Of dolphins, humans, other long-lived animals and Alzheimer's disease (Commentary on Vacher et al.)

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Abstract

Alzheimer's Disease (AD) is a familial or sporadic severe neurodegenerative disorder that leads to short-term memory impairment followed by progressive cognitive deterioration of executive functions. AD frequency is increasing with a consequent socio-economic burden and there is an urgent need to understand its aetiological complexity, find reliable animal models and identify effective therapeutic treatments. AD diagnosis relies on a series of neuropsychiatric criteria and the detection of two pathognomonic protein aggregates in the brain parenchyma: amyloid plaques and neurofibrillary tangles. The concurrence of these aggregates seems to be mostly present in humans. In this issue, Vacher and colleagues demonstrate the notable coexistence of AP deposition and hyperphosphorylated tau in the brains of dolphins. Here we discuss the relevance of this finding and how they could help understanding AD

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(Commentary on Vacher *et al.*)

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Alzheimer's Disease (AD) is a familial or sporadic severe neurodegenerative disorder that leads to short-term memory impairment followed by progressive cognitive deterioration of executive functions. Since its initial description in 1906 (Hippius & Neundörfer, 2003), AD has attracted increasing attention from basic neuroscientists, clinicians, care givers and politicians not only for its increasing frequency and socio-economic burden, but also for the still poorly understood aetiological complexity of its most common sporadic form (Knopman *et al.* , 2021). This complexity precludes the generation of reliable conventional animal models (e.g. mouse, rat) and the existing ones, at best, resemble the identified genetic forms of AD. Rodents do not develop spontaneous AD for a number of reasons (Drummond & Wisniewski, 2017) and, thus, the most commonly used AD-like mouse or rat models are transgenic lines that express the mutated forms of human genes (e.g. APP, PS1, PS2) present in patients suffering from familial AD (Wu *et al.* , 2012). These difficulties hamper understating AD and the identification of effective therapeutic treatments, fostering the quest for alternative means of research progress.

AD diagnosis relies on a series of neuropsychiatric criteria, the analysis of cerebrospinal fluid (CSF) and the use of positron emission tomography (PET) for the detection of two pathognomonic protein aggregates in the brain parenchyma: amyloid plaques (AP), mainly composed of aggregated $A\beta$ monomers, and neurofibrillary tangles (NFT) containing hyperphosphorylated Tau (Wu *et al.* , 2012). Aging is the strongest risk factor for sporadic AD, suggesting that long-living animals are potentially susceptible to developing spontaneous

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AD. However, AD as such seems exclusively to be a human disease (Finch & Austad, 2015). Several animal species, including the great apes and other nonhuman primates, which can have a relatively long lifespan, can accumulate large amounts of Aβ-positive APs and cerebral amyloid angiopathy (CAA) as they age. They also show the presence of phospho-Tau staining but there is little evidence for the accumulation of clear NFTs or widespread brain degeneration (Drummond & Wisniewski, 2017), which characterise human AD. Similar APs or amyloid only accumulations have been observed in other species with shorter lifespans (e.g. rhesus macaque, vervets, lemurs and dogs) (Youssef *et al.* , 2016; Drummond & Wisniewski, 2017). However, no evidence of AD-like protein aggregates has been found in animals with life spans comparable to or double that of humans, such as elephants (Cole *et al.* , 1990) or bowhead whales (Lagunas-Rangel, 2021), that are currently considered as examples of "healthy aging". Furthermore, most animals do not show signs of outright dementia as AD patients do (Drummond & Wisniewski, 2017). In other words, the different animal species so far analysed do not seem to suffer from bona fide AD (Table 1).

Somewhat surprisingly, in this issue, Vacher and colleagues demonstrate the notable coexistence of AP deposition and hyperphosphorylated tau in the brains of dolphins (Vacher *et al.* , 2022), mammals that have undergone considerable anatomical adaptations to their aquatic environment, including in their brain organization. The authors analysed brain samples from twenty-two dolphins of five different species, which were found stranded along the Scottish coasts. They initially focused on the limbic and anterior paralimbic lobes of the cerebral cortex that can be compared to the brain areas in which protein aggregates initially accumulate in AD patients. In three of the eighteen individuals with recorded evidence of advanced age, they identified Aβ-positive compact and diffuse APs, vascular Aβ accumulations suggestive of CAA as well as phosphoTau-positive pre-NFTs (Table 1). These three cetaceans belonged to three different species: *Lagenorhynchus albirostris; Globicephala melas* and *Tursiops truncates* , all of which have an Aβ peptide amino acid sequence identical to that of humans, as also observed in other mammals in which AP accumulation has been detected. Analysis of additional brain regions from the same animals confirmed the variable presence of both Aβ and p-Tau aggregates, which were never found in brain samples from younger animals of the same species.

The link between amyloid deposition and the formation of tau aggregates in AD patients is still unclear. Nevertheless, longitudinal PET imaging studies indicate that Tau accumulation precedes amyloid pathology, whereas amyloid, once it has reached a threshold concentration, seems to foster the spread of tau aggregates and neuronal death (rev in (Karran & De Strooper, 2022). Notably, Vacher *et al.* (2022) found abundant pTau-positive granules within neuronal cell bodies, axons and dendrites as well as accumulations consistent with pre-NFT in additional brain regions of the same individuals, where AP were either absent or very sparse. PhosphoTau-immunolabelling consistent with intracellular neuronal tangles was also found in an additional *Globicephala melas* in which APs were absent. Although rather speculative, these observations suggest that dolphins may have a time course of formation of pathological aggregates similar to that of humans, with phopho-Tau accumulation preceding the presence of amyloid accumulation.

This does not mean that dolphins suffer from AD as this would be a far-reaching conclusion in the absence of information related to cognitive performance. Nevertheless, loss of the sense of direction or similar disorientations (as observed in humans with initial mild cognitive impairment) may explain mass strandings observed in some dolphin species. Indeed, the "sick leader" hypothesis speculates that members of a pod would also strand when following a leader with cognitive decline. Furthermore, Vacher *et al.* (2022) found only mild evidence of reactive astrogliosis or activated microglia surrounding the plaques, a characteristic that is common to AD pathology, although this may again indicate that the brains analyzed were at an early stage of AD-like pathology.

Independently of these considerations, this study shows the susceptibility of odontocetes to develop spontaneous and concomitant aggregates of APs and pre-NFT, the coexistence of which in humans has been always associated with AD. There are previous reports describing the presence of amyloid aggregates and a few neurofibrillary threads or phosphor-tau-positive granules in the neurons of cetaceans' brains (Gunn-Moore *et al.* , 2018; Sacchini *et al.* , 2020), but Vacher *et al.* (2022) are the first to establish a clear correlation

between the presence of APs and pTau aggregates with old age and to identify accumulations that resemble NFTs. In an interesting discussion, the authors review the idea that cetaceans possess some physiological and behavioural traits that may make them a more accurate, spontaneous model for studying AD than non-human primates. Besides being relatively long-lived animals, some species of dolphins live in cooperative groups and show care-giving behaviour towards diseased individuals (Mead, 2023). This means that other dolphins within a pod could help cognitively impaired individuals, compensating for abnormal behaviour and thus allowing for the progression of neurodegenerative pathologies. Supporting this possibility, Vacher *et al.* (2022) found no signs of AD-like pathology in harbour porpoises (*Phocoena phocoena*), a relatively short-lived species of odontocete that lives alone or in small groups, in line with the idea that free-ranging animals with cognitive abnormalities are unlikely to survive in the wild. Some odontocete species have been shown to have a relatively long post-reproductive lifespan that in terrestrial animals is basically limited to humans. How this trait can influence brain degeneration, as suggested previously (Gunn-Moore *et al.*, 2018), is not supported or disproved in this study, but hormonal and related genetic changes may be relevant.

Research in the AD field would benefit greatly from the identification of a non-conventional animal model with spontaneous onset of the disease. Practical and ethical considerations preclude the use of cetaceans as such a possibility. Nevertheless, additional molecular and behavioural research on aged odontocetes kept in captivity in zoos or aquaria, and a more extensive analysis of samples such as those used in this study may find additional commonalities with the human condition, helping identifying additional important players in AD onset. There is a long list of studies addressing the cellular profiles of AD brains (rev in, Murdock & Tsai, 2023) and recent proteomic studies in large cohorts of AD patients point to interesting additional molecules that could be relevant for AD pathogenesis (e.g. Johnson *et al.*, 2022). Dolphin brains could be subjected to similar analyses or at least examined for the presence of similar candidate molecules, thereby helping to understand their possible relevance. These are feasible approaches that may offer new views and therapeutic avenues, both much needed in the fight against neurodegenerative diseases.

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Table 1

Species	APs	CAA	p-Tau	NFTs	RG	NeuroD	CD	Reference
Humans	Y	Y	Y	Y	Y	Y	Y	(Hippius *et al.* 2003)
Dolphin	Y	Y	Y	Y	N	ND	ND	(Vacher *et al.*, 2022)
Chimpanzee	Y	Y	Y	?	ND	ND	ND	(Edler *et al.*, 2017)
R. macaque	Y	Y	Y	?	ND	ND	Y	(Paspalas *et al.*, 2018)
Vervet	Y	Y	Y	N	Y	ND	ND	(Latimer *et al.*, 2019)
Dog	Y	Y	Y	N	Y	ND	Y	(Schmidt *et al.*, 2015)

Presence of pathological signs associated with human AD in different mammalian species. Aps, amyloid plaques; CAA, cerebral amyloid angiopathy; CD, Cognitive deficit; NeuroD, neurodegeneration; NFTs, neurofibrillary tangles; p-Tau, phosphor-Tau; RG, reactive gliosis. N, NO; ND, non-determined; Y, yes; ? unclear.