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Quick Guide to Evolutionary Medicine in Neuroimmunomodulation: Why “Evolved for the Benefit of the Species” Is Not a Valid Argument

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Keywords

Phylogeny · Fitness · Trade-off · Cytokine · Inflammation · Sickness · Disease

Abstract

Background: Evolutionary medicine builds on evolutionary biology and explains why natural selection has left us vulnerable to disease. Unfortunately, several misunderstandings exist in the medical literature about the levels and mechanisms of evolution. Reasons for these problems start from the lack of teaching evolutionary biology in medical schools. A common mistake is to assume that “traits must benefit the species, as otherwise the species would have gone extinct in the past” confusing evolutionary history (phylogeny) with evolutionary function (fitness). **Summary:** Here we summarise some basic aspects of evolutionary medicine by pointing out: (1) Evolution has no aim. (2) For adaptive evolution to occur, a trait does not have to be beneficial to its carrier throughout its entire life. (3) Not every single individual carrying an adaptive trait needs to have higher than average fitness. (4) Traits do not evolve for the benefit of the species. Using examples from the field of neuroimmunomodulation like sickness behaviour (nervous system), testosterone (hormones), and cytokines (immunity), we show how misconceptions arise from not differentiating

between the explanatory categories of phylogeny (evolutionary history) and evolutionary function (fitness). **Key Messages:** Evolution has no aim but is an automatism that does not function for the benefit of the species. In evolution, successful individuals are those that maximise the transmission of their genes, and health and survival are just strategies to have the opportunity to do so. Thus, a trait enabling survival of the individual until reproductive age will spread even if at later age the same trait leads to disease and death. Natural and sexual selection do not select for traits that benefit the health or happiness of the individual, but for traits that increase inclusive fitness even if this increases human suffering. In contrast, our humane aim is to increase individual well-being. Evolutionary medicine can help us achieve this aim against evolutionary constraints.

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Introduction

Why does the psychoneuro-endocrine-immune network, which evolved to protect the individual against disease, sometimes cause disease and even death [1–6]? This is a classical question for the emerging field of evolutionary medicine: *Why* has natural selection left us

vulnerable to disease and ageing instead of favouring mechanisms that keep us young and healthy [7–12]?

Evolutionary mechanisms of increasing fitness are not always in agreement with the aim to increase individual health. Understanding why evolution left us vulnerable for disease can help us better understand disease to improve research and medical treatment [7–12]. Nevertheless, numerous publications by medical researchers, international experts in their bio-medical fields, still use flawed lines of evolutionary arguments to explain disease, including very recent publications [13]. In evolutionary biology, it was realised decades ago that traits cannot evolve for the benefit of the species but for individual benefits [14, 15]. This insight has been ignored by part of the medical sciences. There are many publications in which medical researchers still argue wrongly that traits evolved for the benefit of the species instead of trying to understand how they can increase individual fitness even though causing disease in some individuals ([16]; melatonin production [17]; memory-induced anxiety [18]; obesity [19]; hormonal imprinting [20]). The stress response has been interpreted to have evolved for the benefit of the species [21] with the adrenal medulla controlling catecholamine secretion to ensure species survival under environmental change [22]. It has also been argued that the immune response evolved for the survival of the species [23] and even that an overreaction of the immune system, leading to death of infected individuals evolved to protect the species [5]. The thymus was said to have evolved to regulate immunological self-tolerance as a necessity for the survival of the species [24]. All these reviews are of very high quality with regards to the proximate mechanisms, and if the correct evolutionary arguments about benefits for individual fitness had been employed, they would have achieved a better understanding of why disease occurs.

Here we (1) provide a quick guide to evolutionary biology and levels of selection for medical researchers, and (2) discuss how confusing phylogeny with function can lead to misunderstandings such as assuming that traits that were maintained during evolutionary history (phylogeny) must function to save the species from extinction, a function that does not exist in evolution, which is instead based on individual fitness benefits, before (3) giving examples of how to apply these concepts to topics important in the field of psychoneuroimmunology.

Evolutionary Medicine: Concepts and Misunderstandings

Clinical medicine focuses on understanding pathophysiological mechanisms that cause disease. Evolutionary medicine adds two additional questions: (1)

what is the evolutionary history (=phylogeny) and (2) what are the fitness consequences (=function) of these mechanisms?

Proximate and Ultimate Approaches to Disease

Biological research has traditionally been divided into the study of proximate (including physiological and pathophysiological) mechanisms on the one hand and ultimate (evolutionary) causes on the other hand (Mayr 1961). Tinbergen (1963) formulated four questions which are the basis for an integrative approach to understand biological traits [25–27].

Two questions are about the proximate causes of a trait, asking (i) how did the trait develop in individuals over their lifetime (**Ontogeny**)? (ii) What physiological machinery causes the observable trait (**Causation**)? Questions 3 and 4 are about the ultimate or evolutionary understanding of a trait, asking (iii) what is the **Function**, which means the fitness value of the trait? (iv) What is the **Phylogeny**, which means the evolutionary history of the trait? It is important to note that these four questions complement each other. Figure 1 shows how understanding the ultimate factors can allow us to better understand the proximate factors.

Psychoneuroimmune research is typically proximate (left box in Fig. 1), focusing on the (patho)physiological mechanisms and individual ontogenetic factors underlying, for example, behavioural changes, neuroinflammation, psychiatric conditions, allergies, or chronic inflammatory diseases [3]. Evolutionary medicine instead focuses on the ultimate explanation of disease [8, 12]. For this, evolutionary medicine in psychoneuroimmunology must separate between the function of a trait, i.e., its impact on individual fitness, and the evolutionary history (phylogeny) of the trait (right box in Fig. 1).

Misunderstandings in How to Apply Evolutionary Medicine in Psychoneuroimmunology

Wrong conclusions can arise when the two approaches in evolutionary medicine – function and phylogeny (right box in Fig. 1) – are not considered separately. Seeing a long evolutionary history of a trait that was already present hundreds of millions of years ago is sometimes used to argue that it evolved for the benefit of the species, explaining why the species survived until today instead of going extinct [5, 16–24]. Below, we review in detail why this argument is wrong and explain why we should not use the argument of the “benefit for the species.” We also identify why this argument is so attractive that it is maintained, even though

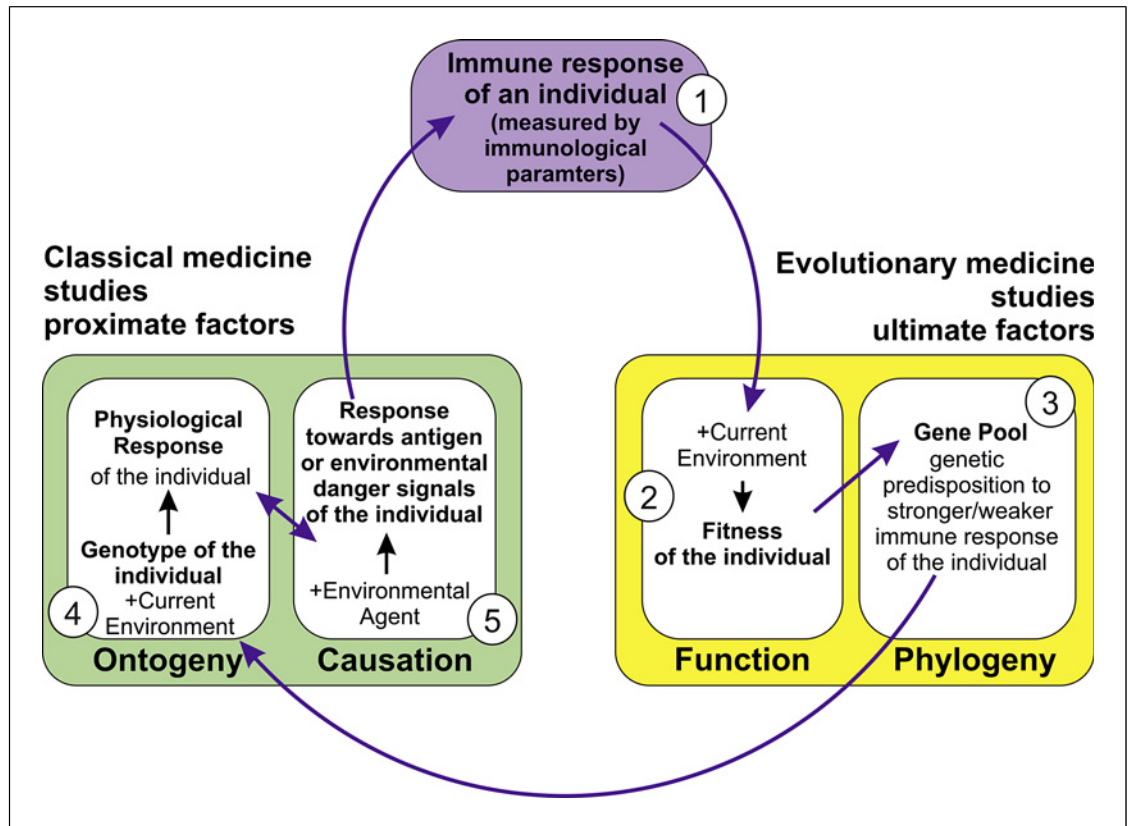


Fig. 1. An integrative approach to understanding immunology. (1) We measure the immunological response of individuals, which (2) influences an individual's survival and reproduction (function, fitness) and as such (3) the gene pool of the population of future generations. Looking back at evolutionary history from today describes the phylogeny of a species and how the trait of interest evolved in its environmental context (3). Function and phylogeny are ultimate factors and studied in evolutionary biology and evolutionary medicine (box to the right). Classical medicine/psychology investigate how the system is influenced during individual ontogeny (4), which depends on the genotype of the individual (coming from the

gene pool of the population) and the influencing environmental factors. The possible genotypes are determined by phylogeny; thus, historical fitness consequences, which determined what genotypes, were passed on over the generations. When exposed to a pathogen, the immune system responds (5. causation), and this response can be measured, for example, as cytokine concentration in the blood stream (1). While the pathway in the right box is unidirectional from function to phylogeny (see arrow), it can be reciprocal in the left box (the genotype influences causative factors, and causative factors can influence the epigenome). Figure modified from [12].

evolutionary biologists explained more than 5 decades ago why it is inappropriate [8, 14, 15, 28].

Evolutionary biology traditionally explains the origin and development of species [29], and this is how it is mainly taught in schools and in museums. This represents the phylogeny or evolutionary history of species (Fig. 1, right box). Now, the problem arises when correlation is confused with causality. E.g., somebody says, "If a trait has a long evolutionary history of hundreds of millions of years, this trait must be beneficial for the species; otherwise, the species would not have persisted for so long." However, it is not phylogeny (the evolutionary history of the trait) causing function (=fitness/

reproductive success), but – contrarily – function causes phylogeny. Traits are beneficial for the fitness of single individuals (not the species!), which means individuals with the trait produce on average more offspring than other individuals. When individuals reproduce successfully, the population and the species are automatically maintained, but this is not the "aim" of evolution but simply a common outcome. As such, the phylogeny of species reflects what happened at the individual level. The pathway from function (fitness/reproductive success) to phylogeny (the evolutionary history of a trait) is unidirectional from the first to the latter and never reciprocal (arrow in Fig. 1, right box).

Evolution Has No Aim

One common misconception is that evolution has an aim, such as the survival of the species, higher complexity, or simply maximising fitness. However, evolution is just an aimless algorithmic process. There are three conditions for evolution to take place: (i) individuals must differ in the expression of traits that (ii) are heritable and (iii) lead to fitness consequences. When all conditions are met, the genetic composition of the population will automatically change over time, which is evolution (there are additional mechanisms like drift that also cause changes in the gene pool and as such evolution, but these will not be reviewed here). For example, individuals can express a new anti-viral supporter of a cytokine signalling pathway such as the IFN regulatory factor 9 [30] that allows them to better cope with infection, live longer, and reproduce more. Consequently, more copies of the underlying gene variant will be transmitted to the next generation compared to the alternative variant. There are many similar examples of beneficial traits in the field of immunology [6, 31].

Even if all individuals of a species have a trait in common, for example, testosterone or a specific cytokine, how much of this trait is expressed (here produced and secreted) often differs between individuals. Differences in the trait expression, for example, cytokine production as response to an infection, can be due to genetic differences in the control of the trait expression or due to differences of exposure (of the same genotype) to different environmental stimuli in ontogeny (the individual's own life history).

Fitness, Function, and the Levels of Selection

Fitness Measures

Fitness is a central aspect in evolutionary biology. It is the relative contribution of an individual to the gene pool of the next generation, either by direct reproductive success (number of offspring produced that survive to reproduce) or indirectly by helping close genetic kin (kin selection). Fitness is typically measured by proxies, such as nutritional status (body mass), number of offspring, or survival. But it is not survival per se that determines whether a trait is adaptive, or not, because survival without reproduction has no evolutionary benefit (unless the individual helps close kin). Fitness is a relative measure, compared to the rest of the population. For example, in many species, most individuals die before reaching reproductive success (fitness = zero) such that all reproducing individuals have above median fitness. Fitness is not related to population size and species survival: a species could be under strong selection and evolving

towards better adaptation, while it goes extinct due to habitat loss.

Fitness is not an absolute but a relative measure: does the genetic background of a trait become more common in the population's gene-pool? If it does, then it will spread, even if it harms other con-specifics. Examples of traits that have high evolutionary fitness for the individual but that are detrimental for the species include female rodents killing other female's offspring [32], male primates, and lions killing other males' offspring [33, 34], and chimpanzees killing con-specifics of neighbouring groups [35]. Examples in humans are behaviours (including cooperative behaviours), leading to climate change which is threatening our species [36]. Traits such as fraud, theft, rape, infanticide, and murder can be explained by evolutionary theory [28, 37], though evolutionary explanations are neither excuses nor justifications for such behaviours [37, 38]. Evolutionary successful traits can even be detrimental for the fitness of the individuals carrying the trait, as exemplified by meiotic drivers, also called selfish genetic elements that manipulate the production of gametes to increase their own transmission rate [39]. The brain and the immune system may be considered as two selfish systems that compete for resources. If genes underline such selfish mobilisation of resources that have impact on pathological behaviour, then the selfish gene concept may apply in this context. Genetic influences for neuropathologies include gene polymorphisms of Alzheimer, serotonin, and interleukin secretion.

Old Group Selection, Kin Selection, and Multilevel (New Group) Selection

The insight that levels of selection matter lead to the rejection of the old group selection theory that claimed that traits will spread because they are beneficial for the group or species [14]. As Williams [14] ended the era of old group selection, biologists realised that the appropriate level to study evolution is typically the individual. The individual level of selection remains central, even though it was subsequently realised that other levels of organisation (gene, cells, traits, groups, populations, species, and clades) can theoretically be under selection. In fact, the Price equation describes higher level selection [40] leads to mathematically identical results as compared to kin selection introduced by Hamilton [41]. Kin selection shows that while cooperative and altruistic behaviours may reduce an individual's direct fitness (number of offspring produced), these traits will still spread if they increase the fitness of close kin sufficiently, with a weighting that is proportional to the genetic

relatedness of the two individuals. Close kin have a high probability of carrying the same alleles underlying these social behaviours [41, 42]. Kin selection thus considers inclusive fitness as the sum of direct fitness and indirect fitness, and a decrease in direct fitness can be compensated by an even higher increase in indirect fitness, leading to overall higher inclusive fitness. For example, if individuals live closely together with close kin, this can influence lifespan evolution by causing earlier death to decrease competition for critical resources, as shown in colony-forming microbes with high relatedness [43], or increased longevity to support highly dependent offspring and grand-offspring as in humans [44]. However, cooperation between bacterial cells is undermined by mutant cheaters who act selfishly and lead to the death of the whole colony [45] – this is the dilemma of multicellularity and another argument against old group selection. Costly enforcement is important on all levels to maintain cooperation against cheaters [46]. The theoretical possibility that avoidance of infecting others could lead to the evolution of adaptive death has been proposed [47]. It is important to note that this is not evolution for the benefit of the group, population, or species (“old group selection”) but to increase inclusive fitness [43].

It is generally argued that explaining the adaptive values of traits is easier when using the individual level including kin selection than the (mathematically identical) group level [15]. For a few social traits of eusocial insects using the group level might be easier [48, 49], though what appears as adaptive at the superorganism level can typically also be explained as the results of selection acting at the individual level [50]. This is sometimes called “new group selection,” though to avoid confusion with the rejected “naïve group selection” approach, the term “multilevel selection” is normally preferred.

Multilevel selection theory states that selection will be strongest at whichever level there is the most variation and the strongest competition [51]. While individuals typically differ widely in their access to resources and resulting reproductive success, variation among groups is much smaller and constantly eroded through migration and other forms of gene flow. Therefore, selection is typically stronger at the individual level rather than the group level. Selection at the species level would require that species-level competition is stronger than competition within species (i.e., among individuals); however, different species typically specialise in different foods and avoid interbreeding, hence, competition for food and mates is almost by definition stronger within species, and species-level selection is unlikely to occur [52–54]. In

sum, while selection at levels higher than the individual is theoretically possible, variation and competition are typically highest at the level of individuals.

Multilevel selection theory has been important for understanding selection *below* the level of individuals, e.g., for explaining the transition from single cells to multicellular organisms. This transition required multicellular organisms to evolve mechanisms for reducing variation and competition among their cells, e.g., by separating soma and germ line to avoid reproductive competition.

Function in Evolutionary Medicine: Why Adaptive Immunological Responses Can Lead to Disease and Death

Why does natural selection leave a species vulnerable to disease? This is generally explained via the limitations of natural selection, mismatch with modern environments, arms races with pathogens, or reproductive success at the expense of individual health and longevity [7–12]. An important concept to understand disease is evolutionary trade-offs. Energy is a restricted resource, and energy investment into one trait means there is less energy available to invest into another trait. This can explain why reproduction ceases when an organism invests heavily into the immune system during infection and why reproductive investment leads to physiological wear and tear and decreased health. It also explains why organisms do not have excess energy to permanently invest into a highly effective immune system controlling all diseases, as this would lead to reduced reproduction and as such low fitness. Traits did not evolve because they increase health, but because they increase fitness, and energy investment into reproduction is traded against energy investment into health.

Function concerns the fitness consequences of a trait (Fig. 1 right). If a trait leads to disease and death in some individuals carrying it and the underlying alleles nevertheless spread in the population, then this must be due to positive selection. This could be because the same individuals have high reproductive success due to the same allele in a previous life history stage before death (i.e., antagonistic pleiotropic effects [55]), leading to higher than average lifetime reproductive success [3]. Or the mean lifetime reproductive success of individuals carrying these alleles is higher than that of other individuals, even though a few individuals have below-average fitness.

A strong immune system is evolutionary beneficial as it increases chances to survive infections, but the same immune response can in some cases lead to harmful

chronic inflammation [3] or even death, as in the case of cytokine storms [56–58]. From an evolutionary point of view, all outcomes that lead to zero future fitness are equal, and natural selection cannot favour one over the other. Thus, (i) a chronic immunological response terminating reproduction has the same fitness consequence as (ii) dying due to the direct impact of an infection (no immunological response) or (iii) death due to an overreaction of the immune system. In other words, there can be no selection favouring (i) over (iii).

If the immune system fails to overcome an infectious disease, it makes no evolutionary difference if the endpoint is death due to infection, infertility due to chronic inflammation, or death due to overreaction of the immune system. A meta-analysis of dozens of studies of cytokine knockout mice suggests that infection is more likely to kill the host than chronic immunopathology. Therefore, on average, the benefits of a strong cytokine response are higher than the costs of chronic immunopathology due to an overreaction that occurs in some individuals [59]. In other words, it is better to raise an immune response stronger than needed than to fail to fight the actual threat of an infection. In sum, if the fitness costs of infection are higher than the cost of chronic immunopathology, then natural selection will favour a strong immunological response, even though this will increase the risk of chronic immunopathology or even death in few individuals [60].

Phylogeny in Evolutionary Medicine

Phylogeny describes the evolutionary histories of species and their traits (Fig. 1 right). Controlling for phylogeny allows to disentangle phylogenetic variance of a trait (inheritance that is due to shared ancestry of species) from residual variance (that may underlie adaptation to local environment). Therefore, to fully understand why physiological mechanisms exist that cause a given disease in a species, it is important to understand their phylogeny.

Many mechanisms of the immune system that can cause chronic diseases and even death are hundreds of millions of years old [3, 56–58]. This indicates that these mechanisms are associated with significant fitness advantages (arrow from (2) to (3) in Figure 1) [6, 13] and illustrates how fitness-increasing traits can be conserved over evolutionary time. The immune system increases survival of young individuals such that they reach reproductive age, leading to increased lifetime reproductive success, even if at old age this leads to disease and suffering, though with low fitness costs, as it is often post reproduction [12].

In evolutionary medicine, when thinking of phylogeny, the concept of “evolutionary mismatch” plays an important role. This refers to traits that were fitness-increasing in the environments of our ancestors but are maladaptive, leading to fitness costs in modern environments [61, 62]. A popular example are thrifty genes allowing survival in an ancestral energy-restricted environment but cause obesity and associated type 2 diabetes in our current environment with high food availability [63, 64].

Psychoneuroimmunology and Evolutionary Medicine

Here we show three examples of how separating between function and phylogeny (the right box of Fig. 1) benefits researchers in neuroimmunomodulation. For each example, we first describe the trait to be explained (1 in Fig. 1), underlying mechanisms related to immunology (4 and 5 in Fig. 1), its fitness benefits (2 in Fig. 1), and its phylogeny (3 in Fig. 1), before explaining how the existence of disease related to this trait can be explained in evolutionary medicine.

Function and Phylogeny in Psychiatry: Sickness Behaviour

What Is Sickness Behaviour and What Disease Can It Cause? (1 in Fig. 1)

Animals and humans infected with pathogens show sickness behaviour characterised by reduced appetite, reduced cognitive skills, inactivity, and fatigue [65–67]. Infectious agents through pathogen recognising receptors stimulate the immune response in the periphery and/or brain leading among others to increased cytokine and chemokine secretion [66] being one of the main proximate causes of sickness behaviour (5 in Fig. 1). In very few cases, sickness behaviour can be a platform to start long-term anorexia, anxiety, and major depression (1 in Fig. 1) [68, 69].

What Is the Evolutionary Function of Sickness Behaviour? (2 in Fig. 1)

Inflammation and immune responses are energetically very expensive. Reduced activity of the brain and muscles decreases energy consumption for behaviours and as such makes more energy available for the active immune system [70]. Reduced cognitive skills and fatigue function reduce behavioural activity. Reduced appetite decreases costly foraging behaviour and helps in overcoming bacterial infections by reducing levels of energy-rich substrates and free iron in the blood, which are important for bacteria to grow and multiply [71, 72], and by reducing eating- and immune-associated costs, like oxidative stress [73].

Phylogeny of Sickness Behaviour (3 in Fig. 1)

Sickness behaviour occurs in all vertebrates including fish, reptiles, birds, and mammals and is at least 500 million years old [72]. It even occurs in some arthropods [74] and causes social immunity in eusocial insects, i.e., an immune response based on social isolation of individuals of high fitness value like the queen [75, 76]. Accordingly, some of the proximate factors leading to sickness behaviour (4 and 5 in Fig. 1) are phylogenetically very old. For example, factors like class-I helical cytokines (IL-6, IL-11, IL-12, IL-23, leukaemia inhibitory factor, and others) are present in bony fish species such as pufferfish and zebrafish, in birds and in mammals [77]. In fish and in humans, IL-6 induces cell proliferation and antimicrobial activity [72]. Similarly, homologues of CD40 are present in lower vertebrates, where it helps regulate the immune response [78]. These factors all induce sickness behaviour.

Evolutionary Hypothesis to Explain Why Sickness Behaviour Can Rarely Lead to Depression and Why Selection Did Not Prevent This

Immunological mechanisms supporting sickness behaviour lead to a better and faster immunoreaction that helps the individual to overcome infection and reproduce afterwards to increase fitness. As pathogens occurred throughout evolutionary history, this can explain why sickness behaviour has a phylogeny of more than half a billion years. There was positive selection for these pro-inflammatory factors, even though they increase the risk of anxiety and major depression in modern humans. However, the risk of developing depression is very small compared to the benefits of allocating more energy to overcome infection. Without sickness behaviour, either chronic infection could occur, leading to a termination of reproduction, or even death, both causing zero fitness. The risk of depression is arguably enhanced by modern pro-inflammatory lifestyle factors [69], which is a case of evolutionary mismatch that natural selection has not had sufficient time to counteract. In conclusion, the benefits of allocating more energy to overcome infection are higher than the costs of the low risk of developing depression or of starving.

Function and Phylogeny in Endocrinology:

Testosterone

What Is Testosterone and What Disease Can It Cause? (1 in Fig. 1)

Male and female mammals both secrete androgens, oestrogens and progesterone but differ in the amount secreted. Females secrete more oestrogens and progesterone, and males secrete more androgens such as testosterone.

Androgens like testosterone are anabolic factors for muscle growth [79] and for male competitive and sexual behaviour [80]. Short-term testosterone surges in males are linked to mating success, female attraction, aggression, and territorial behaviour [81]. Thus, the ability to modulate testosterone levels throughout life is an important driver of male reproductive success [81]. In humans, the importance of testosterone in male reproduction is indicated by the Klinefelter syndrome (47XXY), leading to low testosterone levels, negatively affecting spermatogenesis among other important features of hypogonadism [82].

In male mammals, too low testosterone levels inhibit spermatogenesis [83], but high levels of testosterone can have an immunoinhibitory influence, leading to a trade-off [84]. An outstanding example of this is the unique reproduction of small carnivorous marsupials of the genus *Antechinus* [85]. Mating takes place in spring, with physiological changes being induced by an increase in photoperiod. Males invest time and energy primarily in mating rather than in feeding. Very high testosterone levels and high cortisol levels make energy available but strip the body of protein and fat [85]. Mating can take up to 12 h, and basically, all males die during the short mating season. This male die-off is largely brought on by severe infection, particularly owing to parasites. Removing male *Antechinus* from the natural habitat and keeping them in captivity without the option to breed leads to a much longer life expectancy similar to the one of females that live on to care for their offspring after the breeding season.

A major immunoinhibitory influence of testosterone is inhibition of the pro-inflammatory transcription factor NF-kappaB, M1 macrophages, T helper type 1 immune responses, B-cell immune function, and JAK-STAT pathways [86]. Further, testosterone increases oxidative stress [87] and, in humans, can be associated with anti-social behaviour [88]. The link between testosterone and parasite infection has been clearly established in animals [84], and also human males suffer more and worse infections than females [89]. This can partly be explained by higher testosterone levels, while other genetic factors related to X and Y chromosome play also a role [89]. The immunosuppressive function of testosterone has been demonstrated in multiple studies on animals and humans [84], though contradictory results have also been found [90]. However, in a study on 97 healthy human males, men with higher testosterone levels did not have a decreased but increased immunoresponse after a flu vaccination, indicating androgens to potentially act as immunomodulators rather than immunosuppressants [90].

Similarly, in lizards, opposing effects of testosterone were found for different parasites, indicating an immunomodulatory effect but an overall immunosuppressive effect [91]. A recent meta-analysis found that the empirical evidence for the immunocompetence handicap hypothesis is mixed, with good evidence from experimental (but not correlative) studies for an immunosuppressive function of testosterone [92].

What Is the Evolutionary Function of Testosterone? (2 in Fig. 1)

Testosterone is essential for spermatogenesis, secondary male sexual characteristics such as high muscle mass [93], as well as for the expression of behaviours related to male-male competition and sexual behaviour. As such, it is essential for male reproductive success.

Phylogeny of Testosterone (3 in Fig. 1)

Testosterone occurs in most vertebrate species with the typical anabolic effect on growth and the beneficial effect on reproduction in males [84, 94, 95]. Immunosuppressive function of testosterone also occurs in birds [96]. Testosterone has made its way through hundreds of millions of years of evolutionary history with variance depending on mating system and local environmental factors [97].

Evolutionary Hypothesis to Explain Why Testosterone Can Lead to Immunosuppression, Disease, and (Early) Death

The immunosuppressive function of testosterone is likely due to the energy trade-off between reproductive investment and investment into the immune response, which can also explain why it is not observed in all cases, i.e., when males have sufficient energy available. A higher energy investment into immediate reproduction than immune response often leads to a higher fitness benefits in male mammals. The trade-off between investment into reproduction versus immune response is complex, and experimental increase of testosterone is detrimental for both health [98] and reproductive success [99], while males with very low testosterone levels have no reproductive success and are more prone to autoimmunity. Another not mutually exclusive explanation is that the immunosuppressive action of testosterone functions to decrease the risk of autoimmunity, especially in young males [100].

It is obvious that oestrogens play an important role also in human diseases because prevalence and incidence of autoimmunity are much higher in women compared to

men [101]. Still, the immunosuppressive role of testosterone is evident in the preponderance of men versus women with sepsis on intensive care units [102].

Function and Phylogeny in Immunology: Cytokines What Are Cytokines and What Disease Can They Cause? (1 in Fig. 1)

Cytokines are molecules produced by a broad range of cells for intercellular signalling. Among others, they play an important role in the immune system, modulating the balance between effector and tolerant immune responses [84, 103]. Cytokine secretion increases during infection and contributes to decreasing and finally eliminating the pathogen load. This increases the chance for individuals to overcome infection and as such to survive and reproduce [6].

While cytokines are important for the immune response, they can also cause disease and even death. The cytokine response can be intense, and pro-inflammatory cytokine overproduction causes deleterious side-effects such as tissue damage, neuroendocrine and metabolic disease, and autoimmunity [6]. Cytokine storms during infections can be lethal [104].

What Is the Evolutionary Function of Cytokines? (2 in Fig. 1)

Overcoming infections is the function. Individuals that overcome an infection have a higher survival enabling future reproductive success. Immune responses to infections are energy-expensive and must be fast and effective to shorten the time of infection and reduce total energy expenditure. This also reduces the time for the pathogen to adapt rapidly to the immune response. As such, a fast and very strong cytokine response in most cases increases individual fitness [6, 59, 60].

Phylogeny of Cytokines (3 in Fig. 1)

All organisms face the risk of infection by pathogens, and this competition between hosts and pathogens emerged soon after life evolved and is thus billions of years old. It is therefore not surprising that cytokines evolved at least 700 million years ago and are already present in starfishes and sponges [77, 105].

Evolutionary Hypothesis to Explain Why Cytokines Lead to Disease and Why Selection Did Not Prevent Deleterious Cytokine Effects

Cytokine storms are typically caused by phylogenetically very old cytokines [5]. This shows that these cytokines are evolutionary extremely successful since they have been conserved over evolution in very distant

species, suggesting that they have on average a positive effect on individual fitness. This does not mean that they promote the fitness of every single individual at all life stages, but on average, over the lifetime of all individuals carrying this trait. In some cases, they lead to disease and individual death and, thus, decrease this individual's fitness. Still, if for most individuals these cytokines have a fitness-increasing effect by shortening the duration of infectious disease and decreasing the risk of permanent damage or even death, then these cytokines will be positively selected.

In sum, the fact that phylogenetically very old cytokines can cause disease and death does not imply that this is part of their evolutionary function, as suggested by Besedovsky and Del Rey [5], who hypothesised that individuals are killed by cytokines for the benefit of the species to avoid them transferring pathogens to conspecifics. In contrast, as the strong cytokine response leads to significant fitness benefits in most cases, this trait did spread and is maintained even though in some cases it leads to fitness costs, which is particularly true as their deleterious effects occur mainly in older, post-reproductive individuals [55].

Conclusions and Recommendations

In his book *On the Origin of Species* Darwin described how we can understand the development of species (phylogeny) via natural selection [29]. Darwin already realised that not all traits evolved to increase survival. A peacock's tail most likely reduces his chances of survival (natural selection) but still increases his lifetime reproductive success by making him more attractive to females (sexual selection). Similarly, physiological traits exist that can lead to disease and death but still increase individual inclusive fitness.

In this review, we explained the differences between the phylogenetic and the functional approach in evolutionary medicine. We aimed to give medical researchers a comprehensive review on levels of selection in evolutionary biology, and we presented three short examples in the field of psychoneuroimmunology. Many other topics such as depression, suicide, obesity, cardiovascular disease, metabolic syndrome, autoimmunity would also benefit from being discussed from both a phylogenetic as well as evolutionary functional point of view.

In evolutionary medicine, we study why some physiological mechanisms lead to disease and as such reduced survival. Why did evolution not select against these physiological mechanisms or their deleterious side-

effects? One key insight here is that, in evolution, successful individuals are those that maximise the transmission of their genes, and health and survival are just strategies to have the opportunity to do so. Thus, a trait enabling survival of the individual until reproductive age will have better chances to spread even if at later age (or in a different environment), the same trait leads to disease and death, especially if this later age is at the end or after the reproductive phase of the individual [3, 12].

Evolutionary medicine is important for better understanding illness and health to improve human well-being. It is based on evolutionary theory, i.e., the algorithm that alleles spread whenever they increase individual fitness. Evolution has no aim but is an automatism. Evolutionary biologists realised a long time ago that evolution does not function for the benefit of the species [14]. One more recent and equally important insight from evolutionary medicine is that evolution is often not for the well-being of the individual human but instead increases human suffering if this allows fitness to increase [3]. Natural and sexual selection do not select for traits that benefit the health or happiness of the individual, but for traits that increase inclusive fitness even if this increases human suffering. In contrast to evolution, we humans do have aims, and our humane aim is to increase individual well-being, not to increase individual reproductive success [12]. Evolutionary medicine can help us achieve this aim against evolutionary constraints by investing resources (time, money, medicine) in fighting disease.

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Conflict of Interest Statement

Authors declare no competing interests.

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Author Contributions

C.S. wrote the first version and outline of the manuscript. A.V.J. and F.C. contributed to manuscript text and approved submission of the final version.

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