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In this article...

- Age-related changes to the central and peripheral nervous systems
- How age affects the functioning of the brain
- Common problems caused by nervous system changes in older people

Anatomy and physiology of ageing 5: the nervous system

Key points

1 As the brain ages, neurons reduce in number, neurotransmitters are depleted, blood flow reduces and the blood-brain barrier weakens

2 Age-related problems of the nervous system include gait issues, postural hypotension, reduced bladder control and loss of short-term memory

3 It is often difficult to distinguish normal age-related changes to the brain from pathological changes associated with dementia

4 In normal ageing, the brain reserve declines but cognition is maintained thanks to its in-built redundancy and neural compensation

5 Keeping mentally active throughout life can reduce the effects of age on the nervous system

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Abstract The nervous system controls the activities of all body organs and tissues, receiving input from sensory organs and responding via effector organs. With around 100 billion interconnected neurons, the brain is an extremely complex, and still poorly understood, organ. However we do understand, to some degree, how age affects it, as well as the nervous system as a whole. This fifth article in our series on the anatomy and physiology of ageing describes the age-related changes occurring in the brain, spinal cord and peripheral nerves. These changes lead to a gradual decline in cognitive function and a range of other issues, such as reduced bladder control or postural hypotension, but in health the brain normally continues to function adequately throughout life.

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The nervous system, along with the endocrine system, controls and integrates the activities of all the body's organs and tissues. It receives and processes sensory input from organs such as the eyes, ears and skin, and responds through a variety of effector organs.

The main organ of the nervous system is the brain, which, with around 100 billion interconnected neurons, is extremely complex; despite decades of research, its function remains poorly understood. Ageing leads to a progressive loss of neurons and depletion of neurotransmitters (Mather, 2016), these changes are usually associated with a gradual decline in cognitive function and influenced by environmental, genetic and lifestyle factors (Nyberg et al, 2012).

Age-related changes to the central nervous system Neural tissue

The ageing brain gradually loses neurons and supporting neuroglial cells (Fig 1).

Between the ages of 20 and 60, the brain loses around 0.1% of neurons per year, after which the process speeds up (Esiri, 2007). By the age of 90, brain mass will have decreased by around 11% compared with individuals in their 50s, which equates to a loss of about 150g of neural tissue (Wyss-Coray, 2016). The remaining tissues harbour an increased concentration of potentially harmful materials such as iron, aluminium and free radicals.

Aged neural tissues also show increasing pigmentation, largely due to the deposition of two pigments: one brown, lipofuscin (Ottis et al, 2012), and one black, neuromelanin (Clewett et al, 2016). Lipofuscin is linked to amyloid protein deposition and the formation of neurofibrillary tangles. These abnormal areas of neural tissue are often present at low densities in aged brain tissue, even in the absence of disease (Wyss-Coray, 2016); however, where Alzheimer's disease is present, these are at high densities.

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Cerebral cortex

The loss of neurons is most apparent in the cerebral cortex. The grooves (sulci) that mark the surface convolutions (gyri) of the cerebral cortex are visibly deeper in brains of older people (Fig 1). It was originally thought that the frontal lobes were particularly vulnerable to neural loss, but similar losses have been observed in other cortical regions such as the parietal lobes (Fjell et al, 2014).

Structural changes in the frontal and parietal lobes are related to poor memory. Many people in their 80s have modest levels of amyloid protein deposition and retain their memory, while individuals with higher levels typically have a poorer working (short-term) memory (Nyberg et al, 2012). However, the role of amyloid deposition in impairing memory has recently been questioned and other factors, such as accumulation of tau proteins, may play a more important role (Brier et al, 2016).

Hippocampus

The hippocampus has a key role in memory and the acquisition of new skills. With age, it loses a significant amount of neural tissue (Burke and Barnes, 2006), which may explain why activities such as learning a new language become more difficult with advancing age. Recent research indicated that navigating a computer-generated virtual environment improved spatial awareness and reduced the shrinkage of the hippocampus, both in younger and older people (Lövdén et al, 2012). Virtual reality computer programs could therefore potentially be used to reduce shrinkage in this vital brain area.

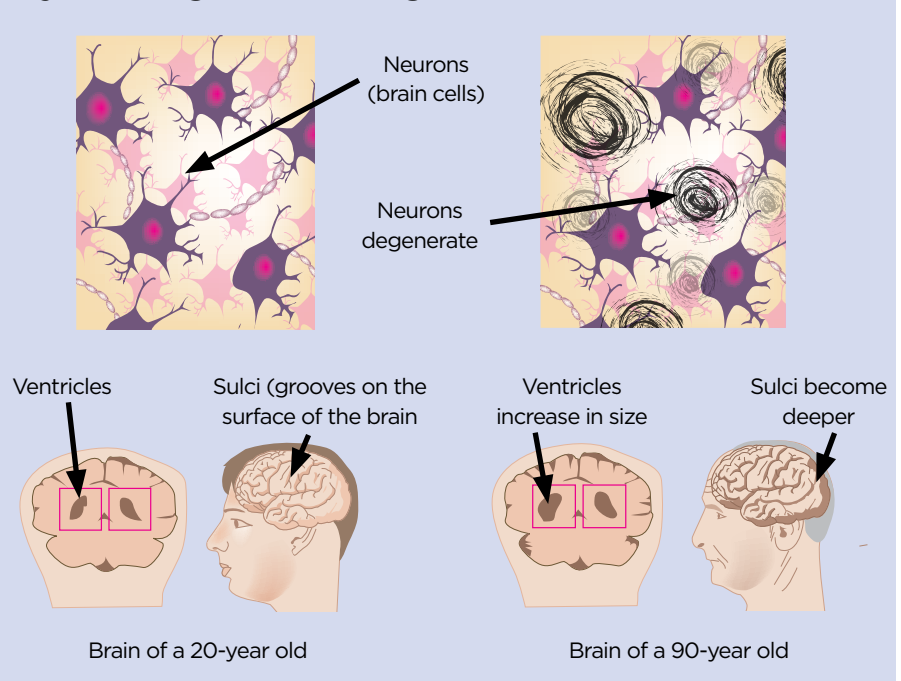
Somatic motor cortex

Around 35% of people over the age of 70 years have gait problems; while there are many contributing factors, including age-related changes to muscles and joints, the nervous system is also implicated. The somatic motor cortex – located in the frontal lobes of the brain – controls the movement of muscles involved in walking. From middle age onwards the neurons in this region show signs of atrophy (Manini et al, 2013), which can contribute to gait problems, potentially reducing mobility in older people (Rosso et al, 2013).

Brain ventricles

Ageing is associated with a gradual increase in the size of the ventricles (fluid-filled chambers) in the brain (Fig 1). This is likely to result from a progressive loss of the cells that line the ventricles. Enlarged

Fig 1. Three age-related changes in the brain



ventricles fill with more cerebrospinal fluid, and are readily observable using techniques such as magnetic resonance imaging. On average, the volume of the ventricular system increases by around 2.9% per year; this expansion appears to accelerate with age, with people over the age of 70 having a median rate of expansion of 4.25% per year (Raz and Rodrigue, 2006). Although ventricular expansion is seen in most older people, the cognitive impact of this remains unclear.

Brainstem and autonomic function

The medulla oblongata and other areas of the brainstem lose fewer neurons than other regions of the brain. The brainstem is probably the best preserved region of the brain, which probably reflects its essential role in supporting life: it controls breathing, peristalsis, heart rate and blood pressure. However, the autonomic function of the brain does decline with age and this can compromise the body's ability to respond quickly to internal and external environmental changes (Hotta and Uchida, 2010). Both branches of the autonomic nervous system (ANS) – the parasympathetic and sympathetic branches – are compromised with age (Parashar et al, 2016).

These changes can negatively affect older people. For example, the blunting of baroreceptor responses increases the risk of postural hypotension, so standing up suddenly can lead to falls and injury. Another negative consequence is the

gradual loss of bladder control. To control micturition, the body relies on the interplay of sensory stretch receptors and the ANS (which together monitor bladder filling) and the conscious areas of the cerebral cortex (which signals when the bladder is full). To initiate micturition, the body needs motor control of the urinary sphincter. All these elements function less well with age, and these age-related changes combine with those in other body systems – such as prostate enlargement in men and weakened pelvic floor muscles in women – to reduce bladder sensitivity and control (Hotta and Uchida, 2010), which can lead to continence problems.

Cerebral blood flow and the blood-brain barrier

Cerebral blood flow decreases by around 0.38% per year, equating to a 27% decline over 70 years of life (Chen et al, 2011). This is a direct consequence of the age-related changes in the cardiovascular system, and may be exacerbated in patients with atherosclerotic occlusion of the carotid arteries.

The blood-brain barrier (BBB) is formed primarily of tight junctions between adjacent endothelial cells within the blood vessels in the brain. Additionally, specialised neuroglial cells called astrocytes wrap around the cerebral vessels, forming a further physical barrier between the blood and neural tissues. The BBB is essential to prevent most pathogens and many toxic materials crossing into the neural networks and

pathways of the brain, but its integrity appears to diminish with age. A recent study indicates that, during normal ageing, the BBB is first weakened in the hippocampus, thereby allowing harmful substances and pro-inflammatory mediators to cross into this vital region of learning and memory. This breaching of the BBB may contribute to hippocampal shrinkage, and therefore to cognitive decline (Montagne et al, 2015).

Neurotransmitters

Ageing is associated with a declining production of many neurotransmitters, including noradrenaline, glutamate, dopamine and serotonin. The decline in dopamine appears to be particularly important: dopamine modulates motor function and the acquisition of new skills, while also acting as one of the brain's reward chemicals (Mather, 2016). The number of dopamine-producing neurons decreases as part of the normal ageing process, and this can adversely affect the ability to learn from past experiences. Recent studies show that many older people who boosted their levels of dopamine by taking L-DOPA (a drug normally used to treat Parkinson's disease) were learning as quickly as young adults again (Chowdhury et al, 2013).

Spinal cord

Few studies have examined age-related changes to the spinal cord. A recent animal-model study shows an increase of cholesterol content in the ageing spinal cord, and the authors suggest this may potentially impair cord function (Parkinson et al, 2016).

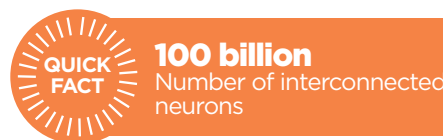
Age-related changes to neurons and neuroglial cells appear to have little effect on spinal cord function. However, age-related changes to the vertebrae and intervertebral discs may increase pressure on the spinal cord and its branching nerve roots. This can slow down the conduction of nerve impulses along motor neurons, contributing to reduced muscular strength (Manini et al, 2013). Reduced sensory and motor conduction will increase the risk of injury due to poor coordination, poor balance and poor fine motor control.

Age-related changes to the peripheral nervous system

With age, some peripheral neurons show a 'dying back' (shrinkage of axonal length), loss of mitochondria and a degeneration of their insulatory myelin sheaths. Some of this damage may be caused by a rise in the concentrations of pro-inflammatory mediators

in the body. The ageing body becomes less effective in clearing toxic metabolites and, as peripheral nerves are not afforded the protection of the BBB, this may contribute to peripheral nerve damage (Manini et al, 2013).

The loss of myelin slows the conduction of peripheral nerve impulses by around 5-10% (Joynt, 2000). In health, this reduction in conductivity causes few problems, but in older people with diabetes it may contribute to, and exacerbate, diabetic neuropathy. Damaged peripheral nerves are not repaired as efficiently in older people as in their younger counterparts, and some of these nerves are never repaired. This can contribute to reduced sensation and motor control.



How does age affect brain function?

In the absence of disease, intellectual ability can be retained throughout life. However, the gradual loss of neurons, depletion of neurotransmitters and slowing of nerve conduction may act together to slow down the processing of information. As a result, older people may take longer to complete certain tasks, and commonly experience the functional brain changes described below.

Short-term and episodic memory

The loss of short-term and episodic memory is probably the earliest indication of age-related changes in the brain. Unlike what happens in dementia, the loss of short-term memory in the absence of disease does not affect life skills (such as the ability to cook), but manifests as inconveniences (such as forgetting an item from the shopping list). Episodic memory (that is, remembering autobiographical events and their timings and sequence) also gradually declines in many older people (Fjell et al, 2014).

Verbal and word skills

Verbal communication skills generally remain strong throughout life (Park and Reuter-Lorenz, 2009), but people over the age of 70 years may have increasing problems using or recalling words. The ability to quickly name a common object usually remains stable up to the age of 70, but then declines with advancing years (Harada et al, 2013).

Reaction time

The progressive loss of neurons, reduction in impulse velocity and minor changes in the spinal cord lead to a slowing down of reaction times (Spirduso, 1995). This can create problems, particularly when a fast reaction is essential (for example, to step out of the way of oncoming traffic).

Depression

In England, around 22% of men and 28% of women over the age of 65 are affected by depression; in care homes, the figures are even greater, with around 40% of residents affected (Age UK, 2017).

It is almost impossible to determine whether depression in older people occurs as a normal consequence of ageing or as a result of chemical imbalances seen in types of depression that also affect younger people. Concentrations of neurotransmitters involved in lifting mood (particularly serotonin) diminish with age and this can contribute to symptoms of depression (Fidalgo et al, 2013). The Royal College of Psychiatrists estimates that >85% of depressed older people receive no help from the NHS (Age UK, 2017). Depression can often produce symptoms that mimic dementia (pseudo-dementia) and this often causes great anxiety.

Emotional reactions

On the whole, older people are less prone to emotional outbursts than younger people. This may be related to the relative structural stability of some of the brain regions linked to emotions. Most studies of the amygdalae – which are heavily involved in impulsive behaviours and emotional reactions – reveal little evidence of atrophy or shrinkage at a much slower rate than in other brain regions. Additionally, the amygdalae also appear to retain most of their functional activity in older age (Mather, 2016).

Neuroactive drugs

Because the overall neural mass reduces with age, neuroactive drugs such as antidepressants and neuroleptics can be more potent in older people. Doses normally prescribed to adults may induce confusion or delirium, and may therefore need to be adjusted.

Normal versus pathological changes to the brain

How normal age-related changes to the brain can be distinguished from pathological changes associated with dementia (for example, Alzheimer's disease) is hotly

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debated. The problem is that three of the main clinical features of Alzheimer's disease – loss of episodic memory, loss of brain tissue and amyloid deposition – are also seen in apparently healthy older people with little or no evidence of dementia. However, it is generally recognised that the main risk factor for developing dementia is advancing age (Fjell et al, 2014).

Brain reserve and cognitive reserve

Unlike cells in many other parts of the human body, most neurons do not undergo cell division so, when they die as a result of age or injury, they are generally not replaced. Fortunately, the brain contains over 100 billion interconnected neurons (the connectome) and many researchers agree that it has an in-built redundancy, known as the brain reserve. This is defined as the physical resources of the brain in terms of brain mass and number of neurons; a larger brain reserve is often associated with better outcomes after brain injury and in various neurological diseases (Tucker and Stern, 2011).

The brain reserve is not necessarily a good predictor of cognitive function (many people with normal cognition have significant brain atrophy), so the concept of cognitive reserve has emerged. People with a high cognitive reserve are able to use their brain reserve more efficiently to perform tasks, and this seems to happen through increased efficiency of functional connections between neurons (Marques et al, 2016).

Good predictors of a high cognitive reserve include high education level, high IQ, highly complex occupation and large amount of social interaction. Recent research indicates that cognitive ability

may also be maintained by neural compensation, a process in which new circuits of neurons are recruited to perform tasks that were once carried out by aged or damaged neural pathways (Steffener and Stern, 2012). In normal ageing, the brain reserve does decline but cognition is maintained thanks to the brain's in-built redundancy.

“It is a misconception that ageing naturally leads to confusion, dementia and delirium”

Encouraging healthy mental ageing

Keeping mentally active throughout life can reduce the effects of age on the nervous system (Mahncke et al, 2006), and engaging in social, sporting and mentally challenging activities can slow down the decline in cognitive performance (Nyberg et al, 2012). It appears the more intellectually demanding and complex an individual's occupation, the better their cognitive performance in later years; however, in retirement, when the mental challenges of work are removed, this effect appears to decline.

Older people should be encouraged to engage in stimulating activities such as socialising, reading and games, which are thought to improve cognitive function and memory, as well as reduce the risk of depression. It is a common misconception that ageing naturally leads to conditions such as confusion, dementia and delirium. The human brain's in-built redundancy allows it to adequately cope with the physical changes associated with ageing. Indeed, in the absence of disease, adequate mental function can be retained throughout life. **NT**

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