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Introduction

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Insights from evolutionarily relevant models for human ageing

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As the world confronts the health challenges of an ageing population, there has been dramatically increased interest in the science of ageing. This research has overwhelmingly focused on age-related disease, particularly in industrialized human populations and short-lived laboratory animal models. However, it has become clear that humans and long-lived primates age differently than many typical model organisms, and that many of the diseases causing death and disability in the developed world are greatly exacerbated by modern lifestyles. As such, research on how the human ageing process evolved is vital to understanding the origins of prolonged human lifespan and factors increasing vulnerability to degenerative disease. In this issue, we highlight emerging comparative research on primates, highlighting the physical, physiological, behavioural and cognitive processes of ageing. This work comprises data and theory on non-human primates, as well as under-represented data on humans living in small-scale societies, which help elucidate how environment shapes senescence. Component papers address (i) the critical processes that comprise senescence in long-lived primates; (ii) the social, ecological or individual characteristics that predict variation in the pace of ageing; and (iii) the complicated relationship between ageing trajectories and disease outcomes. Collectively, this work provides essential comparative, evolutionary data on ageing and demonstrates its unique potential to inform our understanding of the human ageing process.

This article is part of the theme issue 'Evolution of the primate ageing process'.

1. Introduction

Humans are remarkable among mammals for our extreme longevity, and in the past century, lifespans have increased dramatically across the globe [1,2]. In the year 2018, for the first time in history, the world's population of people over 65 years of age exceeded that of children under the age of 5 [3]. This so-called silver tsunami presents a significant global health challenge, leading to prioritization of ageing as one of the most urgent areas of biomedical research. However, contrary to popular belief, humans were living to old ages long before the spread of western medicine and even before the onset of agriculture. Similarly, in contemporary small-scale foraging communities without access to westernized medicine, infant mortality is high, but the modal age of adult death reaches into the late 70s [4,5]. The way that humans age today has been shaped by a long evolutionary history, meaning that the narrow focus of ageing research on humans in modern, industrialized environments constrains our ability to understand the factors that shape health and lifespan. Basic research on the evolution of ageing, including generation of high-quality data from diverse human populations [6] and closely related, long-lived species [2,7–9], is, therefore, an essential complement to the emerging explosion of clinical research on ageing.

This theme issue addresses this neglected line of inquiry by examining the comparative biology of ageing across primates, driven by two major questions. First, what processes would probably have affected health and constrained lifespan in the evolutionary past? Second, what factors contribute to variation in ageing processes within and across species? Our authors address emerging paradigms in the clinical ageing literature (such as dementia, immunosenescence and social isolation) and perform explicit quantitative and theoretical comparisons of their findings with prior reports. We highlight scholars who study non-human primates, as well as those who study humans outside of the typical industrialized clinical study setting. This issue comes at a pivotal time for research in primatology and human ecology when the combination of new methods and exhaustive longitudinal data collection has converged to enable robust analyses of ageing. Contributed papers address the important ways that environment influences senescence; highlight new primate models for features of the human ageing process that are not appropriately captured by existing models; and provide productive discourse on how the ageing process may have been shaped throughout our evolutionary history. In pursuing these goals, the contributed papers not only offer novel comparative datasets on primate ageing, but also provide insights on the complex relationship between ageing and health that have translational potential for shaping clinical interventions.

2. An evolutionary approach to ageing

For decades, research on ageing has been dominated by two interrelated perspectives. The first addresses the immediacy of treating or curing specific degenerative diseases that plague the elderly, including cardiovascular, metabolic and neurodegenerative diseases. The second aims to prevent age-related diseases and slow the rate of ageing, with the goal of extending lifespan or increasing the years of healthy living, the 'healthspan' [10]. Much of this literature characterizes ageing as a disease that can theoretically be cured, or at least delayed [11–16]. However, a number of prominent researchers have argued for a change in perspective to distinguish the process of ageing from the diseases that are affected by age [17–19]. This evolutionarily guided perspective acknowledges that for most species, ageing is a natural and inevitable feature of life.

While evolutionary theorists have long argued that ageing evolved primarily because natural selection was unable to prevent it [20,21], there is increasing recognition that ageing and its mechanisms are in fact subject to natural selection, most notably through resource allocation decisions made earlier in life [22–25]. Additionally, factors that promote degenerative ageing, such as glucocorticoid activity, inflammation and production of reactive oxygen species, also serve functions that are essential for survival, creating selective trade-offs [26–28]. Critically, conflating ageing with disease is problematic because even the most common pathologies of old age only occur in a fraction of individuals, and changes that occur during ageing are not intrinsically pathological. While advanced age is the defining risk factor for degenerative disease, this risk is modified heavily by genes and environment, suggesting that the pathways to successful or pathological ageing can begin early in life. As such, there is a need to better understand the basic biological pathways of senescence and their natural scope of variation, an approach that may yield clues to long-term disease prevention.

Evolutionary scholars view ageing, like other biological phenomena, through a long lens, as the outcome of selective forces shaping our species and its ancestors over millions of years. The essential paradigm underlying the emerging field of evolutionary medicine is that the mechanisms of human ageing have been shaped under dramatically different environments than those in which most humans currently live [6,29,30]. Indeed, the rapid rate of international development means that many elderly people alive today developed under very different nutritional, epidemiological and social conditions than those in which they currently live [31,32]. These evolutionary and developmental 'mismatches' are thought to contribute to the prevalence of many degenerative diseases.

One important evolutionarily informed approach is to examine the health of people living in different environments, particularly in small-scale subsistence populations that are overlooked by the clinical literature. These include foragers, whose hunting and gathering mode of subsistence most closely resembles the lifeway practised throughout most of human existence, as well as pastoralists and those that farm at small scales for family consumption. Populations that have limited access to market goods or westernized medicine, practice natural fertility, and live embedded within strong kin networks are especially informative as they experience resource limitations, high rates of physical activity, prevalent infectious disease and social contexts that best approximate the selective environments that are likely to have shaped the human organism. For example, owing to energetic constraints and long periods of lactation, pre-industrial populations produce relatively low levels of the steroid hormones oestradiol and testosterone [33,34]. High lifetime exposure to these hormones has been linked to the elevated risk of some reproductive cancers [35,36]. Similarly, as the human immune system evolved in a high-pathogen environment, early and frequent exposure to infections, such as gastrointestinal parasites, may promote healthy metabolism and immune regulation. Recent studies of Tsimane horticulturalists, who exhibit high levels of inflammation compared to industrialized populations, suggest that infection with parasites may be protective against musculoskeletal and cognitive decline, and perhaps even atherosclerosis and Alzheimer's disease [37–39]. Rather than increasing 'wear and tear', the high workload in subsistence societies appears to confer some protection against a variety of degenerative diseases, including osteoarthritis [40], cardiovascular disease [41,42] and frailty [43].

Another important facet of the evolutionary approach is to evaluate human ageing biology in the context of our close non-human primate relatives, which share many pertinent biological features with humans through common ancestry [44]. Primates are not only valuable as 'model' species, substituting for humans in experimental research, but as essential comparative referents that can deepen our understanding of the evolutionary forces that have shaped human ageing. Thus, our issue highlights work that situates humans in this broader comparative context, an approach that is vital not only because humans are primates, but because understanding the ageing process requires disentangling true species-level differences from those that may vary according to environment.

3. Challenges and benefits of comparative ageing research on non-human primates

While animals have long been used as laboratory models for the study of ageing, model species have almost always been

selected for convenience, because they have short generation times and can be subjected to invasive manipulations that are not feasible in humans. Yet, ageing exhibits tremendous diversity across species [45,46], and conventional animal models have significant limitations in their applicability to humans [47]. There is a particular paucity of high-quality data on other long-lived species, including non-human primates. We emphasize three principal arguments for investing in research on primate ageing.

First, primate research is *necessary*. Genomic studies indicate that the mechanisms which are the focus of research in conventional model organisms, like worms, flies and rodents, have not been major targets of selection in humans and are unlikely to explain interspecific variation in longevity among primates [48]. The combination of a long life and extensive parental investment has shaped primate life course strategies [49,50], potentially affecting not only how quickly we age but also how we age. Primates are indispensable for examining aspects of cognitive, neurobiological and social ageing that are simply not captured in existing animal models. Older adults show shifts in sensitivity to social information, social reasoning abilities and complex forms of value-based decision-making that can impact social competence, financial stability and other aspects of well-being during ageing [51,52], and there is increasing recognition that strong social support promotes successful ageing [53,54]. Second, non-human primates are *appropriate* comparative models. For example, despite considerable diversity in lifespan, primates exhibit broad similarities in the patterning of mortality that distinguish them from other species [55,56]. Primates share physiological similarities with humans that make them highly relevant models for reproductive ageing, metabolic diseases, musculoskeletal ageing, immune function, cardiovascular disease and cognitive decline [57–64]. Finally, given the overall similarities, the variation among primates is specifically *informative*. When closely related species exhibit differences in ageing, large or subtle, this presents a unique opportunity to identify key pathways of selection, including environmental influences and genetic mechanisms.

For these reasons, there has been recent recognition of the unique applicability of primates for translational research, most notably for studies of caloric restriction and brain ageing [57–62,65]. However, the bulk of primate research to date has focused on a handful of species that are abundant, easy to maintain in laboratory settings and have tractable generation times: mouse lemurs [66,67], common marmosets [68] and rhesus macaques [65]. Work on ageing in primate populations outside of laboratory contexts, by contrast, has been remarkably rare. Indeed, there was a long-held assumption in gerontology that most animals did not live long enough in the wild to experience the physiological effects of ageing [20,69]. However, longitudinal data from a diverse range of animal taxa now make it clear that senescence is widespread in nature [70–72]. Moreover, the effects of captive environments on physiology are substantial, and coupled with a reduction in genetic diversity, can have complex, and sometimes unpredictable, influences on the ageing process [73]. Studies in the wild, therefore, complement captive studies by examining ageing biology under conditions closer to that in which it evolved, and can provide new insights into how ageing is influenced by environmental context.

Data from diverse primate populations are, therefore, essential, but also present several challenges for ageing research. First, many primate species, including our closest living relatives, are endangered, raising ethical considerations about their use. Notably, in 2015, the National Institutes of Health and the United States Fish and Wildlife Service released landmark policy changes that have seriously restricted laboratory research on chimpanzees. However, minimally invasive measures using urine, faeces, blood spots and observational data have developed rapidly over the last 20 years, transforming the ability to monitor health in wild primates, as well as in humans in non-clinical settings [74–79]. Papers in this issue highlight impressive datasets derived from non-invasive specimen collections, post-mortem skeletal analyses and opportunistic sampling during routine health screenings. Second, the relatively long lifespan of primates poses inherent feasibility challenges for obtaining adequate samples. Sample size is additionally constrained by the small numbers in most captive colonies or habituated wild groups, making it difficult to avoid confounds such as mortality election. Yet, these studies have the ability to collect continuous, longitudinal data that are not feasible with large, human cohorts. Finally, it can be difficult to implement experimental treatments and controls in the field, and primates generally cannot be manipulated in the same manner as other species. However, this drawback is balanced by a key strength: the ability to obtain detailed, objective data on individual experience, such as on diet or social interactions. Given the strong associations between social environmental variables, like social integration and social status, for healthy ageing in humans [80], research on primate social groups offers one of the few tangible systems to examine potential mechanisms for such effects [81,82].

4. Key themes from this volume

The work presented in the current volume aims to overcome the challenges associated with studying diverse primate populations, contributing new methodological advances to monitor humans and animals, harnessing rich long-term datasets on long-lived species and evaluating the application of theoretical ideas to these understudied populations. Here, we highlight major themes cross-cutting this work.

(a) Comparative toolkits

While clinical science has developed standard diagnostics of ageing across many domains, these measures can be difficult to translate to naturalistic settings or to different species, hindering direct comparisons. Contributions to this volume demonstrate productive approaches to this problem.

One such approach stems from the recent recognition by gerontology of 'emergent' ageing processes, such as frailty, physiological dysregulation and allostatic load. This approach recognizes that the functional effects of ageing are the result of a complex network of underlying mechanisms that can unfold differently across individuals [83]. As such, examining variation across a range of measures yields a more robust correlation with age and proves more effective in predicting disease and mortality than isolated diagnostic tests [84,85]. Importantly, component measures need not be identical, nor identically measured, across studies, allowing for comparisons across diverse datasets and even across species. Two recent studies, for example, found similar emergent ageing processes in multivariate biomarker datasets of humans and non-human primates that contained overlapping, but not completely

compatible, information [86,87]. Comparative research can be designed by testing for features of previously identified emergent processes (top-down), or by using variation in the data to organically identify axes of age-related change (bottom-up).

Several papers in this volume directly apply emergent process approaches: one examines physiological dysregulation in Amazonian horticulturalists using a large biomarker dataset ([88]), while two others compare age-related changes in gene expression and epigenetic measures of gene-regulation between humans and non-human primates [64,89]. Two other papers translate clinical approaches to frailty to field conditions, examining ecologically relevant measures of physical performance in wild chimpanzees [90] and African foragers and pastoralists [91]. Other papers test for immunosenescence, which is difficult to measure directly in wild primates, but is detectable through its functional outcomes: age-related increases in parasitic [92] and viral infections [93]. Others have taken the opposite approach of dissecting complex phenomena like cognitive [94,95]), neurobiological [96] and skeletal ageing [97] to examine whether they result from common mechanisms across species.

(b) Shared and divergent ageing trajectories

The contributions in this volume highlight extensive similarities in the ageing processes between humans and other primates across a variety of domains. For example, several contributions demonstrate shared patterns of immunosenescence, both in its specific regulatory mechanisms [64] and its effects on infectious disease burden in the wild [92,93]). While the process of immunosenescence in human ageing is well recognized, the role of infectious disease in driving late-age mortality has diminished in industrialized nations relative to the role of degenerative diseases. However, the increased vulnerability to infection with age would have been an important constraint on lifespan even in the very recent past, and it is vital to consider the way that pathogen stress itself would have shaped the evolution of the ageing process [7,39].

Critically, however, several contributed papers conclude that broad similarities in ageing phenomena do not necessarily yield the same functional outcomes. For example, while it might be predicted that physically demanding lifestyles would accelerate musculoskeletal ageing and exacerbate its consequences, contributed studies of wild chimpanzees [90] and human subsistence populations [91] suggest the opposite. These studies support the conclusion that physical performance and body condition are widespread features of ageing, but they also suggest less impairment than has been observed in industrialized human samples. Similarly, Ruff *et al*. [97] report that while the bones of mountain gorillas exhibit several human-like signatures of ageing, they contrast with humans in that bone strength is preserved late into life. Guevara and colleagues report that the brains of chimpanzees recapitulate characteristics of ageing human brains, like neuronal loss in the hippocampus, but do not exhibit the human-specific pathologies linked to dementia and Alzheimer's disease [96].

Collectively, studies in this volume support the hypothesis that the evolution of the extended human lifespan was accompanied by slowing of ageing processes rather than by fundamental changes to these processes. For example, contributions to this volume demonstrate close similarities in age-related DNA methylation between rhesus macaques, chimpanzees and humans, though accelerated and scaled to the expected lifespan of the shorter-lived species [64,89]. Similarly, Kraft *et al*. [88] demonstrate that even in challenging environments, physiological dysregulation in humans proceeds at a slower pace compared with non-human primates. These studies demonstrate a remarkable conservation of the broad regulatory phenomena that govern senescence across primates and across ecological contexts.

(c) Environment and lifestyle

Several contributions highlight the merits of comparative work for addressing how variation in lifestyles and environmental context shape ageing. Studies contrasting humans in industrialized and subsistence cultures demonstrate that some aspects of human ageing are more variable than others. For example, Sayre *et al*.'s [91] comparisons of foragers, pastoralists and industrialized populations suggest some universal features of ageing physical performance but also identify important variation that may be shaped by the different nature and age structure of workloads in the different settings. On the other hand, Kraft *et al*.'s [88] examination of physiological dysregulation in a small-scale horticulturalist population finds only modest differences compared with industrialized samples despite major ecological and genetic differences between these populations. The contrast between captive and wild non-human primate populations also simulates at least some of the changes that have characterized modernization in human societies. As a demonstration of this paradigm, Cole *et al*. [98] report that chimpanzees with species-appropriate diets and ranging opportunities exhibit lower blood lipid levels compared to chimpanzees living a sedentary lifestyle with processed diets in captivity. Though chimpanzees are less vulnerable to atherosclerosis than humans [99], these findings suggest that lifestyle risk factors may operate through a shared pathway.

(d) Sex differences in ageing

Sex is a crucial modulator of the ageing process across species and features in several of the volume's contributions. Primates generally exhibit sexually dimorphic mortality, with males living significantly shorter lives than their female counterparts [56]. Yet higher mortality in human men is juxtaposed against higher rates of many degenerative diseases in women [100]. The reasons for this are still unclear, particularly as global measures of ageing differ little between the sexes. For example, physiological dysregulation does not appear to vary systematically between men and women, a finding confirmed here in a small-scale horticultural population [88]. As in human studies, rates of DNA methylation showed minimal sex differences in chimpanzees and rhesus macaques [64,89].

Sex differences in reproductive effort are predicted to yield differences in health and longevity. Compared with humans, many primates exhibit high levels of aggressive male competition, generating both direct and indirect impacts on health via risk of injury, physiological stress and energetic expenditure [101]. Contributed studies indicate that wild chimpanzee males are more vulnerable to viral infections and losses of physical condition with age than are females [90,93] and that wild male baboons who attain high social status pay the price of a

reduced lifespan [102]. Conversely, among chimpanzees in sanctuaries, females exhibited more proatherogenic lipid profiles than males across the lifespan [98].

For females, the high costs of pregnancy and lactation are expected to compromise health and accelerate ageing. However, evidence for health costs to high fertility remains inconclusive in humans, even in challenging environments where one might expect the strongest trade-off [103]. Is this the biological reality or a product of methodological limitations? In this volume, Jasienska [104] advocates for evolutionarily informed approaches to design more powerful studies of the health effects of reproduction, including more realistic assessments of reproductive effort. However, using detailed measures of reproductive effort, Phillips *et al*. [92] found that wild chimpanzee females experienced only transient increases in faecal parasites during pregnancy, and high fertility predicted lower, not higher parasitism with age. This is surprising because, unlike humans, chimpanzees do not receive support from others to raise their offspring, suggesting instead that they may have effective strategies to resist the trade-offs between reproduction and health.

(e) Ageing in mind, brain and behaviour

During ageing, humans show marked changes in aspects of complex cognition, neurobiology and sociality that are difficult to study in distantly related taxa. For example, executive functions (including inhibitory control and working memory) and the neurobiological substrates that support these processes show key age-related changes both during healthy ageing and in the context of neurodegenerative disease [105]. Lacreuse *et al*. [95] review the increasing evidence that declining executive function is a common and early sign of cognitive ageing across many diverse primate species, even though the neurobiological basis of these changes varies. For example, Edler *et al*. [96] report that the brains of chimpanzees exhibited regional neuronal losses that could impact cognition, though these losses were less severe than those associated with dementia in humans. By contrast, Rathke & Fisher [94] report that age had little effect on measures of executive function in semi-free-ranging Barbary macaques, though individuals showed declines in motivation to engage with the cognitive tasks overall. These changes parallel patterns observed in humans and emphasize that there are diverse pathways to declining cognitive performance with age. As motivation may be highly affected by an individual's surroundings, this finding reinforces the need to evaluate cognition in appropriate social and ecological contexts.

Another line of work highlights the important interactions between an individual's social environment and their ageing trajectory. In fact, recent evidence from non-human primates indicates that social stress and ageing yield congruent physiological and molecular effects [106,107]. In this issue, Campos *et al*. [102] report that baboons of both sexes experienced increased survival when they had strong social bonds, but as the mechanisms of social competition varied between the sexes, so did the effect of social rank on survival. However, social integration is also affected by ageing. Machanda & Rosati [108] report that while shifts in social behaviour and social cognition occur commonly across primates, these changes vary by species and can manifest differently in males and females. The human social ageing phenotype appears to be unusual, though available evidence points to important similarities in our closest relatives, chimpanzees.

5. Conclusion

We present this theme issue in 2020, at the onset of the World Health Organization's 'Decade of Healthy Ageing', one among many international initiatives targeted at improving the lives of older people. As ageing research expands its horizons, there is an essential place for evolutionarily informed research on the ageing process and a growing need for comparative data on closely related, long-lived species and on humans living under diverse environmental conditions. Already, these data fundamentally challenge the notion that longer life is equivalent to successful ageing and provide surprising insights into the relationship between ageing and disease. As we dissect these pathways and examine them in context, we can provide better answers to which aspects of ageing are broadly conserved and how lifestyle shapes health across the life course. In addition to describing novel empirical findings for the comparative biology of ageing, the contributed papers provide theoretical guidance and methodological innovations to shape future work.

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