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Review

# Long live the axon. Parallels between ageing and pathology from a presynaptic point of view

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ABSTRACT

All animals have to find the right balance between investing resources into their reproductive cycle and protecting their tissues from age-related damage. In higher order organisms the brain is particularly vulnerable to ageing, as the great majority of post-mitotic neurons are there to stay for an entire life. While ageing is unavoidable, it may progress at different rates in different individuals of the same species depending on a variety of genetic and environmental factors. Inevitably though, ageing results in a cognitive and sensory-motor decline caused by changes in neuronal structure and function. Besides normal ageing, age-related pathological conditions can develop in a sizeable proportion of the population. While this wide array of diseases are considerably different compared to physiological ageing, the two processes share many similarities and are likely to interact. At the subcellular level, two key structures are involved in brain ageing: axons and their synapses. Here I highlight how the ageing process affects these structures in normal and neurodegenerative states in different brain areas.



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## 1. Introduction

Thanks to a modern lifestyle and accessible health care, people in the western world are living longer than ever before. The enhanced life expectancy of individuals has significantly increased the average age of the population, current projections show that by 2050 the proportion of people over 60 will represent more than a third of the population in Europe, Japan and North America (Lutz et al., 2008). The shift towards an older population carries social and economic issues, with particular pressure on welfare and national health care systems. However, the rate of ageing of individuals is probably slower than what it was in the past, as, on average, people have more years ahead of them to live (Gray and Barnes, 2015). Thus, the population is ageing simply based on numbers of years lived, though it is also true that the biological age of people is lower due to the improved living standards. Therefore, the productive life of people is extended together with their overall health span. Nevertheless, a society of people with longer life spans poses new scientific challenges as the risk of chronic diseases, such as cancer and neurodegenerative disorders, dramatically increases with age. Besides representing a great economic cost to society as a whole, age-related neurodegenerative pathologies have a huge impact on the patients and their families, with dramatic effects on cognition and motility. Because ageing has often been recognised as the key risk factor underlying a plethora of conditions, great efforts in basic and clinical research have been channelled in understanding the ageing process within the field of neuroscience. Uncovering the genetic, cellular, physiological and environmental causes of ageing may lead to effective strategies to tackle a wide array of age-related diseases and perhaps slow down the normal cognitive decline that healthy subjects experience in old age. In this

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review I focus on how the ageing process impacts the anatomy and function of the nervous tissue, specifically the axons of neurons and their synaptic contacts. Parallels with some common neurodegenerative disease and their impact on axons will be briefly discussed and differences and similarities to the ageing process will be highlighted.

Axons are a remarkable specialized subcellular structure. During development, the axon of a typical neuron originates from one of the processes that emanate from the soma, while the remaining neurites will be committed to become dendrites. The axon specification process initiates a series of events that leads to the extension of the axonal process, its branching and the formation of presynaptic terminals onto its specific targets (Barnes and Polleux, 2009; Lewis et al., 2013). The size and shape of axonal arbours can vary greatly, from the intricate but local connections of inhibitory interneurons, to the long-range innervation of projecting neurons. Remarkably, some axonal projections can exceed over 20,000 times the length of the mature cell body from which they originate from (Wang et al., 2012). For example, the neurons that innervate the periphery can extend over large distances, while within the brain, a single axonal projection can produce a complex net of synaptic terminals arranged over multiple branches spanning hundreds of millimetres in length and containing thousands of boutons (Debanne et al., 2011). Once a neuron and its axon have survived the tumultuous developmental stages of excessive proliferation and successive pruning they settle in the adult brain as a relatively stable anatomical structure (Luo and O'Leary, 2005). In the absence of traumatic events or pathological conditions, the overall expanded axonal arbour will remain stable for the entire adult life of an organism, while experience and learning will continue to shape the fine structures of the presynaptic terminals and small axonal branches through a phenomenon known as structural plasticity (De Paola et al., 2006), one of the mechanisms thought to be at the basis of memory formation (Holtmaat and Svoboda, 2009). The ability to encode new memories requires the network to allow physical changes in order to modify the synaptic connections between neurons and therefore reconfigure the circuits involved. At the same time it also requires stabilization of new synaptic configurations to consolidate memories and store them for extended periods, potentially a life time (Roberts et al., 2010; Xu et al., 2009; Yang et al., 2009; Chen et al., 2015). The required stability of the network together with the intricacy of the connections formed in the adult central nervous system (CNS) make the great majority of neurons irreplaceable. This characteristic is key in the context of ageing. It is fascinating to think that such delicate cells are successfully protected, together with their axons, during adulthood through to the later stages of life in long-lived organisms. In humans, this means that an axon and the majority of its varicosities, which lie far from the soma and nucleus, has to fire action potentials and redistribute ions for up to a century. To achieve such a complicated feat the organism invests many resources to support neurons and their axons throughout life. However, for long-lived neurons years of accumulated damage and stress can make them vulnerable to ageing and age-related conditions, which represents a major risk factor for many neurodegenerative conditions such as Alzheimer's disease (AD), Parkinson's disease (PD), amyotrophic lateral sclerosis (ALS) and glaucoma (Adalbert and Coleman, 2013). All of these major pathologies are characterised by axon degeneration and extensive neuronal death in different regions, whereas ageing in physiological conditions typically does not lead to a generalised loss of neurons. In mice, rats and rhesus monkeys neuronal cell death caused by advanced ageing has been shown to be limited and restricted to confined brain areas (Peters et al., 1998; Curcio and Coleman, 1982; Madeira et al., 1995; Merrill et al., 2001). Accurate measures of nerve cell death in humans are difficult to achieve, but the current consensus appears to be that neuronal loss is restricted to specific areas and that less than 10% of neurons actually die (Pakkenberg and Gundersen, 1997; Morrison, 1997). Therefore, it is likely that the cognitive decline that inevitably affects ageing individuals arises from morphological and functional alterations, rather than neuronal cell death. Many changes in neuronal morphology during ageing have been described. These include the accumulation of lipofuscin granules, dendritic and axonal retraction and synapse loss (Pannese, 2011). However, it should be noted that age-related functional and structural changes of neurons are cell type and area specific (Burke and Barnes, 2006).

## 2. Age-related axon loss and neurodegeneration

Axonal loss is a prominent feature of normal ageing. Cross sectional studies on human brain samples have shown how white matter fibres are susceptible to ageing, where by the age of 80 white matter is reduced by 45% compared to young subjects aged 20 (Marner et al., 2003). The reasons behind this prominent reduction of white matter tracts is not well understood, one theory points to changes in small cerebral blood vessels causing micro-ischemic lesions that determine the death of oligodendrocytes and the loss of myelin (Pantoni, 2002). It is still unclear how much of the volume reduction of the white matter is due to actual axonal retraction and how great is the contribution of demyelination (Marner et al., 2003). The myelin sheath is fundamental to the physiological functioning of the axon, providing protection, nourishment and granting efficient signal transmission (Sherman and Brophy, 2005). It is therefore not surprising that demyelination has often been cited as a cause of the cognitive decline of normal aged subjects, where the speed and synchronization of neural transmission might be compromised. The reduction of axonal projections has been reported in many other brain regions and in different animal models. Aged dogs, that experience cognitive impairment, have been found to lose white matter density in the frontal lobe compared to younger animals. Demyelination is mainly due to the breakdown of the myelin sheath rather than a reduction of oligodendrocytes (Chambers et al., 2012). In the cingulate bundle of rhesus monkeys, the myelinated axons are reduced by up to 20% compared with younger controls, and the reduction correlates with the cognitive performance of tested animals (Bowley et al., 2010). In the same species, myelin structure is also compromised in the anterior commissure (Sandell and Peters, 2003) and in the genu of the corpus callosum (Bowley et al., 2010). Thus, it appears that damage progresses with increasing ages and that it eventually leads to nerve fibre loss while the overall number of oligodendrocytes remains relatively stable across age groups. Similarly, the optic nerve is susceptible to age-related damage as the axons that project from the retinal ganglion cells (RGCs) in the eye are reduced in old animals. These studies have been conducted in rhesus monkeys (Sandell and Peters, 2001), rats (Cepurna et al., 2005) and mice (Samuel et al., 2011). Age-related changes have also been described in the hippocampal circuitry of rodents (Gray and Barnes, 2015). With progressive ageing in rats, axon collaterals originating in the entorhinal cortex that form the perforant path are diminished in their target region, the dentate gyrus (Barnes and McNaughton, 1980). For the mossy fibre projection, on the other hand, it is not clear whether the weaker synaptic output seen in aged rats is due to a reduction in axon number (Gray and Barnes, 2015). Moreover, the Schaffer collateral pathway, connecting CA3 with CA1, seems to maintain axon and synapse number in ageing rats, compared to the young hippocampus (Geinisman et al., 2004), although the efficacy of the older synapses is reduced (Nicholson et al., 2004). Similar to rodents, the parahippocampal white matter of humans, which includes the performant path, is reduced in older individuals