Rapid review

Imaging cerebral atrophy: normal ageing to Alzheimer’s disease

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Context With ageing populations, the prevalence of dementia, especially Alzheimer’s disease, is set to soar. Alzheimer’s disease is associated with progressive cerebral atrophy, which can be seen on MRI with high resolution. Longitudinal MRI could track disease progression and detect neurodegenerative diseases earlier to allow prompt and specific treatment. Such use of MRI requires accurate understanding of how brain changes in normal ageing differ from those in dementia.

Starting point Recently, Henry Rusinek and colleagues, in a 6-year longitudinal MRI study of initially healthy elderly subjects, showed that an increased rate of atrophy in the medial temporal lobe predicted future cognitive decline with a specificity of 91% and sensitivity of 89% (Radiology 2003; 229: 691–96).

Where next? As understanding of neurodegenerative diseases increases, specific disease-modifying treatments might become available. Serial MRI could help to determine the efficacy of such treatments, which would be expected to slow the rate of atrophy towards that of normal ageing, and might also detect the onset of neurodegeneration. The amount and pattern of excess atrophy might help to predict the underlying pathological process, allowing specific therapies to be started. As the precision of imaging improves, the ability to distinguish healthy ageing from degenerative diseases should improve.

Greater numbers of us are living longer than ever before. This increasing longevity will inevitably lead to a rise in the number of patients with degenerative dementias such as Alzheimer’s disease, the prevalence of which increases exponentially after the age of 65. In addition to devastating cognitive impairment, these disorders are characterised by early1,2 and accelerating cerebral atrophy.3 MRI could therefore be used to distinguish these conditions from normal ageing, and might also detect the onset of neurodegeneration. The amount and pattern of excess atrophy might help to predict the underlying pathological process, allowing specific therapies to be started. As the precision of imaging improves, the ability to distinguish healthy ageing from degenerative dementia should improve.

Cross-sectional imaging in normal ageing

The introduction of computed tomography and then MRI provided the opportunity to assess cerebral volume non-invasively and repeatedly. Early cross-sectional studies implied that brain volume decreased and cerebrospinal fluid volumes increased with advancing age.4,5 In addition to global volume loss, imaging studies revealed regional variations in the effects of ageing on the brain. Early studies used time-consuming manual outlining of specific structures of interest on each scan slice. Although this approach has anatomic specificity, it is limited by the need to make a-priori judgments as to which areas to assess, and the technique is open to operator error and bias.

Several more sophisticated computerised techniques (often grouped as computational neuroanatomy)6 have since been used to provide a less biased assessment of brain atrophy. These techniques, by negating the need for decisions by raters about which regions of interest should be selected and what boundaries should be chosen, allow more accurate assessment of regional brain differences. One such approach is voxel-based morphometry, which involves aligning patients’ volumetric MRI scans into the same spatial framework. These groups of scans can then be statistically compared on a point-by-point (voxel-by-voxel) basis. Results with this technique suggested that normal ageing is associated with a linear decline in grey matter with relative sparing of medial temporal lobe structures.7

A compromise between manual measures and automated techniques involves combining an individual’s scans in the same space and additionally using manual delineation of the major sulci to position cortical surfaces accurately.8,9 This technique has been used to show that different brain regions lose volume at different rates, with non-linearity being the rule (figure 1).10

Postmortem studies—atrophy in normal ageing

Early evidence about the effect of ageing on brain structure came from autopsy studies from the 19th century. This work suggested that brain weight declined gradually but only slowly (about 0.1% a year) from early adulthood until around age 60.1 Such studies were limited by the inclusion of few elderly people, a lack of clinical data, and were also confounded by the profound secular changes that were taking place in the 19th and 20th centuries in the UK: as nutrition improved, populations had been growing taller and heavier. In the 1960s Miller and Corsellis4 showed that the brain was not immune to these changes: brain weights increased by about 1 g or 0.05% a year for those born between the mid-19th and mid-20th centuries. Accounting for these changes led to the conclusion that brain weights were stable between the ages of 20 and 50 but fell progressively thereafter.1 Later studies with thousands of autopsies suggested that brain weight peaks by the mid-to-late teens and declines slowly (0.1–0.2% a year) until age 60–70, after which losses accelerate.1,2 An understanding of cerebral atrophy in the individual in life had to await the advent of non-invasive imaging.

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The broad conclusion from several cross-sectional studies with various techniques is that the ageing brain loses volume in a non-linear and region-dependent manner, with prefrontal cortical volume declining more rapidly than other brain regions.10,17

**Longitudinal imaging in normal ageing**

Cross-sectional studies are limited: there is large inter-individual variation in brain size and structure; the progression and rate of atrophy can only be inferred from a one-off scan; and it must be assumed that progression of brain ageing is similar between individuals.

Longitudinal studies, by using subjects as their own control, allow progression of atrophy to be quantified at the individual level. Within the past few years, powerful computerised methods have used the complexity of the brain to match precisely (register) an individual’s serially acquired three-dimensional MRI scans to one another.13 Cerebral atrophy can thus be accurately assessed and localised.16,18,19

Several longitudinal imaging studies have assessed the changes associated with normal ageing, typically over 1–5 years. These studies, with high-resolution MRI, show that rates of global atrophy in healthy people increase gradually with age from an annual rate of 0·2% a year at age 30–50 to 0·3–0·5% at age 70–80.19–23

Thus, in an unbiased longitudinal MRI study of normal ageing, while white-matter loss was diffuse, grey-matter change was more prominent in frontal and parietal cortices than temporal and occipital lobes.19

Despite sometimes conflicting evidence, some conclusions about changes in brain volume can be drawn. Brain volume loss is an inevitable feature of “normal” ageing, with rates of loss increasing with comorbidity and advancing age. However, very healthy individuals in the 60–80-year age-range have rates of cerebral loss only slightly in excess of those in individuals decades younger.18 Within this gradual global cerebral decline, there are, however, regional differences in the rates at which different brain structures atrophy.

**Atrophy in neurodegenerative disorders**

There are both qualitative and quantitative differences in rates and patterns of atrophy in neurodegeneration compared with normal ageing. In Alzheimer’s disease, annual rates of global brain atrophy are about 2–3%,23 compared with 0·2–0·5% in healthy controls. Silbert et al24 reported annual rates of global brain atrophy to be 2% in Alzheimer’s disease compared with 0·4% in age-matched controls, and found that this excess atrophy predicted the accumulation of Alzheimer’s disease pathology at post-mortem.24 Furthermore rates of brain atrophy have been shown both to increase before the onset of symptoms (figure 2)22–25 and to accelerate as the disease progresses.4

Different diseases with different phenotypic presentations may be associated with specific patterns of regional atrophy. Unbiased image analysis, such as non-linear registration of serial volumetric MRI scans, can highlight in vivo patterns of regional atrophy that may help distinguish these diseases from one another.16,26,27

Pathology within the medial temporal lobe has long been
known to be associated with memory impairment, and pathological studies in Alzheimer’s disease have shown prominent early involvement of medial temporal lobe structures, especially the entorhinal cortex and hippocampus. Volumes of these structures can be measured on MRI, and we now know that excess atrophy not only predicts progression from mild memory impairment to established Alzheimer’s disease, but also from normal ageing to cognitive decline. Longitudinal studies of apparently healthy individuals suggest that hippocampal atrophy rates increase from around 0·1–0·2% a year in those aged 30–50, to 0·8% in those in their mid-70s, rising further to 1·5–2% a year at 80–90.

However, these rates are much lower than the hippocampal atrophy rates of 4–8% a year in very early Alzheimer’s disease. Because hippocampal atrophy accelerates several years before diagnostic criteria for Alzheimer’s disease are fulfilled, without extended follow-up it is not possible to be certain that some individuals in studies of “normal” ageing were not already in the earliest stages of Alzheimer’s disease. In a recent such extended longitudinal imaging study, Henry Rusinek and colleagues followed up healthy subjects, aged over 60, for 6 years. Of the 45 participants completing the study, 13 showed cognitive decline and 32 remained healthy. Using a registration-based computerised method to compare serial MRI scans, these researchers found that atrophy in the medial temporal lobe significantly predicted cognitive decline. Studies such as this and that by Resnick et al are beginning to reveal the importance and time course of increased rates of global and regional atrophy.

Imaging atrophy: the future

If specific therapies for neurodegenerative diseases become available, serial brain imaging could be used to assess the earliest onset of disease. Individuals at risk of neurodegeneration on the basis of age, genetics, or family history, could have a baseline scan which could be compared with a follow-up scan if there was any question of cognitive decline. Excess atrophy above that expected for normal ageing might suggest the development of neurodegeneration, and the regional pattern of the excess atrophy could provide clues to the underlying disease process. Such serial brain-imaging, possibly in combination with patterns of cognitive decline measured with serial neuropsychometry, could permit prompt treatment when maximum effect might be expected and provide a means of assessing an individual’s response to therapy. This approach has ethical, genetic, and financial implications, which limit its routine use until disease-modifying treatment becomes available.

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