The neurology of ageing: what is normal?

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ABSTRACT
Ageing is associated with changes in the nervous system with consequent alterations in some neurological examination findings: understanding what is ‘normal’ at different ages is essential when evaluating patients. In seminal papers published in 1931, Dr MacDonald Critchley summarised his observations and the prevailing evidence on the effects of ageing on, among others, sensation, reflexes, ocular function, olfaction, movement and cognition. In this review, these observations are re-evaluated in light of contemporary evidence. Factors influencing the measurement and interpretation of these clinical findings are then discussed, including reproducibility, the influence of comorbidities, secular trends, how ‘normality’ should best be defined, the problems of extrapolating group data to individuals and the influence of presymptomatic neurodegenerative disease states. The case is made that context is critical, and that combining life course data with detailed clinical and biomarker phenotyping is required to understand the determinants of normal neurological function associated with ageing.

INTRODUCTION
As with all aspects of human physiology, the nervous system alters with ageing. Even in the healthiest elderly, there is more neuronal loss, more vascular pathology and numerous changes at the cellular level compared with healthy younger adults. These changes have consequences, and all neurologists will recognise that when examining a patient, what can reasonably be determined to be ‘within normal limits’ for a healthy 70-year-old differs from that for a healthy 20-year-old. Inherent therefore when evaluating any patient is knowledge of what can reasonably be considered to be within the normal range in any given age group. While there is considerable dogma about what constitutes ‘normal’ neurological ageing — there can be few neurologists who will not recall being told that one can disregard absent ankle jerks or impaired distal vibration sense in somebody in their 70s or 80s — the evidence base for such assertions is rather less clear.

While numerous papers have considered aspects of neurological ageing in isolation, relatively few have attempted an overview. A notable exception are the three seminal papers in the Lancet in 1931 by Macdonald Critchley, based on his Goulstonian Lectures to the Royal College of Physicians that same year. In these papers he covered the pathological, clinical and cognitive changes associated with ageing.

In Part 1 of this paper, Critchley’s original observations are reviewed and critiqued in light of contemporary evidence. In Part 2, some factors relevant to the interpretation of these findings are discussed, with particular reference to what might influence what is, or is not, ‘normal’ ageing.

Part 1: Macdonald Critchley revisited
Dr Macdonald Critchley, CBE (1900–1997) (figure 1), was one of the foremost neurologists of his era, President of the World Federation of Neurology, Vice-President of the Royal College of Physicians and author of over 200 books and papers including seminal works on the parietal lobes, aphasia and headache. His prodigious output was based in large part on his detailed and meticulous observations of patients. What follows are selected quotations from some of his writings on ageing including sensation, reflexes, vision, hearing, taste and smell, gait, hypokinetic and hyperkinetic movements and cognition along with a brief review of contemporary evidence for each domain.

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The outstanding and perhaps the earliest alteration is seen in respect of vibratory sensibility. There is with advancing years, a progressive impairment of this form of sensation, leading eventually to a total loss. This is demonstrable first at the extremities of the limbs. Thus vibratory sense may be impaired at the fingers and toes only; later it is lost at the wrists and ankles, though it is still present proximally.

These observations are largely borne out by contemporary studies. Table 1, adapted from a meta-analysis of 50 studies, shows results from 9996 presumed healthy individuals who underwent clinical assessment of pain perception, light touch, vibration and joint position sense. While people between 18–39 years showed no consistent abnormalities, there was impaired vibration sense at the big toe in approximately a third of those aged 60 and above. By contrast, fewer than 10% had vibration sense loss at the fingers, with a similar number having impairments of joint position sense, light touch and pain perception. Distal vibration sense loss is therefore confirmed as the the most common sensory deficit associated with ageing, but is not universal, being seen in fact in a minority of individuals.

### Reflexes

Thus (with ageing), the tendon jerks tend to be sluggish and are frequently lost. The ankle jerks illustrate this point especially well; with advancing years, this tendon reflex becomes more and more difficult to elicit and finally disappears. So frequently does this occur, in the absence of other neurological manifestations, that one is driven to the conclusion that absence of the ankle jerks in old age is without pathological significance.

Table 2 shows a summary of reflex tendon loss by age, again from the meta-analysis by Vrancken et al. By the age of 80 years, around one third of healthy people have lost their ankle jerks, with only a very small number having lost their knee, triceps and biceps jerks. Again, however, loss of ankle jerks is not universal, being retained in the majority of elderly individuals.

### Vision

Progressive impairment of visual acuity is, of course, characteristic of advancing age, if we except for a moment those cases of myopia which improve as the years pass. Wharthin, indeed, describes the three cardinal signs of senescence as sexual neurasthenia, chronic fatigue, and presbyopia.
Alterations in the pupillary reactions are important. With advancing years there is a progressive sluggishness in the response of the pupils, both to light and on accommodation, and ultimately a condition of pupillary immobility may occur. Still more often one sees an absence or impairment of the conjugate movements of upwards deviations of the eyeballs; lateral and downward movements rarely suffer. Nystagmus does not occur except where focal lesions within the cerebellum happen to be present.

Table 3 provides a summary of the prevalence of ocular pathology in adults aged 40 years and older in the USA.6 Blindness occurs in <1% until the age of 80 years, increasing to ~7% thereafter; a much greater proportion have impaired vision. As Critchley observed, myopia declines with increasing age, but non-neurological causes of visual impairment including cataract (affecting almost two thirds of individuals over 80) and glaucoma (nearly 10%) are clearly age related.

Figure 2A shows data for age-related changes in pupil diameter in both the dark-adapted and light-adapted eye.7 Maximum pupil diameter occurs around the age of 20 years, declining thereafter, with changes more clearly apparent in the dark-adapted eye.

Figure 2B shows that saccadic latency to all degrees of amplitude reaches a nadir between ages 30 and 50, before progressively increasing8; in parallel (figure 2C), the mean peak saccadic velocity is highest in the teenage years, declining progressively thereafter.8 There is relatively greater variability, however, as shown by the increased error bars, in the eighth decade and beyond. While the angle of maximal upgaze is lower in the 70s and 80s than earlier, the angle of maximal downgaze begins to diminish earlier from the 60s.9

Hearing

Deafness due to inter-current disease of the middle ear is, of course, not uncommon but even in the absence of gross aural disease, some degree of impaired auditory acuity is present. The latter is characterised by a loss of hearing or whisper, and for high tones together with shortened bone conduction.

Taste and smell

The faculties of taste and smell are probably less acute, for most very aged individuals are indifferent to the quality of what they eat, provided that the quantity is adequate. A liking for pungent or piquant substances is suggested by the frequent excessive use of condiments.

Figure 4 provides normative data using the University of Pennsylvania Smell Inventory Test (UPSIT). Sense of smell is relatively stable until 60 years, but declines thereafter. By 65–80 years, ~60% of healthy people have a major olfactory deficit (UPSIT score of <19/40). By the age of 80 years or above, this proportion is around 80%.11

Gait

The most characteristic type of gait in old age is seen in the marche à petits pas. In the early stages it is betrayed by a mere loss of elasticity, some shortening of the steps, and a slight widening of the base. Such a gait may almost be regarded as characteristic of healthy old age.

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Figure 2  (A) Pupillary responses by age (from Meisami et al).7 (B) Mean saccadic Latency for different amplitudes of saccade by age (from Irving et al).8 (C) Mean peak saccadic velocity by age (from Irving et al).8 (B) and (C) Republished with permission of Investigative Ophthalmology. Permission conveyed through Copyright Clearance Center, Inc.

Figure 3  Change in hearing threshold (medians, quartiles, deciles) between 18 and 55 for men (upper panel) and women (lower panel). Reproduced with permission from Robinson and Sutton.10

Figure 4  Sense of smell across the life span (reprinted with permission from Doty et al).11 UPSIT, University of Pennsylvania Smell Inventory Test.
...it must be remembered that an abnormal gait in this age is frequently the result of disease outside the nervous system.

Figure 5 illustrates the normal walking speeds at different ages in men and women from the Baltimore Longitudinal Study of Ageing. While there is very wide variability in the normal walking speed between people of the same age and sex, there is a clear and consistent trend for gait speed—relatively stable until aged 60 years—to decline thereafter.

Parkinsonian signs

The forgoing components of extra pyramidal disease namely flexion attitude, rigidity, poverty of movement, and bradykinesia when present in some intensity constitute a picture of Parkinsonism. But it is probably that in some degree these manifestations are present in the majority of all senile patients, if we except those that show the more obvious signs of hyperkinesis or motor agitation.

A degree of Parkinsonism is common in elderly people, with an estimated overall presence of some, often mild, features in 30%–40%. Table 4 shows the prevalence of different items of the United Parkinson’s Disease Rating Scale, where there is a score of 1/4 (mild symptoms), or ≥2. These data, based on 1339 people aged >75 years (mean 77) and excluding people with Parkinson’s disease, show marked differences in the frequency of abnormalities in different domains: 2% had rest tremor, 20% had some axial bradykinesia, and around 30% had some degree of postural instability.

Tremor

Senile tremor constitutes the commonest incidence of hyperkinesis, although by no means often

<table>
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<th>UPDRS Item</th>
<th>Score=1 (%)</th>
<th>Score≥2 (%)</th>
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</thead>
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<tr>
<td>Speech</td>
<td>6</td>
<td>1</td>
</tr>
<tr>
<td>Facial expression</td>
<td>10</td>
<td>1</td>
</tr>
<tr>
<td>Rest tremor</td>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td>Rigidity neck</td>
<td>4</td>
<td>2</td>
</tr>
<tr>
<td>Rigidity arms</td>
<td>7</td>
<td>1</td>
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<tr>
<td>Rigidity legs</td>
<td>5</td>
<td>2</td>
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<tr>
<td>Posture</td>
<td>20</td>
<td>7</td>
</tr>
<tr>
<td>Axial bradykinesia</td>
<td>17</td>
<td>3</td>
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</tbody>
</table>

Table 4 Prevalence of Parkinsonian signs in individuals aged 75 years and older

UPDRS, United Parkinson’s Disease Rating Scale. Adapted from Louis et al.13

Figure 5 Usual walking speed in 711 men and 766 women from the Baltimore Longitudinal Study of Aging (with permission from Ferrucci et al).12

Figure 6 Tremor in older people (reproduced with permission from Deuschl et al).14
encountered. Its usual rate is 100 beats per minute, the common sites for its occurrence at the head and lower jaw, the hands and forearms.

Tremor in older people has been the subject of considerable recent interest. Figure 6 (graph reproduced from Deuschl et al.) shows tremor is minimal up to 40 years increasing thereafter, to a prevalence of ~10% by 90+. The authors suggest that the incidence of hereditary and sporadic essential tremor peaks by 50 years and accounts overall for only 2%–3% of tremor in older people. The implication therefore is that another form of tremor that they term ‘aging-related tremor’ emerges in midlife, increasing to a prevalence of ~8% by 90 years. The exact nature of this tremor remains unclear, but it is seems not to be a benign phenomenon, being associated both with increasing cognitive impairment and mortality.

Chorea

Without doubt the term senile chorea has been applied too readily to cases with characteristic movements associated with old age. In order to make this diagnosis, one must be scrupulous to exclude: 1) cases associated with a family history of chorea or insanity; 2) cases in which the chorea has commenced in middle age and persisted into advanced age; 3) cases of apoplectic onset usually unilateral in their manifestations. When these criteria rigidly apply, senile chorea is found to be a rarity.

The decades since Critchley’s papers have led to huge advances in our understanding of chorea. Table 5 (adapted from Kimber and Thompson) shows the much wider range of causes than were recognised in 1931. It is likely that this means that even fewer cases of chorea will remain undiagnosed and reinforces Critchley’s observation that idiopathic ‘senile chorea’ is very rare, if indeed it exists at all.

Cognition

Psychic senescence . . . (is) the pattern of psychological processes which is to be expected in healthy old age. The outstanding features include the diminished acuity of memory or better a loss of adherence to recent events; impaired faculty of rapid evocation of events; loss of fluidity; a weakness of creative imagination.

What is, and what is not, normal cognitive performance with age is the subject of intense investigation. Figure 7, reproduced from a review by Hedden and Gabrieli, confirms that the ageing process affects different cognitive domains variably. Thus, verbal ability is relatively preserved (the basis of the National Adult Reading Test as an estimation of premorbid intelligence), as is numeracy, while, as Critchley

Table 5 Causes of late-onset chorea

<table>
<thead>
<tr>
<th>Causes of Late-Onset Chorea</th>
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<tr>
<td>Cerebrovascular</td>
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<td>Medications</td>
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<td>Toxins</td>
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<td>Metabolic</td>
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<td>Infectious</td>
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<td>Other</td>
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Part 2: Interpreting age-related changes

It is striking that careful clinical observations reported mainly by a single neurologist some 85 years ago are largely borne out by contemporary clinical research. While Critchley wrote at length about factors that need to be accounted for when interpreting such observations, research in the intervening decades has observed, there is a progressive, slow decline in speed, reasoning, spatial skills and episodic memory from aged 25 years onwards.

Figure 7 Cognitive changes in different domains across the life course. Cross-sectional data from the Seattle Longitudinal Study (reprinted with permission from Hedden and Gabrieli).
provided further insights, some of which are reviewed below.

Reproducibility
Critical to comparing clinical signs between individuals is an understanding of how reproducibly they can be elicited. When comparing findings across the life course, it is also vital to know if there is a systematic reason why the method of assessment might be affected by age per se. In some instances, e.g. with neuropsychological cognitive testing, standard methodologies allow for (although not always perfect) between-subject and within-subject comparisons to be made. In routine clinical practice and for most of the domains discussed previously, this is not the case and there is often huge variability in how various tests are elicited and interpreted. For example, O’Keefe et al investigated 12 people of average age 82 years, half of whom were reported to have absent ankle jerks. They compared the ‘plantar strike’ and ‘tendon strike’ methods for obtaining the ankle jerks (Figure 8) between and within physicians of different levels of experience. The median kappa values for intra-observer and inter-observer agreement were higher for the plantar strike (0.47 and 0.57) compared with the tendon strike method (0.2 and 0.21, respectively), suggesting that the plantar strike is more reliable—at least in this age group, where for instance musculoskeletal disease may make positioning the foot for the tendon strike more difficult. However, neither method is very reproducible, with the kappa values consistent with weak reproducibility for the plantar strike and minimal reproducibility for the tendon strike method.

Comorbidities
What constitutes a ‘neurological’ sign is not always clear, as Critchley wrote; and in many cases, non-neurological factors may influence signs that fall within the broad remit of the neurologist. Musculoskeletal disease is self-evidently likely to impair gait; sense of smell is influenced by sinus disease and other local pathologies; visual impairment by the presence of glaucoma and cataracts; and cognition by mood, pain and a wide range of prescribed and illicit drugs. Some degree of brain white matter change is almost inevitable with advancing age—and anyone attending a neuroradiology case conference will be used to allowance being given for ‘one or two white dots per decade’. While excess white matter disease more often than not indicates vascular pathology and has clinical consequences, its pathological underpinnings vary. As imaging techniques become ever more sensitive, more changes are detected; accordingly, how much white matter change is really ‘allowable’ for ageing is at least in part arbitrary.

Importantly, comorbidities in elderly people are the rule rather than the exception. Thus in the MRC National Survey of Health and Development, a representative UK sample recruited at birth in 1946 and followed prospectively, by the ages of 60–64 years people had on average two medical conditions: 54% had hypertension, 31% obesity, 26% hypercholesterolaemia and 25% either diabetes mellitus or impaired glucose tolerance. By contrast only 15% were free from any comorbidity. In an unselected sample of individuals over the age of 85, the prevalence of hypertension, osteoarthritis, atherosclerosis and cataract were each around 50%, and ~90% had three or more conditions.

Secular trends
What we consider to be ‘normal’ is not fixed but alters over time. If one takes life expectancy, when Critchley wrote his papers the chance of living to the age of 100 from birth was 2.5% for men and 5.1% for women; by 2011 these figures were 26.0% and 33.7%, respectively. It is likely therefore that 80-year-olds described by Critchley might fall into a ‘super ageing’ category that we might now reserve for centenarians. Lifestyle changes mean that individuals will have different exposures depending on their year (and country) of birth. Thus, the incidence of

Figure 8 The tendon strike (A), and plantar strike (B) methods for eliciting the ankle jerks (reprinted with permission from O’Keefe et al).
smoking has radically declined in recent years in high-income countries, and there have been major changes in screening for, and treatment of, hypertension, hypercholesterolaemia and diabetes mellitus. Conversely, individuals now in their 70s were brought up in an age of rationing, compared now to very readily available high-calorie foods with consequent rises in obesity.

Defining ‘normality’
How we define normality in the context of ageing is a debatable question. One approach is to assess those who are the best performers in their age group. This approach confirms that there are limits to what can be expected with age. Figure 9 illustrates the world record time for running 5 km by age and by sex. While the best performing 80-year olds still run this distance faster than the average runner of any age, peak performance is still seen between the ages of 20 and 40 years, deteriorating slowly to the age of 80 years and rapidly thereafter.

Age-related normative data are commonly used in neuropsychological testing, as illustrated by the Recognition Memory Test for Faces (Figure 10). A score of 36/50 on this test is ‘normal’ above 50 years, but is abnormal (<5%) below the age of 40. Such normative scores can be based on relatively small numbers (eg, 15–40 people in each of the three groups shown); they are grouped into relatively crude age-related groups with everyone over the age of 55 years considered together; and importantly assumptions must be made that the individuals these norms are derived from are ‘normal’.

In other domains, it is not always clear whether or to what extent to take age into account when defining normality. For instance, in the context of brain volume there is debate in the literature as to whether hippocampal volume loss is part of normal ageing, occurs only in the context of one or more pathological processes or whether different hippocampal regions are vulnerable to ageing and pathology; this has fundamental implications for whether it is appropriate to index brain volume against younger individuals—in which case many more elderly people will be determined as pathological—or to allow for ageing.

Moving from groups to individuals
While group level data help in understanding the processes underpinning ageing, it is not always easy to extrapolate from these to individuals. With ageing, it is important wherever possible to compare an individual’s performance against their premorbid abilities: any clinician will be much more concerned about an elderly person presenting with gait difficulties if that person was a regular marathon runner until recently than if they had long-standing walking difficulties. While in the case of cognition it is possible at least to some extent to extrapolate premorbid performance by estimating years of education or occupation, this can be much more difficult in other domains. Even within the range of ‘normality’ it is very likely that individuals have different trajectories of decline, likely related to life course exposures, to genetics and to other comorbidities. In the case of child development, using growth charts allows people to be tracked along their own personal trajectories; it would be ideal to have longitudinal data on which to assess individuals’ change over time, but such measurements are rarely made outside of research studies.
Furthermore, in many clinical settings it is often necessary to define what are inevitably arbitrary cut-offs for normality or abnormality. Thus, to define somebody as having amnestic mild cognitive impairment—an intermediate state between normal ageing and dementia—requires both decline from premorbid functioning and ‘objective memory impairment for age’. If the latter is operationalised, as is often done, to define performance below a pre-specified score (e.g., <1.5 SD below age norms), this will inevitably be a lower bar for individuals with premorbid weak memories than those with superior abilities. An example of this, reported by Archer et al, was of a very high functioning man, a keen chess player, who presented to clinic complaining that he could previously think seven moves ahead at chess but could now only manage three or four. While initially performing within normal limits on cognitive testing, he declined sufficiently to fulfil criteria for mild cognitive impairment 2 years later. He died a year later of other causes (but still with a diagnosis of mild cognitive impairment) and at postmortem was determined to have already advanced Alzheimer’s disease retrospective review of his scans revealed that he had progressive and excess hippocampal atrophy predating the emergence of objective impairments (Figure 11).

‘Normal’ ageing contains individuals with presymptomatic neurodegeneration

As the previous case demonstrates, and is now clear from numerous postmortem and biomarker studies, the pathological change, and in some cases allied symptoms, associated with the core neurodegenerative diseases are present and begin to accumulate many years prior to the onset of symptoms. Thus, subtle but detectable cognitive decline occurs before the onset of Alzheimer’s disease; anosmia precedes the development of both Alzheimer disease and Parkinson’s disease; REM sleep behaviour disturbance and constipation occur before the onset of Parkinson’s disease; and the emergence of subtle Parkinsonian signs may not only predict Parkinson’s disease, but also subsequent clinically significant cognitive decline.

The emergence of biomarkers has allowed the detection of aspects of pathology in vivo that in Critchley’s day could only be determined at post-mortem. In the case of cognition, positron emission tomography (and cerebrospinal fluid) have shown that over one in three people aged over 70 years have significant beta (β)-amyloid brain pathology; MRI confirms that amyloid positive elderly individuals have excess atrophy; and it is currently hypothesised that a high proportion, if not all, these individuals may develop Alzheimer’s disease should they live long enough. This concept has led to changes in diagnostic criteria that, at least on a research basis, now include a presymptomatic phase of Alzheimer’s disease. Similar findings in people destined to develop neurodegenerative diseases on a genetic basis concur with these conclusions.

Studies incorporating multiple imaging biomarkers are revealing that there may also be a group of healthy elderly people with biomarker profiles suggesting non β-amyloid brain pathologies—although whether these individuals all have presymptomatic neurodegenerative diseases, and if so which one(s), is the subject of considerable debate.

Figure 11  MRI scans show coronal sections of the brain and right hippocampus at baseline, 9 months, 2 years (when he was diagnosed with mild cognitive impairment) and 3 years from presentation. Excess hippocampal atrophy is seen prior to the onset of objective cognitive impairment (from Archer)
These uncertainties aside, the inevitable conclusion from such studies is that a significant proportion of apparently healthy people who may be recruited as, or considered to be, ‘normal’, will be in the early stages of developing disease.

Clinical relevance?
Although it is important for a neurologist to determine if the clinical signs they elicit are or are not within the normal limits for age, it is also important that the clinical context is taken into account. This relates to many aspects including whether the patient is symptomatic or not; whether signs occur in isolation or combination; where there are biomarkers available, whether they are positive or not; and what are the consequences of finding pathology. In a recent population study investigating polyneuropathy, the combinations of signs—that is, not just the prevalence of isolated vibration sense loss or decreased tendon reflexes—and (in all but a few case) nerve conduction studies abnormalities were required to define the presence of a definite polyneuropathy. Using these criteria, 13.2% of those over the age of 80 years had a polyneuropathy. While this represents a considerably smaller proportion of those with either absent ankle jerks or sensory disturbance alone (tables 1 and 2), importantly, 50% of this group were previously undiagnosed, and a potentially treatable cause was determined in a proportion.

CONCLUSIONS
As Critchley elegantly delineated some 85 years ago, ageing is associated with changes within the nervous system, and some aspects of the nervous system are more vulnerable than others. Ageing is associated with accumulation of many pathologies, notably cerebrovascular disease, but also with the emergence of neurodegeneration, and often the signs typically associated with ‘normal’ ageing and pathology can overlap. In general, ‘within-individual’ changes are likely to be more powerful than comparisons between individuals; and longitudinal research studies incorporating life course data with detailed clinical phenotyping and biomarkers provide a powerful paradigm for understanding the complexity of the ageing process. As and when disease-modifying therapies for neurodegenerative diseases become available, using biomarkers to determine the presence of specific pathologies will become increasingly important, both to ensure that treatments are given to symptomatic people with the pathology in question and also to determine which elderly people with presymptomatic disease may benefit most from treatment.

Key points
- Ageing is associated with changes in the nervous system: understanding what is ‘normal’ at different ages is important when evaluating patients.
- As Macdonald Critchley recognised over 85 years ago, some aspects of the neurological examination are more vulnerable to ageing than others.
- Interpretation of neurological signs in the elderly depends on context: factors that must be taken into account include the influence of comorbidities, the problems of extrapolating group data to individuals and the influence of presymptomatic or asymptomatic disease.
- Longitudinal studies incorporating detailed phenotyping, biomarkers and life course data are starting to reveal the complexities of the ageing process.

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