Dementia and ageing

Catriona D Good
Wellcome Department of Cognitive Neurology, Institute of Neurology, University College London, London, UK

Sophisticated imaging techniques are required to characterise the complex dynamic neuro-anatomical changes that occur over time in health and disease. With the advent of potential therapies for the treatment of degenerative dementias, imaging strategies need to enable early diagnosis and facilitate monitoring of disease progression in treatment trials. This chapter highlights some of the innovative structural and functional imaging techniques that have impacted on the clinical management of Alzheimer’s disease.

Alzheimer’s disease is one of the most common terminal illnesses amongst ageing populations, and its prevalence continues to increase along with increased human life expectancy. This disease compromises memory, personality and independence of a substantial sector of the ageing community and impacts severely on families and national health budgets. Early diagnosis is a key problem with this disease. A definitive diagnosis relies on post mortem assessment, and a presumptive clinical diagnosis is usually delayed owing to the incipient presentation of Alzheimer’s disease in later life that may be particularly difficult to distinguish from normal ageing. The two chief pathological hallmarks of Alzheimer’s disease – neurofibrillary tangles and neuritic amyloid plaques – occur frequently in non-demented ageing brains, and their number increases with age. Furthermore, their distribution in elderly brains, matches the hierarchical vulnerability exhibited in Alzheimer’s disease. Such observations have fuelled controversy about whether ageing and Alzheimer’s disease lie at two ends of a continuous spectrum or whether they are truly separate entities.

Despite the prevalence of Alzheimer’s disease, the current treatment options remain limited for sufferers, so there is a great demand to enable timely detection and monitoring of the disease in its earliest phases, particularly in presymptomatic, genetically at-risk individuals, so that new putative treatment strategies to be tested. In vivo brain structural imaging has an established role in the evaluation and monitoring of neuro-anatomical changes in Alzheimer’s disease, acting as a surrogate marker for the underlying histopathological changes and, by inference, disease progression. But identification of individual patients in the...
earliest phases of the disease remains a challenge due to the overlap between the dynamic imaging appearances of normal ageing and early pathology. This is because complex interindividual variations in cerebral anatomy make it difficult to quantify individual patterns of atrophy against a normative population. With the development of a number of sophisticated imaging strategies, a clearer picture of the patterns of atrophy in physiological ageing and dementia is now possible. This chapter will highlight some of the most important imaging techniques that have allowed advances in clinical diagnosis and management of Alzheimer’s disease, but such advances will obviously apply to the broader group of dementias.

**Methodological considerations**

Most imaging studies of the neuro-anatomical changes in ageing and dementia have been cross-sectional in design, i.e. studying a group of subjects of different ages at one time point. Cross-sectional studies are practical to implement and can accommodate wide age spectra and large study groups, but have inherent drawbacks. Firstly, dynamic effects are not actually measured, but are inferred from measured differences between age cohorts. Secondly, systematic differences between age cohorts such as differences in body size (and corresponding brain size) can potentially reflect spuriously as age-related effects. For example, body size has increased over the past century, so younger cohorts will have spuriously larger brains for age than elderly cohorts). In order to model dynamic change properly, a longitudinal study is required, where a group of individuals are followed over time. For practical reasons such studies are generally limited to very short time windows and small study groups.

Structural scanning techniques have advanced considerably over the past decade, and high resolution volumetric magnetic resonance imaging (MRI) sequences are now the required norm for brain morphometry. Measurement techniques vary considerably making comparisons between laboratories difficult. Broadly speaking, there are two main approaches to the measurement of local brain structures: Region of interest (ROI) approaches are based upon the a priori definition of specific brain regions by skilled anatomists. Whole brain approaches involve sophisticated warping algorithms to map brains into a common anatomical framework followed by voxel-wise analysis of anatomical maps. The latter approach allows appraisal of all brain structures and does not require a priori assumptions. ROI-based approaches are the current gold standard, but are extremely laborious and are subject to inter-and intrarater variability. Whole brain approaches, of which there
are many hybrids, have been introduced more recently and offer a number of advantages not least because they are semi or fully automated, and thus reproducible and applicable to large groups for cross-sectional and longitudinal studies. The simplest methods apply rigid body registration within a single subject over time to provide information about global change. Less constrained non-linear registrations can also be used within subject over time to characterise local deformations.

To make meaningful regional comparisons between brains from groups of subjects, confounding factors such as extrinsic differences (e.g. head position and orientation) and intrinsic differences (e.g. brain size and shape and gyral variability) need to be catered for. To achieve this, more sophisticated brain mapping models are required. These involve complex linear or non-linear registrations to map multiple images into a common stereotaxic space enabling region-by-region comparisons in cross-sectional or longitudinal studies followed by robust statistical analyses. At one end of the spectrum, methods that aim to match global brain shapes are relatively quick and easy to perform. At the other end of the spectrum, methods that aim to align gyri and sulci precisely employ very high dimensional warping algorithms that are computer intensive and relatively time consuming. An example of the former method is voxel-based morphometry (VBM). This is a fully automated technique that maps brain images to a template in stereotaxic space followed by voxel-wise statistical analysis of the spatial distributions of grey matter, white matter and CSF. An example of the latter method is precise cortical mapping and generation of probabilistic brain cortical atlases.

Neuro-anatomical changes in ageing

There is convincing evidence from cross-sectional and longitudinal structural MR imaging studies that the brain shrinks with age. There is also general consensus that there is age-related shrinkage of the grey matter compartment with concomitant increase of the cerebrospinal fluid (CSF) space. It is less clear whether the white matter compartment declines globally with age, although recent work suggests that cerebral white matter volume appears to remain relatively stable until age 70 years, after which the decline is rapid. Several researchers have shown an interaction of sex with ageing, with accelerated decline in global grey matter in males compared with females. Reports of regionally specific effects of ageing are generally limited and more conflicting, predominantly because of the wide variety of imaging and measurement techniques used. Two recent morphometry reports of age-related
Neuro-anatomical changes in dementia

There is a large body of structural imaging literature on the anatomical changes observed in Alzheimer’s disease. Most reports have been based on cross-sectional studies using CT or MRI and ROI-based measurements of mesial temporal structures. The majority of these studies report volume loss in the hippocampi and entorhinal cortex in Alzheimer’s disease relative to controls. Such studies have some inherent drawbacks. Firstly, measurements are based upon a limited number of
regions according to *a priori* assumptions of their involvement in Alzheimer’s disease, whilst precluding assessment of other brain structures. This explains the focused attention to the measurement of mesial temporal structures in Alzheimer’s disease with the exclusion of posterior structures such as parietal and posterior cingulate cortex (which are consistently implicated in functional studies of resting glucose metabolism, even in presymptomatic individuals at genetic risk for Alzheimer’s disease). Secondly, because of the wide physiological variation in interindividual neuro-anatomy, subtle pathological changes can be easily missed. Certain brain regions (such as the left peri-Sylvian language cortex) exhibit great spatial variability. In order to reveal early pathological change within such regions as well as distinguishing pathological asymmetries from physiological asymmetries, specialised registration approaches are needed. It is now possible to create accurate three dimensional hippocampal maps using high dimensional non-linear warping methods. These maps encode the physiological variability in normal subjects and can discriminate mild Alzheimer’s disease from age-matched controls\textsuperscript{13, 14}. A few groups have applied whole brain morphometric techniques to characterise the patterns of atrophy in groups of Alzheimer’s disease patients more accurately. Voxel-based morphometry (VBM) confirms mesial temporal atrophy in patients with mild Alzheimer’s disease\textsuperscript{15}, but also shows symmetric posterior cingulate and precuneus atrophy as well as asymmetric (left more than right) atrophy in the angular gyrus, peri-Sylvian and frontal cortices\textsuperscript{16}. A recent VBM study of moderately affected Alzheimer’s disease patients shows predominant posterior cingulate and precuneus atrophy. Within the temporal lobes, the inferior and lateral temporal structures appeared more affected than mesial structures\textsuperscript{17}. Using accurate cortical mapping techniques, Thompson and co-workers have created detailed, population-based maps of cortical grey matter loss in Alzheimer’s disease\textsuperscript{12}. Their method allows the mathematical separation of variations in gyral patterns from early pathological changes, revealing greatest grey matter reductions in the temporoparietal cortices. In addition, they show exaggerated Sylvian fissure asymmetry in Alzheimer’s disease patients compared to controls.

Longitudinal studies of Alzheimer’s disease offer some distinct advantages over cross-sectional studies, not only because dynamic changes can be monitored, but also because subjects can be used as their own controls. In this way, subtle pathological changes within individuals are not masked by wide physiological variability. A number of important studies by Fox and co-workers have shown a clear distinction between the rates of atrophy in patients with Alzheimer’s disease compared to controls\textsuperscript{3, 18–24}. Importantly, they have shown quantifiable rates of atrophy in presymptomatic patients at risk for Alzheimer’s disease. Their earlier studies used sub-voxel linear co-registration and digital subtraction of serial MRI scans. This rigid body co-registration technique allows the
quantification of whole brain atrophy (Plate IX see p.xiii) and they show global volume loss of 5–20 ml/year in patients versus 2 ml/year in controls. However, local pathological deformations in small complex structures such as the hippocampus cannot be accurately mapped with linear registration. Less constrained, non-linear warping techniques are required. More recently, they have used non-linear registration methods based on a compressible viscous fluid model to characterise local pathological shape deformations in Alzheimer’s disease (Plate IXB see p.xiii). Importantly, they have documented the evolution of pathological changes from presymptomatic, at-risk individuals to mild and moderately affected Alzheimer’s disease patients (Plate X see p.xiv). They demonstrate significantly increased rates of precuneus and posterior cingulate atrophy in all stages of Alzheimer’s disease, with increased rates of atrophy with increasing disease severity. The pattern of temporal lobe atrophy varies with the stage of disease. In presymptomatic individuals and mildly affected patients, significant rates of volume loss are seen in the hippocampi. However, in mild and moderately severe Alzheimer’s disease, the distribution of temporal atrophy shifts from mesial structures to inferolateral structures. It thus appears that precuneus and posterior cingulate atrophy may be useful surrogate markers of disease progression throughout the course of Alzheimer’s disease, with hippocampal atrophy being a useful index for the early stages.

Structural imaging can thus characterise the macroscopic neuro-anatomical sequelae of the underlying pathological process in some detail; however, different strategies are needed to gain insight into the pathological changes at a neuronal level. A variety of specialised imaging techniques can now inform about brain functional parameters such as regional cerebral perfusion and diffusion properties, neurochemical receptor distributions, regional glucose metabolism, local tissue biochemistry and the response of brain regions to specific tasks. By using a multimodal imaging approach, functional information can be refined with accurate structural localisation to understand more about the underlying pathophysiology of dementia.

**Functional imaging**

In Alzheimer’s disease, cerebral perfusion studies with single photon emission computed tomography (SPECT) and MRI consistently show reduced cerebral blood flow first in the posterior cingulate and precuneus, even in presymptomatic subjects with the apolipoprotein E (APOE) genotype. As the disease progresses, flow reductions are seen in the temporoparietal association cortices and medial temporal structures. This pattern is mirrored with PET studies of glucose metabolism. 


Magnetisation transfer imaging (MTI) is a specialised MR sequence that informs about the integrity of cell membranes. This technique appears to be more sensitive to distributed tissue damage than routine MRI sequences in a number of neurological diseases such as multiple sclerosis, systemic lupus erythematosus and schizophrenia. In Alzheimer’s disease patients, magnetisation transfer ratio measurements from grey matter are reduced relative to controls, correlating with cognitive impairment. Diffusion tensor imaging informs about diffusion properties of brain tissue and, in particular, the integrity of white matter tracts. Patients with probable Alzheimer’s disease show a significant reduction in the integrity of the association white matter fibre tracts, such as the splenium of the corpus callosum, superior longitudinal fasciculus, and cingulum, but preservation of the pyramidal tracts. This finding is consistent with the clinical presentation of Alzheimer’s disease, in which global cognitive decline is a more prominent feature than motor disturbance. The mean diffusivity of grey matter is also altered in Alzheimer’s disease patients.

Another strategy for investigating the pathophysiology of Alzheimer’s disease is to image the brain after specific cells or chemicals have been labelled with radioligands. For example, amyloid ligands (such as [125I]-TZDM, 2-(4′-dimethylaminophenyl)-6-iodobenzothiazole, a thioflavin derivative or [125I]-IBOX, 3,2-(4′-dimethylaminophenyl)-6-iodobenzoazol) can inform about the overproduction and accumulation of β-amyloid plaques in the brains of Alzheimer’s disease patients. Activated microglia have a key role in the brain’s immune response to neuronal degeneration. Quantitative in vivo measurements of glial activation can be obtained with PET and a specific ligand for the peripheral benzodiazepine binding site ([11C]-(R)-PK11195). Alzheimer’s disease patients show increased regional binding in the entorhinal, temporoparietal, and cingulate cortex, suggesting that microglial activation is an early event in the pathogenesis of the disease.

Magnetic resonance spectroscopy (MRS) allows the assessment of the biochemical composition of brain tissue in vivo and provides information about the neurochemistry of Alzheimer’s disease. Proton MRS consistently shows decreased NAA (marker of neuronal density) and increased myo-inositol (sugar alcohol similar in structure to glucose which may act as a marker of glial cell numbers) in the occipital, temporal, parietal and frontal regions in patients with Alzheimer’s disease, even at the early stages of the disease. The NAA/MI ratio in patients with Alzheimer’s disease has been shown to correlate significantly with Mini Mental State Examination (MMSE) scores. Phosphorus MRS allows the assessment of high-energy chemicals involved in oxidative metabolism in the brain. Initial studies of post mortem Alzheimer’s disease brain tissue showed increases in cell
membrane phosphomonoesters and phosphodiesters (indicators of ATP levels) compared with normals. The few in vivo clinical studies have so far produced mixed reports; however, there are suggestions that in early and possibly presymptomatic Alzheimer’s disease phosphocreatine levels decline and phosphomonoester levels rise, and these phosphorus metabolite levels normalise with disease progression.38

Activation studies in demented patients provide technical challenges, but PET and fMRI have been feasible and indicate differences in neural metabolism and activity between carriers of the APOE ε4 allele and those who are not at risk for Alzheimer’s disease. Persons without dementia carrying the ε4 allele showed greater magnitude and extent of brain activation than non-carriers in regions required for memory, suggesting they performed additional cognitive work to accomplish the same task.39

Conclusions

At present, no imaging modality is considered the standard diagnostic test for Alzheimer’s disease, particularly for the individual case. With the considerable advances in medical imaging techniques and computational power over the last few years, accurate brain mapping is now possible. By using a multimodal imaging approach, functional information can now be mapped with anatomical precision, providing a greater understanding of the dynamic pathological processes in dementia. With the concomitant advances in gene mapping, asymptomatic but genetically at risk individuals can now be identified. This group offers the greatest hope for potential disease modifying agents, and neuroimaging will continue to play a major role as a surrogate marker for disease progression in treatment trials.

Key points for clinical practice

• An understanding of the complex dynamic neuro-anatomical changes in physiological ageing is fundamental to the appreciation of pathological changes

• High-resolution, three dimensional MRI is the required norm for brain morphometry

• Whilst brain imaging may be useful for clinical diagnosis in the dementias, subtle pathological structural changes are easy to miss because of the wide overlap with normality

• Brain imaging plays an important role as a surrogate marker for disease progression in treatment trials
• Sophisticated brain mapping techniques are required to compare groups of diseased brains with controls
• Longitudinal studies are the optimal method to characterise the dynamic neuro-anatomical correlates of disease, but such studies are often limited to short time-windows because of practical issues
• Multimodal structural and functional imaging mapped to the same anatomical framework allows the most comprehensive characterisation of pathological processes in the brain

References

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Plate VII  Regionally specific effects of ageing detected with VBM. Accelerated grey matter loss (over and above global grey matter loss) with age (depicted in green) is seen in the pre- and post-central gyri. Relative preservation of grey matter with age (depicted in red) is seen in the mesial temporal lobes and thalami.

Plate VIII  Regionally specific effects of ageing on the CSF compartment detected with VBM. Accelerated expansion of the CSF space (over and above global CSF expansion) with age is seen in Sylvian and interhemispheric fissures, chiasmatic and supracerebellar cisterns, cisterna magna and third ventricle.
Plate IX  Rigid body registration (A) and fluid registration (B) of serial brain MRIs of a 48-year-old male familial Alzheimer's disease subject after an interval of 2 years. In (A), red represents tissue loss and green tissue gain. In (B), red and yellow represent expansion, green and blue represent contraction. There is evidence of diffuse tissue loss throughout the brain. Reproduced with kind permission from the Dementia Unit, Institute of Neurology, University College London, UK.

Plate X  (see p.*171 opposite) Fluid registration and corresponding statistical parametric maps demonstrating brain tissue loss in patients with Alzheimer's disease compared to controls. (A) Mild Alzheimer's disease; (B) moderate Alzheimer's disease; and (C) presymptomatic genetically at risk individuals. Reproduced with kind permission from the Dementia Unit, Institute of Neurology, University College London, UK.
Plate X (see p.*170 opposite for details)