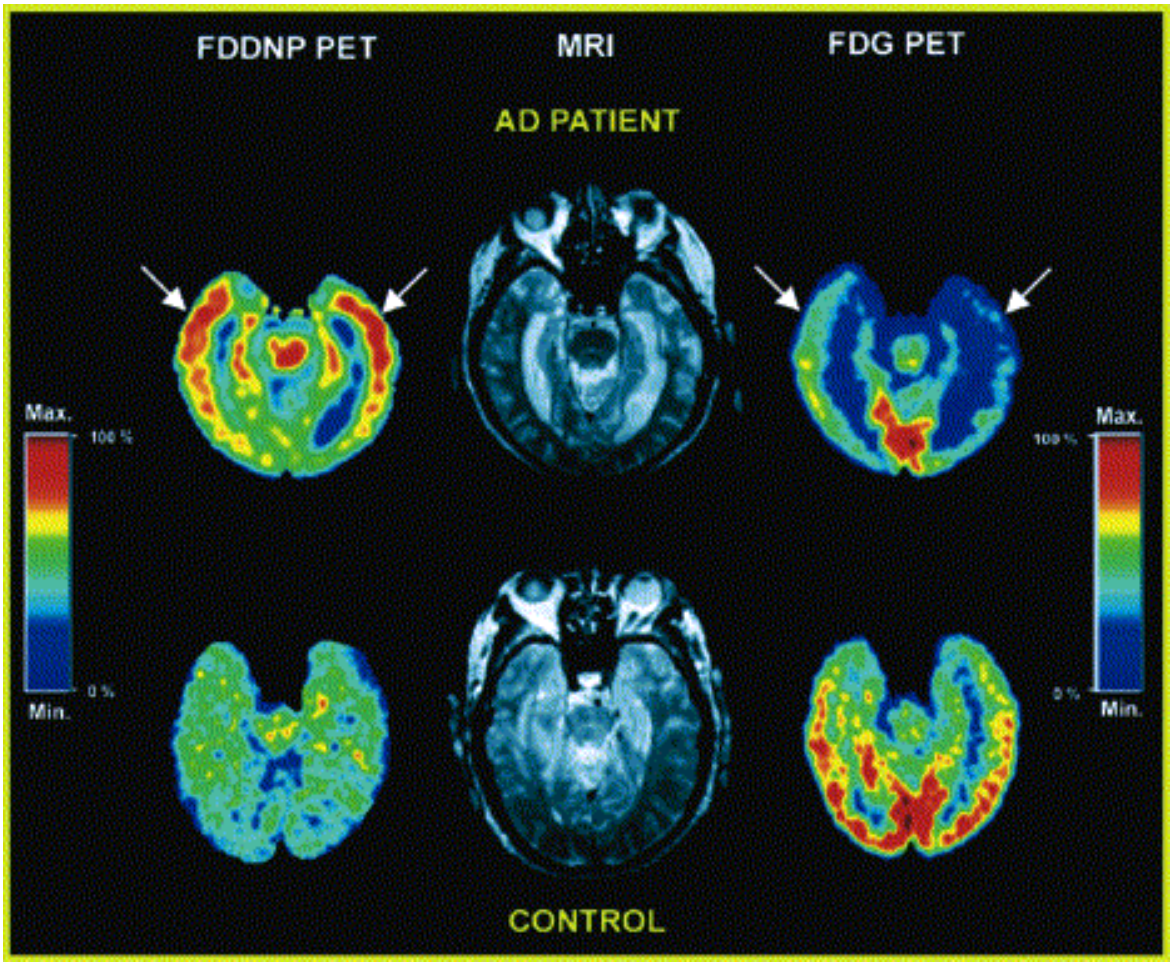


Figure 8 AD and normal brains as imaged with [^{18}F]FDDNP and [^{18}F]FDG PET and with MRI. The colour bar indicates the magnitude of radiopharmaceutical uptake. Arrows show concordance between regions of high [^{18}F]FDDNP uptake, indicating high SP and NFT concentrations, and low [^{18}F]FDG uptake, indicating hypometabolism. *Source: Agdeppa* et al. *(2003)*

This study also found that the relative residence times (RRTs) of [^{18}F]FDDNP *in vivo* correlated significantly with cognitive performance (**Figure 9**). RRT is the duration of the radioligand's persistence in AD-affected brain regions relative to a reference brain region which is relatively unaffected. Early AD is characterised by a slow decline in Mini-Mental State Examination (MMSE) scores but a rapid increase in [^{18}F]FDDNP binding capacity - indicated by RRT increase - whilst the later, more rapid MMSE decline is associated with a slower increase in RRT.

The authors interpret the fact that [^{18}F]FDDNP retention increases more rapidly with early, rather than later, cognitive decline, as evidence that at later stages "compensatory resources have been exhausted in a brain already devastated by the advanced disease." Alternatively, or in addition, the finding is consistent with a view that amyloid-associated inflammation is a more significant component of early, rather than later, AD pathology. As Slosman *et al.*'s 2001 activation study found (*see*

Section 6), baseline perfusion was not significantly lower in AD patients than in controls. Inflammation recruits increased blood flow, so a substantial proportion of baseline blood flow in AD may be due to inflammation rather than to normal brain activity. Inflammation also leads to increased glucose uptake (Rennen *et al*., 2001), so some pathology may be missed by [^{18}F]FDG-PET at early stages of AD. Gridley *et al*. (1997) observed an increase in glucose utilisation in human neuroblastoma cells treated with Aβ *in vitro*.

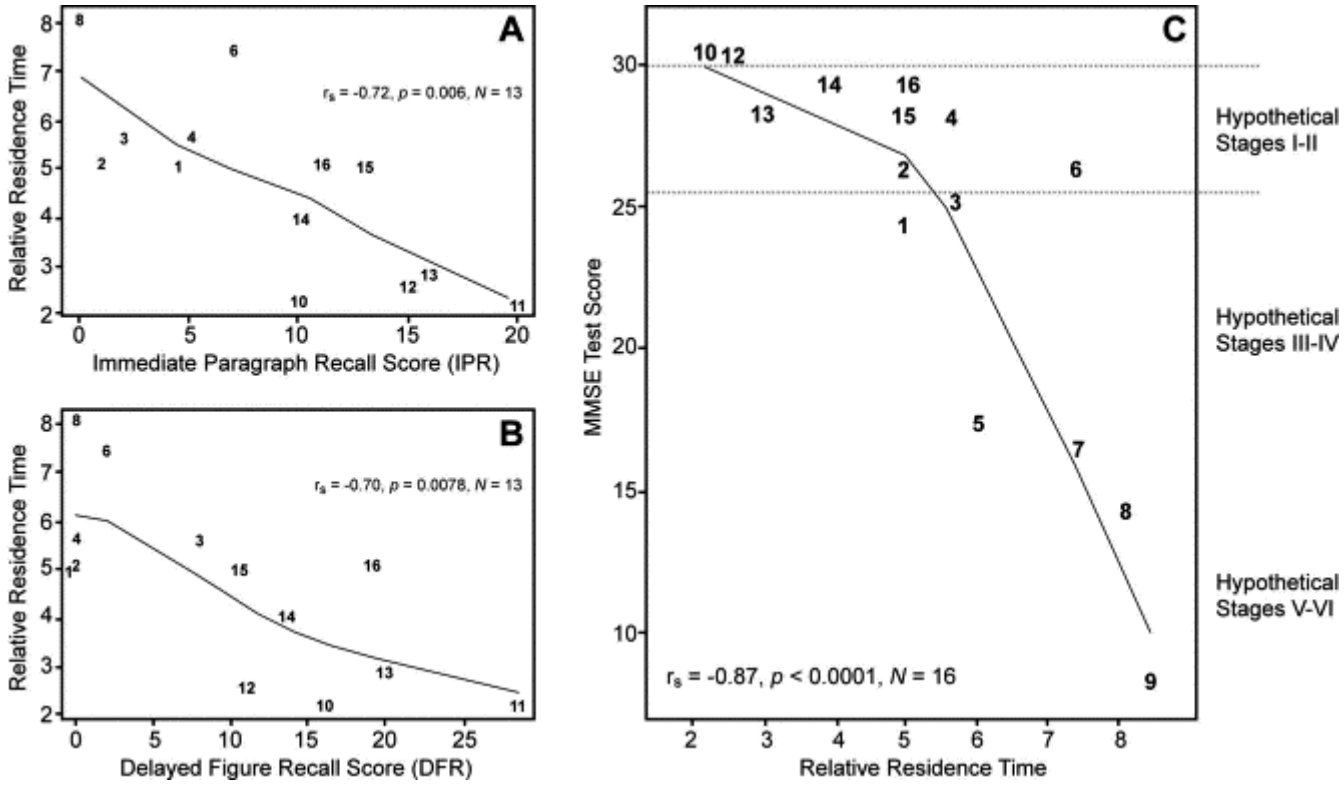


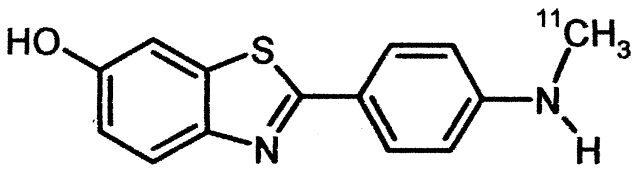
Figure 9 Correlations of the relative residence time for [^{18}F]FDDNP in human brains *in vivo* with cognitive test scores. MMSE scores below 25 are widely considered to indicate AD. The dashed lines represent hypothetical staging of a brain region afflicted early in the evolution of AD.
Source: Agdeppa et al. *(2003)*

Agdeppa's team's *in vitro* studies showed that [^{18}F]FDDNP binds to SPs at the same binding sites as some non-steroidal anti-inflammatory drugs (NSAIDs), which is consistent with epidemiological studies finding that chronic users of NSAIDs have a significantly reduced risk of AD, and with *in vitro* and post-mortem studies which have found high levels of inflammation in the vicinity of SPs. An important finding of the Agdeppa study is the different degree of competition for the [^{18}F]FDDNP binding site from different NSAIDs, some of which may be protective via anti-inflammatory mechanisms, some by inhibiting the production of Aβ and some by preventing aggregation of the protein into focal plaques. This holds promise for the use of [^{18}F]FDDNP in combination with different NSAIDs in clinical or population

studies to research the mode of action of the NSAIDs and the pathological pathways which lead to AD initiation and/or progression.

Agdeppa and colleagues suggest that analogues of [^{18}F]FDDNP might aid the development of new anti-AD drugs.

Other amyloid-detecting radiopharmaceuticals in development include imidazo-pyridine derivatives, such as 2-(4′-dimethylaminophenyl)-6-iodo-imidazo[l,2-a] pyridine (IMPY) (for SPECT), a lipophilic thioflavin-T analogue (2-[4′ -(methylamino)phenyl]benzothiazole), and stilbene derivatives (Zamrini *et al*., 2004). One of the latter - *N*-methyl-[^{11}C]2-(4-methylaminophenyl)-6-hydroxybenzothiazole (known as PIB – **Structure 2**) - was used by Klunk *et al*. (2004) to image SPs with PET in 16 mild-AD patients and 9 controls, 3 young and 6 middle-aged-to-elderly.



Structure 2

N-methyl-[^{11}C]PIB
Source: Klunk et al. *(2004)*

As with [^{18}F]FDDNP, PIB binding correlated inversely with [^{18}F]FDG-PET metabolic findings, although it showed some non-specific binding to white matter, and binding did not correlate significantly with cognitive proficiency; indeed, the oldest control subject showed AD-typical binding, whereas three mild-AD patients did not. PIB binds *in vitro* to SPs but not NFTs, offering the potential to also image the distribution of NFTs – which correlate more closely post-mortem with dementia status than do SPs - by digitally subtracting PIB images from those obtained with [^{18}F]FDDNP.

7.2 Imaging inflammation

Radioligands are also being developed specifically to image biomarkers for inflammation. Versipt *et al*. (2003) used the SPECT radioligand ^{123}I-labelled 1-(2-chlorophenyl)-N-(1-methyl-propyl)-3-isoquinoline carboxamide (known as [^{123}I]iodo-PK11195) to image the peripheral benzodiazepine receptor (PBR). This receptor is upregulated in inflammation through its expression on microglia, which are involved in brain inflammation processes. From a sample of 10 AD patients and 9 controls, the team found that mean uptake of the ligand was greater in AD in almost all neocortical regions (*see* **Figure 10**) but only significantly in frontal and right mesotemporal regions, and that uptake correlated significantly with cognitive deficit.

Uptake in specific regions correlated with performance on specific cognitive tasks, a finding which suggests that this ligand might be able to increase understanding of the relationships between brain physiology and cognition.

High binding regions were those showing hypoperfusion as measured by SPECT using [^{99m}Tc] ethyl cysteinate dimer ([^{99m}Tc]ECD).

The same ligand labelled with PET radionuclide ^{11}C has demonstrated increased uptake in the entorhinal, temporoparietal and cingulate cortices of mild dementia patients, regions also showing glucose hypometabolism (as was the case for [^{18}F] FDDNP and PIB), and the fastest atrophy as demonstrated by serial volumetric MRI imaging. This suggests a possible causal role for inflammation, perhaps mediated by SPs, in this atrophy.

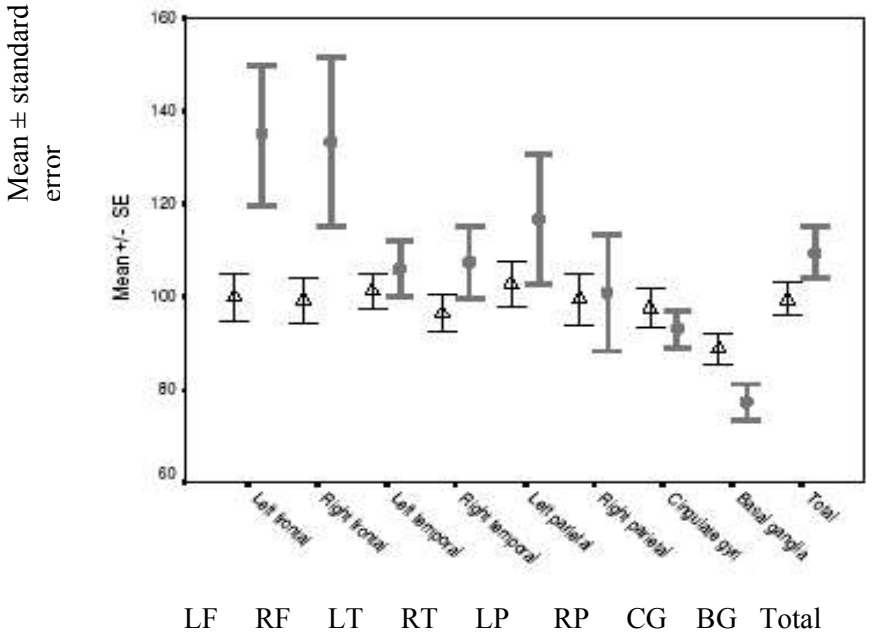


Figure 10

Grouped mean (± standard error of the mean) [^{123}I]iodo-PK11195 uptake values

LF = left frontal cortex; RF = right frontal cortex; LT = left temporal; RT = right temporal; LP = left parietal; RP = right parietal; CG = cingulate gyri; BG = basal ganglia

△ controls ■ AD patients *adapted from Versipt* et al. *(2003)*

7.3 Imaging other receptors

7.3.1 Serotonin receptors

Another SPECT radioligand, [^{123}I]4-amino-N-[1-[3-(4-fluorophenoxy)propyl]4-methyl-4-piperidinyl] 5-iodo-2-methoxybenzamide ([^{123}I]5-I-R91150) revealed differences between age-related and AD-related neocortical decline in 5-HT_{2A} receptors (*see* **Figure 11**).

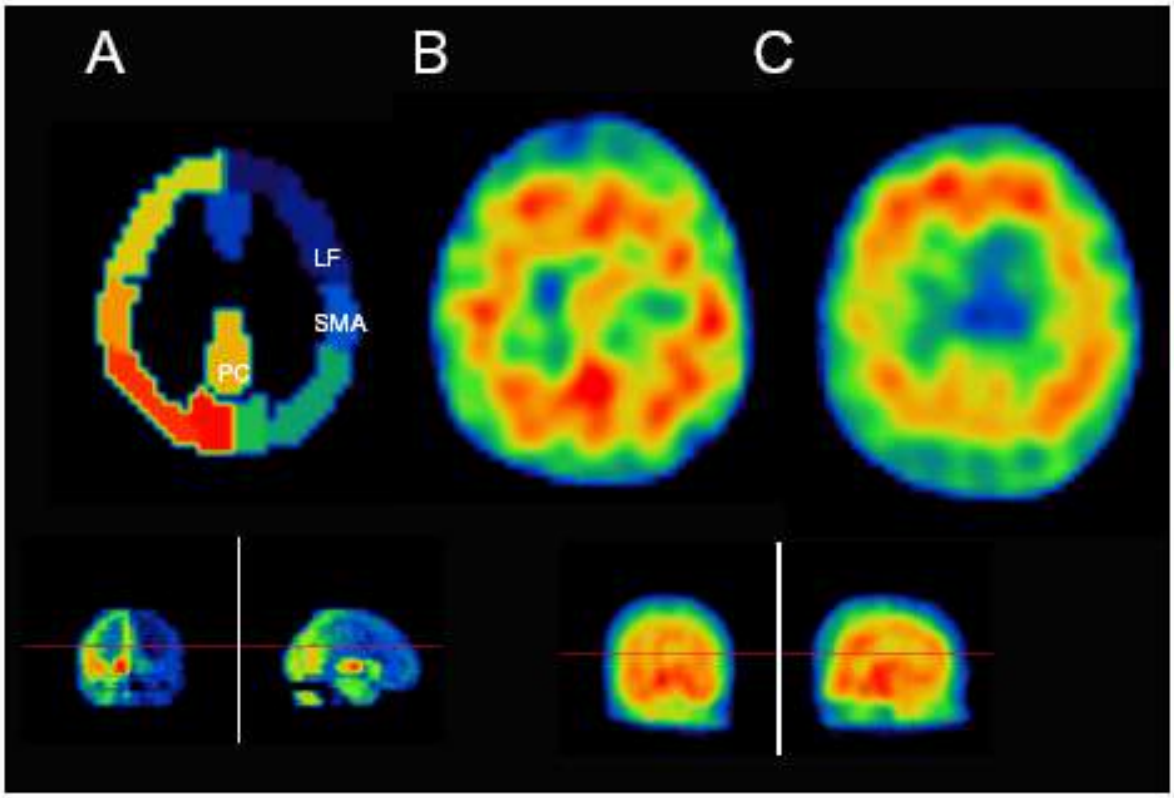


Figure 11 Volume-of interest (VOI) map (A) together with a representative slice of an age-matched healthy volunteer (B) and an AD patient (C). Note free ligand and non-specific binding in the cerebellum and

specific uptake decreases in the lateral frontal (LF), sensorimotor (SMA) and the posterior cingulate

These are a subtype of receptor for the neurotransmitter serotonin, which may be involved in the secretion of amyloid precursor protein (APP), the protein whose abnormal processing leads to the formation of SPs (Versipt, 2003, Chapter 7). No post-mortem examinations had been conducted at the time of publication, but these usually show reduced 5-HT_{2A} receptor density, rather than reduced binding affinity, in AD brains. These findings might have implications for developing treatments directed at the serotonergic system.

The study found that the hippocampus was relatively unaffected, although this region is a major site of NFT deposition. The only region which showed a significantly greater decrease in AD patients than in age-matched controls was the sensory and motor cortices, which the author suggests reflects deficits in planning physical actions and processing sensory information. Primary sensorimotor impairment is not characteristic of AD until the late stages.

If these findings reflect real changes and not artefacts, they could increase understanding of the relationships and connections between different brain regions with regard to dementia progression.

Knowledge of normal age-related changes can facilitate optimal age-matching of patients to controls in imaging studies. However, this study contains apparent contradictions on the pattern of age-related binding decrease, with a Figure showing a

linear decline from age 10 to age 90 but the text referring to a lack of decline after age 60 and an *increase* in binding after age 70.

The chapter refers to PET studies with other 5-HT_{2A} radioligands [^{18}F] altanserin and [^{18}F] setoporone, which found decreased binding in the frontal, cingulate and temporal regions in AD. In the book's summary the author suggests that AD may not be a single disease. He recommends serial imaging of different types of lesion in the same patients and comparing them to laboratory serum and/or cerebrospinal fluid (CSF) tests and post-mortem findings to try to throw further light on chronology and chains of causation.

7.3.2 Acetylcholine receptors

As stated in Section 4, AD patients carrying the allele APOE-4 have a reduced number of nicotinic receptor binding sites. Pimlott *et al*. (2004) found distinctive patterns of binding in different dementias and controls for the SPECT radioligand [^{125}I] 5-iodo-3-[2(*S*)-2-azetidinylmethoxy]pyridine (5-[^{125}I]-A-85380) to the $\alpha4/\beta2$ subtype of nicotinic ACh receptors in post-mortem brain tissue, and they consider that the radioligand has *in vivo* applications. However, the four mild AD brains could not be differentiated from controls or VaD brains. This could be a consequence of the small sample size, or may indicate that the method is not useful for detecting early AD. Even this apparent failure provides potentially-useful information, as it may indicate that this receptor subtype is indeed not affected in early AD. As with other specific radioligands, findings from imaging this receptor could throw light on the pathological pathways involved in dementia and their chronology.

Kimes *et al*. (2003) tested an [^{18}F] version of this radioligand in healthy individuals and concluded that it was suitable for quantitative PET imaging.

7.3.3 Other receptor radioligands in development

The H_3 histamine receptor regulates the release of acetylcholine, serotonin and some other neurotransmitters which may be involved in AD. Sigma-Aldrich (*see* reference list) report on the development of radioligands for this receptor. The neurotransmitter glutamate has altered activity in AD (*see* following section), and scientists at Zurich University (*see* reference list) are among those developing radioligands for glutamate receptors. Also *see* Section 5.1.1.

8 Some other applications of imaging and related modalities in dementia research

Magnetic resonance spectroscopy (MRS) can be used to detect biochemical abnormalities in dementia patients. This is potentially useful in increasing understanding of the biochemical sequences in AD development and progression. A study using quantitative [^{1}H]MRS found that patients with a diagnosis of 'probable AD' had 20% less cerebral [glutamate + glutamine] than normal (Moats *et al*., 1994). Finch and Cohen (1997) interpret this as supportive of evidence of ammonium fixation being reduced in both AD and normal ageing due to a decrease in the activity of the enzyme glutamine synthetase, which *in vitro* studies suggest may be associated with the production of SPs. The Moats team also found a 50% increase in myoinositol in the cognitively-impaired sample, consistent with the 2002 MRS

findings by Waldman *et al*. of a higher myoinositol:creatine ratio in AD patients compared with controls and patients with SIVD, a type of vascular dementia.

Versipt (2003, Summary) states that MRS-measured levels of N-acetyl aspartate are indicators of neurocellular viability or neuroaxonal integrity, but Waldman's team found no significant differences between AD, SIVD and control groups for the ratio of this compound to creatine, nor between the ratio of choline to creatine; Versipt considers MRS choline measurement potentially useful for measuring the activity of glia, which have a range of neuron-supporting roles including provision of the insulating myelin coating on neurons. However, microglia are upregulated in inflammatory conditions (*see* Section 7.2), which might compromise the utility of such measurements, especially in early AD.

Versipt also favours magnetic transference imaging (MTI), which can provide evidence of damage to cell membranes, and diffusion MRI to measure the integrity of brain tissue compartments.

9 Comparing and combining modalities

CT is a widely-available and routinely-used structural imaging modality in dementia diagnosis. A number of scientists do not favour MRI due to its slowness for AD-lesion-specific imaging (e.g. Agdeppa *et al*., 2003), its poorer diagnostic accuracy compared to [^{18}F]FDG PET (de Santi *et al*., 2001; Jagust, 2004; Knopman *et al*., 2001; Silverman, 2004) and its noisiness which risks frightening cognitively impaired individuals. However, it is sometimes used instead of CT to provide a higher-resolution structural image to co-register with, or present alongside, SPECT or PET functional images, providing more precise information on the location of functional deficits and also on structural lesions such as atrophy and vascular disease.

Spatial resolution is generally better for PET than for SPECT, and hypometabolism is a more consistent marker for dementia than is hypoperfusion (Silverman *et al*., 2004).

Combining findings from different modalities, such as atrophy of the medial temporal lobe, as measured with CT, with parietotemporal hypoperfusion as measured with SPECT, can apparently improve diagnostic accuracy for AD, as this combination is much less common in other dementias and rare in normal brains (Jobst *et al*., 1998). Using this combination, Jobst's team obtained a significant number of false-positive AD diagnoses which were found on post-mortem to be Pick's disease/FTD. However, this form of dementia is easy to detect using neuropsychological tests. False-positives were also obtained for individuals with cerebrovascular disease, but these could be excluded through evidence of cerebral ischaemia in the CT images. It is important, though, to be aware of the potential tautological pitfalls of excluding patients with a vascular component to their dementia from a diagnosis of AD (*see* Introduction and Section 4).

10 Analytical methods

There is disagreement between scientists on the best method of analysing imaging data. Simple visual interpretation of images can clearly suffer from inter-rater bias

and is perhaps the least objective. Alternative methods include statistical parametric mapping (SPM) and region-of-interest (ROI) or volume-of-interest (VOI) analysis.

De Leon *et al*. (2001) are concerned that the algorithm used in SPM may produce poor alignment of the entorhinal cortex, a region notably affected in early AD which has considerable anatomical variability between individuals. In contrast, Yang *et al*. (2002) emphasise the greater objectivity of the SPM method, pointing out that drawing ROIs on brain images is time-consuming and can be subject to operator error. Selecting ROIs risks missing important information, relying on presumptions based on previous findings, whilst SPM analyses the whole brain. Slosman *et al*. (2001) found that SPM revealed differences between mildly-demented patients and controls in activation studies, whereas simple visual evaluation did not (*see* Section 6).

Some studies use absolute values of perfusion/metabolism reduction; others normalise values to, for example, overall brain perfusion or perfusion/metabolism in areas deemed to be unaffected in the condition being studied. These techniques require a high degree of diagnostic certainty to avoid producing misleading results.

Toga *et al*. (2004) report on the creation of brain atlases derived from imaging data from large numbers of subjects, including atlases specific to particular diseases and 4-dimensional atlases to show changes over time. Brain atlases can be created by fusing *in vivo* images with biochemical maps produced from brains post-mortem, and deformable maps allow adjustment for variation between individual patients. This approach is perhaps the ultimate attempt to remove subjectivity in the interpretation of brain images, but no approach can be completely free from bias, artefact or error, and the maps will only be as reliable as the algorithms used to create them.

11 How should imaging-based dementia research be validated?

A number of studies compare findings from imaging with those from non-imaging clinical diagnostic protocols and use post-mortem pathology as the 'gold standard'. However, inconsistencies in post-mortem diagnosis (*see* Introduction) pose questions as to the suitability of this accepted standard, and cast doubts on its appropriateness for validating findings from imaging studies.

Hoffman *et al*. (2000) state that "there is excellent agreement between histologic diagnosis of AD and the metabolic finding of temporo-parietal hypometabolism." Where imaging appears to improve diagnostic accuracy, what is actually being measured is its concordance with clinical and post-mortem protocols. Thus, where such concordance is strong, this may simply indicate that the different protocols are detecting the same phenomena, which may or may not closely reflect disease severity or causal relevance.

The findings from imaging studies of dementia should therefore perhaps be validated mainly by comparison with other imaging studies. Firstly, a meta-analysis of well-designed imaging studies which examine the same phenomena, for example hypoperfusion or SPs, could be conducted to ascertain the consistency of such findings. Then a further meta-analysis could be conducted of the findings from disease-progression and treatment-response studies which use the imaging methods found by the meta-analysis to be most consistent. If these findings show greater

consistency than post-mortem findings, perhaps the methods used should replace post-mortem studies as the 'gold standard' for defining dementia.

12 Conclusions

Imaging has great potential to enhance our understanding of the development and progression of disease and response to treatment in dementia research, from angiographic or ultrasound imaging of early vascular risk factors and response to treatment of these, through CT and MRI gross-structural imaging, quantitative microstructural measurement with MTI and diffusion MRI, biochemical analysis with MRS, to metabolic and perfusional imaging with PET and SPECT and finally the use of PET and SPECT radioligands specific to brain molecules characteristically involved in dementia. Imaging is a promising candidate to replace post-mortem examination as a gold standard for dementia diagnosis.

Imaging may help us to complete the picture of dementia causation by drawing together the pathological strands detectable by the various modalities, enabling prevention and treatment at an early stage and, it is hoped, averting a dementia epidemic threatened by demographic changes and the possible exacerbating contribution of environmental pollution.

This work is a reformatted version of an assessable component of the author's Masters degree from the Open University and was produced in 2004. The author is now a freelance researcher and writer and has a website at http://www.vivienpomfrey.co.uk/.

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APPENDIX 1
Glossary

Glossary

acetylcholine	a neurotransmitter which is depleted in AD
acetylcholinesterase	enzyme which breaks down acetylcholine
Aβ	beta-amyloid protein, the main component of SPs
ACh	acetylcholine
AChE	acetylcholinesterase
AD	Alzheimer's disease
allele	version of a gene
APOE-4/apolipoprotein E-4	allele 4 of gene for apolipoprotein E
biomarker	a characteristic which indicates normal or pathogenic processes or responses to intervention
blood-brain barrier	physiological interface between blood and brain tissue
CATCH	critically attained threshold of cerebral hypoperfusion
CT	X-ray computed tomography
entorhinal cortex	part of the anterior parahippocampal gyrus which is involved in memory and where most nerve fibres to the hippocampus originate
FTD	frontotemporal dementia
Hachinski Ischemic Score	a measure of risk factors for vascular dementia, including abrupt dementia onset, history of stroke and history or presence of hypertension
hypometabolism	impaired metabolism
hypoperfusion	impaired blood flow
MCI	mild cognitive impairment
MRI	magnetic resonance imaging
neocortex	highly developed area of cerebral tissue representing most of the cerebral cortex. Includes lateral temporal lobe.
neurofibrillary tangles	lesions formed from abnormally phosphorylated tau protein
NFTs	neurofibrillary tangles
PET	positron emission tomography
pons	region of the brainstem
prodromal	preclinical
radioligand	molecule with radioactive tracer attached, which binds to another specific molecule
senile plaques	lesions consisting mainly of insoluble Aβ
SPECT	single-photon emission computed tomography
SPM	statistical parametric mapping
SPs	senile plaques

Transient ischaemic attack	"mini-stroke" causing sudden, brief decrease in brain function
VaD	vascular dementia