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The Darwinian concept of stress: benefits of allostasis and costs of allostatic load and the trade-offs in health and disease

S. Mechiel Korte[a,*], Jaap M. Koolhaas[b], John C. Wingfield[c], Bruce S. McEwen[d]

[a]*Animal Sciences Group, Wageningen University and Research Centre, Box 65, Edelhertweg 15, 8200 AB Lelystad, The Netherlands*
[b]*Department of Animal Physiology, University of Groningen, Box 14, 9750 AA Haren, The Netherlands*
[c]*Department of Zoology, Box 351800, University of Washington, Seattle, WA 98195, USA*
[d]*Harold and Margaret Milliken Hatch Laboratory of Neuroendocrinology, Rockefeller University, 1230 York Avenue, New York, NY 10021, USA*

Abstract

Why do we get the stress-related diseases we do? Why do some people have flare ups of autoimmune disease, whereas others suffer from melancholic depression during a stressful period in their life? In the present review possible explanations will be given by using different levels of analysis.

First, we explain in evolutionary terms why different organisms adopt different behavioral strategies to cope with stress. It has become clear that natural selection maintains a balance of different traits preserving genes for high aggression (*Hawks*) and low aggression (*Doves*) within a population. The existence of these personality types (Hawks–Doves) is widespread in the animal kingdom, not only between males and females but also within the same gender across species.

Second, proximate (causal) explanations are given for the different stress responses and how they work. Hawks and Doves differ in underlying physiology and these differences are associated with their respective behavioral strategies; for example, bold Hawks preferentially adopt the fight–flight response when establishing a new territory or defending an existing territory, while cautious Doves show the freeze–hide response to adapt to threats in their environment. Thus, adaptive processes that actively maintain stability through change (allostasis) depend on the personality type and the associated stress responses.

Third, we describe how the expression of the various stress responses can result in specific benefits to the organism.

Fourth, we discuss how the benefits of allostasis and the costs of adaptation (allostatic load) lead to different trade-offs in health and disease, thereby reinforcing a Darwinian concept of stress. Collectively, this provides some explanation of why individuals may differ in their vulnerability to different stress-related diseases and how this relates to the range of personality types, especially aggressive Hawks and non-aggressive Doves in a population.

A conceptual framework is presented showing that Hawks, due to inefficient management of mediators of allostasis, are more likely to be violent, to develop impulse control disorders, hypertension, cardiac arrhythmias, sudden death, atypical depression, chronic fatigue states and inflammation. In contrast, Doves, due to the greater release of mediators of allostasis (*surplus*), are more susceptible to anxiety disorders, metabolic syndromes, melancholic depression, psychotic states and infection.

Keywords: Stress; Allostasis; Allostatic state; Allostatic load; Coping; Evolutionary stable strategy; Hawks; Doves; Fight–flight; Freeze–hide; Darwin; Evolution; Natural selection; Brain; Amygdala; Hippocampus; Locus coeruleus; Prefrontal cortex; Atypical depression; Melancholic depression; Chronic fatigue; Psychosis; Rat; Birds; Human

* Corresponding author.
E-mail address: mechiel.korte@wur.nl (S.M. Korte).

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1. General introduction

Due to the pioneering work of Hans Selye [1], the use of the word '*Stress*' has become popular all over the world. However, despite the vast amount of scientific research generated in this field the term stress has been a stumbling block right from its first use. The term has so many different meanings [2] that it becomes counterproductive by inhibiting a proper application and critical interpretation of experimental results. Stress has mostly been associated with negative events and consequences, i.e. it can take its toll on physical and mental health. There is, however, no justification for the assumption that the expression of stress responses always compromise health and/or welfare. Indeed, the functional aspects of stress have been neglected too often. The paradox of stress lies in the simultaneity of its adaptive nature and its possible maladaptive consequences. A somewhat modified version of Marius Tausk's metaphor [3] of 'water used by firemen' can illuminate this paradox. Firemen may use water to extinguish certain fires or to prevent them. But if much water is used it can cause more damage than the flames. Another risk is that increased water

usage can lead to a loss of water pressure, thereby making efficient fire fighting impossible and contributing to the spread of the fire. Just like the fireman's water stress responses are ideally beneficial but they can impose a cost to the body, particularly when they are either elicited too often or are inefficiently managed [4]. Recently, a new stress concept has been developed. '*The concept of Allostasis*' [5–7] introduces new terminology that avoids the ambiguity of the word '*Stress*'. In this concept, allostasis is defined as the adaptive process for actively maintaining stability through change [8]. The brain plays a central role in allostasis. By controlling all the mechanisms simultaneously, the brain can enforce its command and incorporate influential factors such as experience, memories, anticipation, and re-evaluation of needs in anticipation of physiological requirements [9]. Allostasis is important during both unpredictable events, e.g. conflict in social hierarchies, competition for resources, storms and natural disasters, and predictable events, e.g. seasonal changes that trigger migration and hibernation. The central idea is that cost to the body arises if mediators of allostasis: adrenal hormones, neurotransmitters, or immuno-cytokines, etc. are released too often or if they are inefficiently managed [4,7]. That cost is referred to as '*Allostatic Load*' which can be described as the cumulative wear and tear.

It is well known that, dependent on the environment, some individuals are more vulnerable to stress-related disease than others. This implies that a certain environmental condition may differentially affect allostatic loads in different individuals. Charles Darwin [10] was the first to understand that animal populations consist of individuals that differ from one another in their adaptive qualities and limitations. Those individuals possessing a variation that confers some survival advantage in their natural habitat and allows them to live long enough to successfully reproduce are the ones that pass on their traits more frequently to the next generation. This process has come to be known as natural selection [10]. It is important to realize that natural selection exerts genetic benefits by maximizing reproductive success of the adapted organisms even at the expense of individual happiness, health and longevity [11–13]. Thus, individual health is not necessarily the primary goal. Without doubt, the balance between allostasis and allostatic load has been shaped in the course of evolution by trade-offs on the basis of costs and benefits that occur at different stages of the life cycle or that are affected by season, social status, sex, or environmental change.

In building a new conceptual framework it is important to consider different levels of analysis that can lead to complementary explanations [14,15].

First, we provide evolutionary explanations for the fact that different organisms adopt different behavioral strategies in order to cope with stressful events. We discuss the evolutionary significance of the stress response and the variation of responsiveness among individuals in their natural or ancestral environment.

Second, we give proximate (causal) explanations for the different stress responses and we describe how they work.

Third and fourth, we emphasise that stress research should consider a cost benefit analysis of the different behavioral and physiological stress responses. Such an analysis forms the basis of '*The Darwinian concept of stress*' since the '*benefits of allostasis*' and the '*costs of allostatic load*' produce trade-offs in health and disease. We discuss how different personalities, each with associated differences in underlying physiology and behavior, vary in their vulnerability to stress-related diseases.

2. Evolutionary explanations for individual variation in behavior

2.1. Theoretical considerations: evolutionary stable strategies

Why do organisms adopt different behavioral strategies for coping with stress? The question arises why variation is maintained in a population or why a population does not simply drift towards a homogeneous group of the most successful phenotypes. There is some theoretical support for the maintenance of individual variation within a population. For instance, Maynard Smith [16] applied '*Game Theory*' to animal behavior and found that natural selection tends to maintain a balance between different behavioral traits and strategies. The best example of such an evolutionary stable strategy is the '*Hawk–Dove game*' in which the aggressive individuals are the so-called '*Hawks*' and cooperative, relatively passive ones are the so-called '*Doves*' (see Table 1), even though they may be members of the same species. In a competitive situation the Hawk shows aggressive behavior, stopping only when injured or when the opponent submits. The Hawk generally wins the entire resource. A successful Hawk produces more and larger offspring than a hungry Dove but an unsuccessful Hawk may have lower fitness because of energy loss, wounds, blood loss and infection (Table 1).

When a Dove is faced by a Hawk that is likely to attack, the Dove retreats and thereby avoids incurring any cost. This strategy rests on the assumption that Doves are able to recognize Hawks. Different types of information gathering that may aid such discrimination have been described. Thus, eavesdropping may allow the assessment of the aggressiveness and fighting ability of potential opponents before any direct contest occurs [17,18]. Perception of visual (e.g. size, breast stripes or colors), acoustic (e.g. song or vibration) or chemical signals (pheromones) can also underlie discrimination [19]. When two Doves meet, they will equally share the resource without a fight and hence at low cost. Thus, from the perspective of controlling resources, both strategies may be successful. The existence of different behavioral strategies is a widespread phenomenon in the animal kingdom, not only between males and females, but

Table 1
The different gene–environment interactions in Hawks and Doves and the consequences for fitness depend heavily on their biological role in a population, the adopted behavioral strategy, the environmental context, food availability, and population cycle (see Sections 2.1–2.3)

	Hawk	Dove
Behavioral strategy	Fight–flight	Freeze–hide
Coping style	Proactive	Reactive
Emotional state	Aggressive and bold	Non-aggressive and cautious
Biological role	Establish territory or defend existing territory	Adopt strategy to avoid danger within territory, e.g. immobility
Exploration	Fast and superficial	Cautious and thorough
Behavioral flexibility	Rigid and routine-like	Flexible
Energy metabolism	High energy consumption	Energy conservation
Body damage (e.g. wounds, blood loss)	High risk	Low risk
Advantage according to food availability	When stable and abundant	During food scarcity
Advantage according to population cycle	When density is high	When density is low

also within the same gender across species. In the following paragraphs we provide (field) data of the Hawk and Dove strategy in birds and rodents showing that both strategies can be successful but under different environmental conditions.

2.2. Variation in behavioral strategies in birds (*Parus major*)

Field data, particularly in the great tit (*Parus major*) suggests that the Hawk–Dove strategy can be observed in birds, e.g. [20–23]. More specifically, juvenile males that quickly visit all trees and explore the environment in a superficial way are very aggressive (fast superficial explorers). In contrast, juvenile males that explore an environment more thoroughly (slow-explorers) are non-aggressive [20,21]. The fast-superficial explorers take greater risks in fighting (Hawks) and they approach novel objects faster than the slow-explorers (Doves) ([21,24]; Table 1). Recent field studies support the view that the two coping strategies have differential evolutionary fitness, measured in terms of survival, in years that vary according to food availability (Dingemanse et al. in press). The aggressive fast-superficial explorers are more likely to become founders of new populations because natal dispersal distance correlated positively with aggression and because immigrants were faster than residents [25]. Interestingly, the different traits underpinning these strategies (e.g. high versus low aggression, fight–flight versus freezing, superficial versus thorough exploration, rigid and routine-like versus flexible behavior) may not have evolved in isolation, but rather as a package due to pleiotropy, gene-linkage or co-selection [26].

Superficial fast-explorers (aggressive Hawks) may have an advantage in areas with high food availability and stable food distribution because they search for food in a routine way, concentrating their search mostly on usual and known items ([27]; Table 1). In contrast, when food is scarce, the non-aggressive slow-explorers have an advantage because they spend more time exploring the surroundings thoroughly. This difference was elegantly demonstrated when slow-explorers extended their search to many feeders whereas superficial fast-explorers kept going to a food bowl that has formerly contained food but that was now empty [21,24]. The slow-explorers (non-aggressive Doves) pay more attention to changes in their environment and thereby probably gain more detailed knowledge of it [21]. By thorough exploration, they learn where they can find water, food, shelter and opponents. Interestingly, superficial aggressive fast-explorers (Hawks) may profit from viewing the behavior of slow-explorers because they copied a trained tutor or even stole its food [27]. Hawk–Dove strategies also exist in mammals, like rodents, pigs and humans, as well as in birds [28–32].

2.3. Variation in behavioral strategies in rodents (*Mus musculus; Rattus norvegicus*)

Rodents are probably the best-studied species with respect to Hawk–Dove strategies [33,34]. When exposed to a large dominant conspecific, aggressive rats and mice (Hawks) show flight behavior while the non-aggressive ones (Doves) show freezing ([34]; Table 1). In addition, non-aggressive rats and mice show more freezing in response to sudden silence and in the defensive burying test, whereas the aggressive ones show more active behavior [34,35]. Further support for this dichotomy came from observations of the aggressive and non-aggressive mice in the forced swim test [36]. The aggressive mice continued to display escape behavior, more climbing and swimming, even when no escape was possible whereas the non-aggressive mice showed relatively passive floating behavior, which can be interpreted as very adaptive because it saves energy [37]. Surprisingly, wild-type rats showed no differences in learning tests, such as the 8-arm radial maze or the Morris water maze, nor in acute fear measured in the elevated plus-maze [34]. However, when tested for the second time in the elevated plus-maze, the non-aggressive individuals spent less time than aggressive ones in the open arms, suggesting they had higher anxiety levels [36,38].

Interestingly, the non-aggressive mice showed active defensive burying behavior when given sawdust from

their own home cages but they froze if fresh sawdust was used, i.e. reactive coping. The aggressive mice always showed burying behavior, i.e. proactive coping, regardless of the type of bedding material [35]. In line with these results, it has been suggested that aggressive individuals (Hawks) easily develop routines relatively independently of environmental stimuli (rigid behavior) whereas non-aggressive ones (Doves) are more perceptive of changes in their environment and consequently show more flexibility in their behavior [30,39,40].

Although female mice do not usually show territorial aggression, those of a high aggression selection line showed much more defensive burying than the females of the non-aggressive line, supporting the view that aggression is only one of a larger set of behavioral characteristics that make up the Hawk phenotype [30].

Field observations in wild house mice support the view that fitness varies between the different behavioral phenotypes according to environmental conditions. Thus, low aggressive male mice seem to be adapted to variable conditions such as those encountered during migration, whereas high aggressive male mice function better in stable environments [41].

Clearly, the above-mentioned benefits of being a Hawk or a Dove depend heavily on their biological role in a population, the adopted behavioral strategy, the environmental context, food availability, and population cycle. Hawks and Doves differ in emotional state, exploration rates and energy metabolism that make them more or less able to adapt to different environmental changes (Table 1). Therefore, it is not surprising that the different behavioral strategies require different underlying physiological mechanisms (see below). In the literature there is some confusion about the dichotomy of behavioral phenotypes [30] but clear bimodal distributions have been observed in feral rodent and bird populations [24,42]. Recently, three peaks in the frequency distribution of attack latency emerged above a certain age in a population of 2500 laboratory-bred adult male wild-type rats [30,34]. The existence of an intermediate group was explained by the fact that there is little or no natural selection pressure in the laboratory. In contrast, aggressive Hawk type individuals appear to be missing from Wistar rat populations, probably because these rats have been genetically selected for easy handling [34].

3. Proximate explanations for individual differences in physiology

3.1. Neuroendocrine differences between Hawks and Doves

In order to adapt to a changing environment Hawks and Doves not only differ in the type of behavioral responses shown, i.e. fight–flight versus freeze–hide, but also in their underlying physiology, neuroendocrinology (Table 2) and neurobiology (Table 3). We provide proximate (causal) explanations for the requirement for different stress responses and for how they exert their actions. First though, we list the differences in the physiological responses of Hawks and Doves (Sections 3.1 and 3.2). Much of our current thinking on variation in physiological responsivity is derived from the work of Jim Henry [43]. He suggested, on the basis of social conflict in mice, that two physiological response patterns may be distinguished. This model was further developed by Béla Bohus, Jaap Koolhaas and their colleagues [30,44].

Table 2
Differences between the neuroendocrine responses of Hawks and Doves to acute threat

	Hawk	Dove
HPG-output (testosterone)	High	Low
HPA-output (cortisol or corticosterone)	Low	High
Hypothalamus (CRF mRNA)	No response	High
Hippocampus (MR mRNA)	No response, except CA1↑	High
Hippocampus (GR mRNA)	No response	No response
Pituitary (ACTH as % of basal)	Low	High
Adrenal cortex sensitivity	Low	High
Neurosympathetic (NE)	High	Low
Adrenomedullary (E+NE)	High	Medium
Parasympathetic (heart rate variability)	Low	High

Definitions of acronyms: HPG, hypothalamic–pituitary–gonadal; HPA, hypothalamic–pituitary–adrenal; CRF, corticotropin-releasing factor; mRNA, messenger ribonucleic acid; GR, glucocorticoid receptor; MR, mineralocorticoid receptor; ACTH, adrenocorticotropic hormone; NE, norepinephrine; E, epinephrine.

Hawks show a fight–flight response originally described by Cannon [45]. This behavioral response is characterized by high activation of the sympathetic adrenal–medullar system. Sympathetic activation of the adrenal medulla results in high levels of epinephrine (E) in the blood, while nerve terminals release large quantities of norepinephrine (NE) into the synaptic cleft and consequently into the bloodstream ([46]; Table 2). Furthermore, during fight an activation of the hypothalamic–pituitary–gonadal (HPG) axis, as reflected by an increase in plasma testosterone, has been observed [47]. On the other hand, the freeze–hide response shown by Doves is characterized by the activation of the hypothalamic–pituitary–adrenal (HPA) axis. More specifically, the hypothalamus produces a neuropeptide locally in the brain called corticotropin-releasing factor (CRF) that, in turn, stimulates the pituitary gland to secrete adrenocorticotropic hormone (ACTH) into the blood. This stimulates the adrenal cortex to release corticosterone (in birds, rodents) or cortisol (in pigs, humans). Interestingly, it has been suggested that increased levels of corticosterone operating via hippocampal mineralorticoid receptors (MRs)

Table 3
Structural differences in the dorsal hippocampus of Hawks and Doves

	Hawk	Dove
5-HT_{1A} receptors (incl. mRNA)	High	Low
Activity of MAPK1 cascade	Low	High
Growth arrest specific 5 (GAS5)	High	Low
Cytoskeleton gene-expression	Low	High
Intra and infra-pyramidal mossy fiber terminal fields	Small	Large

Definitions of acronyms: 5-HT_{1A}, 5-hydroxytryptamine 1A; MAPK1, mitogen-activated protein kinase 1 pathway; mRNA, messenger ribonucleic acid.

induces fear-induced freezing behavior in rats [48]. There is mounting evidence that individuals that preferentially show the freeze–hide response are characterized by high parasympathetic reactivity [46,49]; this is particularly apparent at times of high attention during the orienting reflex that often precedes the freezing response [50]. Such individual differences in physiological traits have also been observed in fish, chickens, pigs and humans [28–32,51–53].

Differences at the brain level have also been observed in aggressive and non-aggressive male mice. For example, the level of MR mRNA in the CA1 of aggressive mice was significantly higher than baseline 24 h after forced swimming [54]. Furthermore, forced swimming significantly increased MR mRNA in all hippocampal regions (CA1, CA2, CA3 and dentate gyrus) of non-aggressive mice (Table 2). No effect of forced swimming was observed on GR mRNA expression [54].

Under baseline conditions, high aggressive mice showed a clear fluctuation in circulating corticosterone concentrations around the circadian peak with significantly higher levels than non-aggressive mice in the late night phase [54]. In the dark phase this difference disappeared [54] or even reversed [55]. No differences have been observed in mRNA expression of the hippocampal mineralocorticoid receptor (MR), the hippocampal glucocorticoid receptor (GR), or hypothalamic CRF between aggressive and non-aggressive mice under baseline conditions [54,56]. Independent of circadian rhythm, baseline plasma ACTH levels were always higher in the aggressive mice [54], suggesting that the adrenal cortex is less sensitive to ACTH in aggressive than non-aggressive mice. Furthermore, aggressive mice had higher prenatal HPG axis activity [57]. Under baseline conditions though, no differences in sympathetic and parasympathetic activity were observed between aggressive and non-aggressive rats [58].

In summary, Section 3.1 clearly shows that Hawks and Doves differ in their underlying neuroendocrinology. Hawks are characterized by high sympathetic reactivity and high HPG axis activity, and by low parasympathetic reactivity and low HPA axis reactivity. In contrast, Doves are characterized by low sympathetic reactivity and low HPG axis activity, but high parasympathetic reactivity and high HPA axis reactivity. It is well known that the hippocampus plays an important role in the regulation of these neuroendocrine responses, but the hippocampus is also involved in behavioral adaptation during and after stressful conditions. Therefore in Section 3.2 special attention is given to the structural neurobiological differences in the hippocampus of Hawks and Doves.

3.2. Structural differences in neurobiology in Hawks and Doves

The brain plays a central role in maintaining stability during times of change (allostasis). The structural differences, especially in the hippocampus (Table 3), between Hawks and Doves may enable their respective ways of coping, i.e. proactive and reactive. In agreement, high aggressive rats have greater 5-hydroxy-tryptamine (5-$HT)_{1A/1B}$ inhibitory autoreceptor function than non-aggressive ones [34,59]. Postsynaptically, both the number of 5-HT_{1A} receptors and the sensitivity of the 5-HT_{1A} receptor–effector system are increased in aggressive rodents [60–62]. This could well be a compensatory up-regulation induced by a lower basal 5-HT neurotransmission, which is in agreement with the '*serotonin deficiency hypothesis*' of aggression as a trait characteristic [62]. In contrast, aggressive behavior as a state characteristic shows the opposite relationship, during aggression 5-HT neuronal activity increases and the prevention of such activation inhibits the expression of aggressive behavior [60–62].

Other neurotransmitters may also be involved in aggression. For instance, high levels of vasopressin release (low storage levels) in the septum of high aggressive rats and mice are associated with high aggression [34], probably via the involvement of the vasopressin V1a/1b receptor [63,64]. There is some evidence that testosterone 'organizes' aggression during development or that it increases the likelihood of aggression in a certain context by stimulating vasopressin synthesis [65]. Higher impulsivity in aggressive animals may well be a consequence of lowered activity of the tonic 5-HT neurotransmitter system.

Differences in the dopaminergic system have also been observed in mice and rats. A relatively low dopaminergic reactivity of the nigrostriatal system has been reported in active coping (fleeing) rats whereas a relatively higher activity was apparent when reactive copers show freezing in an open-field test [66,67].

Remarkably, the non-aggressive mice are characterized by a better developed hippocampus (Table 3). Recently, in Ron de Kloet's laboratory [68,69] it has been shown that non-aggressive mice (Doves) showed a higher expression of cytoskeleton genes (e.g. alpha-tubulin, cofilin, dynamin) and signal transduction genes (calmodulin-related genes, MAPK1 or ERK2, raf-related oncogene, neurogranin), but lower gene expression of growth arrest specific gene (GAS5). Therefore, they speculated that in the non-aggressive mice an upregulation of the calmodulin related ras-raf-ERK2 pathway (MAPK1 cascade) might be related

to differences in the behavioral strategies of non-aggressive and high aggressive mice [68,69]. It is quite conceivable that the observed changes in expression of cytoskeleton genes may differentially influence neuronal outgrowth, morphology, and neural plasticity. In line with these findings larger hippocampal mossy fibers have been observed in the non-aggressive mice [70]. Previously, it was shown in mice that were bred for individual differences in two-way avoidance performance in a shuttle-box, that those showing freezing had more mossy fibers synapting on basal dendrites of hippocampal pyramidal neurons, whereas high avoidance mice (flight) were characterized by less extended intra and infra-pyramidal mossy fiber (IIP-MF) projections [71]. Therefore, it is hypothesized that the different behavioral strategies shown by Hawks and Doves, especially in behavioral flexibility, are related to the differences in their hippocampal morphology. Interestingly, the lower GAS5 expression throughout the entire brain of non-aggressive mice (Doves) suggests that morphological differences may also be present in other brain structures [68,69].

In summary, with their morphologically better developed hippocampus, it is suggested that Doves are very well able to organize contextual information and incoming sensory input (e.g. predator's appearance, location, smell and sound, avenues of escape, shelter, or storage of food) according to relevant relationships among them. However, the trade-off is a higher risk that Doves will develop anxiety disorders, because Doves are more aware of danger signals in their environment than are the bold Hawks.

3.3. The inverted U-shape curve of allostasis

Hippocampal functioning is highly dependant on the circulating levels of corticosteroids. In healthy animals there is a clear inverted-U relationship between allostasis and its mediators (e.g. corticosteroids). Interestingly this inverted-U relationship can also be observed for other mediators of allostasis (serotonin, cytokines, etc.) and its effects on emotional behavior, metabolism, immune system and cardiovascular system. Munck and colleagues [72,73] described a mechanism that may be relevant to allostasis in the periphery: opposing curves of 'mediator concentration' and 'receptor concentration' result in an inverted-U curve of glucocorticoid concentration and effect [73–75]. For example, glucocorticoids permissively enhance target tissue sensitivity to cytokine while simultaneously lowering the concentration of cytokine [73]. However, an inverted-U curve effect of glucocorticoid on the immune system can also result from a dose-dependent difference in the stimulation of mineralocorticoid receptors (MRs) and glucocorticoid receptors (GRs), because low corticosterone levels enhance T cell responses through MRs but suppress them at high concentrations through GRs [76].

The brain is also a target for mediators of allostasis (e.g. corticosteroids [77], testosterone, cytokines, central serotonin, central CRF, etc.). The presence of two receptor types (MRs and GRs) for corticosteroids, with a difference in neuroanatomical distribution and in affinity and binding capacity for corticosteroids, forms the basis of an inverted-U relationship between brain functioning and glucocorticoid concentrations [78,79]. In rodents, MRs have a high affinity for corticosterone and aldosterone and are almost saturated under basal conditions. In contrast, GRs have a 10-fold lower affinity for corticosterone than MRs and become occupied only during danger and at the circadian peak, when glucocorticoid levels are high [78,79]. Due to their lipophilic nature glucocorticoids readily enter the brain [80] and either bind to membrane receptors [81] or freely cross neuronal cell membranes to bind to specific cytoplasmatic receptors [77,82]. Through the latter mechanism, corticosteroids may lead to altered transcription of specific genes resulting in changes in protein synthesis and, consequently, in the regulation of enzymes, neurotransmitters and receptors [80,83]. In neurons, corticosteroids may bind to two dramatically different intracellular receptors, the mineralocorticoid receptor (MR) and the glucocorticoid receptor (GR) [78]. Interestingly, the MRs and GRs are co-located in those brain structures (limbic system) that are involved in the regulation of allostasis, such as hippocampus, septum, and amygdala [78,84]. GRs are widely expressed in the brain and the highest concentrations are found in most monoaminergic nuclei in the brainstem, cerebral cortex and in regions involved in feedback regulation of the HPA axis, for example hippocampus, paraventricular hypothalamus, and pituitary [78,85,86]. The numbers of MRs display a circadian rhythm whereas the GR system does not [87]. Therefore, it is postulated that in healthy organisms the hormone level mainly regulates GR action while MR action is influenced by receptor density.

The inverted U-shape curve of allostasis has been clearly demonstrated at the level of the hippocampus. The co-localization of both MRs and GRs in the hippocampus is at the basis of this phenomenon. Glucocorticoids have biphasic effects upon excitability of hippocampal neurons that may underlie their biphasic actions during the diurnal rhythm and after challenge and influence the magnitude of long-term potentiation (LTP), as well as producing long-term depression (LDP) [88–93]. It has been suggested that hippocampal cholinergic theta activity, a rhythmic, sinusoidal waveform that occurs in alert, immobile rats presented with threatening stimuli [94], is modulated by corticosterone acting through MRs and GRs, and the rapidity of the response suggests a non-genomic mechanism [94]. More precisely, MR blockade by spironolactone produced a marked decrease in theta amplitude whereas GR blockade by RU 38486 produced exactly the opposite response [95].

Other evidence for biphasic actions is observed when low to moderate levels of glucocorticoids enhance acquisition of tasks that involve the hippocampus, whereas high levels of glucocorticoids disrupt task acquisition [96–98].

The above mentioned biphasic actions can be explained by the following cellular mechanisms in the hippocampus: (a) under baseline conditions where mostly MRs but few GRs are activated they are associated with small Ca^{2+} currents, and stable responses to repeated stimulation of glutamatergic pathways and relatively small responses to biogenic amines. Activation of MRs, therefore, seems to guarantee a stable background of neuronal firing [79,99,100]; (b) activation of GRs in addition to MRs, as is seen, for example, after an aversive challenge, results in enhanced Ca^{2+} influx, and marked responses to biogenic amines, such as 5-HT-induced hyperpolarization [101–106]. Such activation, thus, seems to reduce cellular activity, which agrees with the feedback mode by which corticosteroids facilitate recovery [99]; (c) after aversive stimulation high glucocorticoid levels are able to replenish reduced serotonin levels in the terminals to quicken recovery. In agreement it has been reported that different challenges, e.g. foot shock, ether anesthesia, cold exposure and noise stress [107–110] or systemic corticosterone administration enhances 5-HT turnover in the hippocampus and medial amygdala in rats [111]. Corticosteroids via GRs [109,112], but not MRs [112], in the dorsal raphe nucleus increase extracellular 5-HT levels by enhancing the catalytic efficiency of tryptophan hydroxylase [113,114]. In agreement, the corticosteroid synthesis blocker reduces 5-HT release in the dorsal hippocampus [115]. Also, through another mechanism, corticosteroids acting via GRs in the dorsal raphe nucleus may restore 5-HT levels by functional desensitization of 5-HT_{1A} autoreceptors, resulting in increased electrophysiological activity of 5-HT neurons [116,117,118].

In summary, it can be concluded that in the course of normal diurnal variation, at the start of an active day, relatively low levels of corticosteroids exert permissive effects via MRs. Such a MR-activation brings the mediators of allostasis to peaks of readiness for the activities of the day, while via GRs they prevent the mediators of allostasis from overshooting [79]. As shown below corticosteroid actions depend highly on the environmental context and thereby play an important role in allostasis.

3.4. The benefits of allostasis

Before we go into detail about what role corticosteroids play in the benefits of allostasis in the emotional brain, in metabolism, in cardiovascular and immune system, it is important to realize that steroids do not regulate physiology or behavior, rather they mainly induce chemical changes in particular sets of cells or networks of neurons, making certain physiological and behavioral outcomes more likely in a certain context (natural environment) in time, as a result of the strengthening or weakening of particular cellular pathways [99,119–121]. Thereby, steroids may exert permissive, preparative, stimulating and suppressive actions [120].

3.4.1. Allostasis in relation to the animal's natural environment

In the laboratory, it has been shown that the effects of steroids highly depend on the environment, for example experimental elevation of circulating corticosterone levels in captive white-crowned sparrows (*Zonotrichia leucophrys*) resulted in decreased activity [122]. However, these same birds dramatically increased their perch hopping activity if food was also removed from their cages [122,123].

Although in the laboratory physiological differences related to animal behavior has received much attention, the question of how phenotypic flexibility of animals in their natural environment is reflected in neuroendocrine mechanisms is much less well understood. Such natural environments can be hostile due to unpredictable perturbation factors like food shortage and adverse weather, that may disrupt the current life history stage, e.g. breeding, migration [124–131]. It has been shown in free-living birds that the above mentioned labile perturbation factors trigger an emergency life history stage, which consists of the following major components [122,123].

1. Deactivation of the current life history stage
2. Active responses to the labile perturbation factors can be:
   (a) Movements away from the source of the labile perturbation factors ('leave-it' strategy).
   (b) If the individual remains it will seek a refuge ('take-it' strategy).
   (c) Seek a refuge first and then move away if conditions do not improve ('take-it' at first and then 'leave-it').
3. Mobilization of stored energy sources such as fat and protein to fuel the movement or to provide energy while sheltering in a refuge.
4. Continued movement until a suitable habitat is discovered or the perturbation passes followed by resumption of the normal life history stage.

As will be shown in several examples below, the hypothalamic–pituitary–adrenal (HPA) axis, plays a major role in this emergency life history stage via a rapid increase in corticosterone in order to maximize survival [126,129,131–136]. This emergency life history stage is temporary (hours to days) and, once the perturbation passes, the individual will return to its normal life history stage [129,130].

In breeding pied flycatchers (*Ficedula hypoleuca*), a slight increase in circulating corticosterone enhanced the frequency of parental feeding of young but greater increases led to decreased feeding of the nestlings and resultant high mortality [137]. Body weights of adults remained constant throughout this period. A further increase to very high levels of corticosterone resulted in abandonment of territories and nests and the death of all nestlings. The parents, however, increased their body weight, and probably their survival rate [137]. Breeding male white-crowned sparrows exposed to

severe storms in spring 1980 abandoned their nests and territories. Plasma levels of corticosterone three-fold higher than the normal baseline levels for that time of year [138, 139] and behavioral and physiological changes characteristic of the emergency life history stage were expressed [140].

The HPA axis is also involved in regulating the emergency life history stage outside the breeding season. Willow tits, (*Parus montanus*), in southwest Sweden form stable winter flocks with a dominance hierarchy consisting of two adults that previously bred in the territory and two to four unrelated juveniles [141–144]. Because the forest area can only host a limited number of winter flocks, competition among juveniles for membership in a flock is intense, even at the potential cost of becoming a subdominant individual. No willow tits survive the winter as solitary floaters [145,146]. Plasma levels of corticosterone were higher in dispersing juvenile willow tits than in those that had established themselves in a winter flock [146]. It is possible that a relatively slight increase in corticosterone secretion may be sufficient to trigger dispersal behavior thereby providing floaters with opportunities to find better feeding conditions and/or empty places in winter flocks. It is unlikely that elevated corticosterone levels reflected aggression among juveniles because this has never been found in territorial juveniles defending their flock status [146]. However, it cannot be excluded that elevated corticosterone in dispersing juvenile willow tits were due to the energy demands of the migratory flight. To address this, free-living willow tits were given corticosterone implants when juveniles were fighting to become established in a flock [125]. Corticosterone treatment resulted in restlessness associated with dispersal in the juvenile birds, but not in adults. Furthermore, most juveniles implanted with corticosterone disappeared from the forest whereas controls remained. Those juveniles that were treated with corticosterone and remained never actually settled in a territory, but kept wandering over the entire study area (several km^2). In contrast, adults implanted with corticosterone never left their territory. Although the latter observation may reflect prior residency of adults and dominance, mechanisms underpinning the juveniles' responses remain unknown [125].

It appears that patterns of corticosterone secretion may also be highly variable in social groups of other birds. In a wintering population of European blackbirds in southern Germany subdominant juveniles reacted to labile perturbation factors such as cold and snow, by increasing their corticosterone secretion whereas adults did not. Because juvenile blackbirds are subordinate to adults, they migrate away from the area [132] whereas willow tits are strictly year-round territorial residents and live in flocks with a strong hierarchy. Thus, it is highly likely that ecological and behavioral differences between species have resulted in differential responses of the HPA axis to adverse conditions.

It is important to bear in mind that the emergency life history stage (leave it strategy) should ideally be triggered while individuals have sufficient fat storage to fuel their flight to a more benign area. Indeed, in dark-eyed juncos, plasma levels of corticosterone were elevated when they abandoned home ranges and moved away from a storm [147], suggesting that hormones of the HPA axis are involved in the regulation of survival strategies. Plasma levels of corticosterone fell after the birds had found a refuge [147].

The great tit (*Parus major*), which is a tree foraging non-hoarding Northern European species, leaves the forests if the winter weather deteriorates and foraging sites become covered with snow or ice. A related species, the willow tit, hoards food as an emergency source and can therefore remain in its winter territories [148]. Similar endocrine data documenting the effects of severe winter weather have been obtained for European blackbirds and Harris' sparrows (*Zonotrichia querula*) [132,149]. Note, however, that Harris' sparrows did not leave their home range (leave-it strategy), but instead became inactive and waited for the storm to pass (take-it strategy).

There may be common endocrine responses to labile perturbation factors despite differences in taxa, distribution and habitat. Oceanic birds such as common diving petrels (*Pelecanoides urinatrix*) that forage in open ocean also showed increased corticosterone secretion in response to severe storms and changed their behavior consistent with an emergency life history stage, i.e. they flew to islands presumably to shelter (take it strategy) [134]. Collectively, the results of field studies and of controlled laboratory experiments indicate that glucocorticoids play a major role in the regulation of emergency life history stages. The biological function of an emergency life history stage is to increase survival to maximize reproductive success in the long-term. There is general agreement that natural selection has favoured the laying and fertilizing of eggs (read genes) rather than the health or welfare of the individual per se.

The most striking example can be observed in salmon [2] that migrate back upriver to the waters of their birth where they spawn the next generation. This trek is initiated by a rise in cortisol and can take up to 9 months [90]. When they begin their migration they stop feeding and the digestive tract atrophies. The newly available energy is used for migration and to optimize the structures involved in reproductive success. By the time they spawn, after laying and fertilizing the eggs, the high levels of cortisol have exhausted their stores of energy and devastated their immune systems [150,151]. The prolonged elevation of cortisol is the presumed cause of death but this fatal adaptive response enables the inception of the next generation of salmon.

In summary, the activation of the HPA axis in diverse hostile natural environments play a major role in the emergency life history stage via a rapid increase in corticosterone in order to maximize survival to maximize reproductive success in the long-term. Corticosteroids especially may be involved in triggering survival strategies,

such as moving away from a storm, dispersal and wandering in juveniles, and migration.

3.4.2. Allostasis and the emotional brain

In the laboratory in rodents it has been shown that corticosteroids act via the emotional brain to influence behavior. Here we start with the preparative action of corticosteroids. Prior to awakening an increase in corticosteroids stimulates exploratory behavior and food seeking [152–154]. In addition, MRs display a pronounced circadian rhythmicity peaking around feeding time [87]. Such an increase in MR function makes it possible that organisms can detect sensory signals at significantly lower levels, which may be functional because at feeding time many species are more vulnerable to predation [155–158]. There is a growing body of evidence that glucocorticoids via MRs play a critical role in mediating freezing behavior [48,121]. The freeze–hide strategy (e.g. in Doves) may be a very adaptive response when a predator or other source of danger is detected. All ongoing activities, such as feeding, drinking or exploration, are suppressed. Freezing behavior itself may reduce the likelihood of detection and attack from an aggressive animal or a predator. If caught, freezing behavior or a tonic immobility response may result in the predator or attacker losing interest and moving away. During freezing the animal remains very alert.

Early in life glucocorticoids (probably via GRs) can already exert developmental actions on the septo-hippocampal cholinergic system that may serve to assist in setting the tone of behavioral inhibition expression by modulating the individual's underlying levels of threat-induced arousal and attention to stimuli associated with threat [159,160]. Glucocorticoids via MRs may be involved in the process of evaluating the situation (including surroundings), and selecting an appropriate response through increased attention and the sensory integration of the relevant information [86,161].

Circulating glucocorticoids reach a peak some minutes after a dangerous event. There is a growing body of evidence that suggests that glucocorticoids via brain GR-mechanisms (especially hippocampal GRs) promote processes underlying contextual fear conditioning and fear potentiation, consolidation of acquired information, episodic, and spatial memory [86,121,161–168]. It is thought that the hippocampus organizes contextual information and incoming sensory input (e.g. predator's appearance, location, smell and sound) according to relevant relationships among them [167,168].

Glucocorticoids may also bind to GRs in noradrenergic cell bodies in the nucleus tractus solitarius (NTS) to potentiate norepinephrine release in the basolateral amygdala, as well as postsynaptically in the basolateral amygdala to facilitate the norepinephrine signal cascade [169,170]. The consolidation of such memories is helpful to predict the occurrence and nature of the next encounter and thereby maximize the likelihood of survival. Interestingly, besides glucocorticoids, catecholamines play also an important role in the formation of strong emotional memories. It has been reported that behavioral (muscle) activity is associated with higher norepinephrine levels, while emotional stimuli are more related to high epinephrine levels [171,172]. This epinephrine release may also be functional because epinephrine indirectly affects the brain to strengthen emotional memory. More precisely, epinephrine does not cross the blood–brain barrier but activates vagal afferents to the NTS. The NTS induces, indirectly via locus coeruleus (LC), directly the release of norepinephrine into the basolateral amygdala [169,170]. In agreement, it was shown that people remember a series of images better when they are told emotional details about them and epinephrine's memory-enhancing effect can be diminished by beta-adrenoceptor blockers [173,174].

During a second encounter, visiting the prior dangerous location, the animal's first reaction is conditioned freezing behavior, which is made possible by a permissive MR-action. Hippocampal MRs are already largely occupied at low levels of corticosteroids and enable, via a non-genomic action, the animal to freeze almost immediately after its perception of warning signals (e.g. mix of contextual stimuli such as smells, sounds or locations) previously associated with danger [121,168].

When the environment is safe (e.g. no predators present) extinction of passive avoidance, via a MR-mechanism [175] and extinction of active avoidance, probably via a brain GR-mechanism will take place [176]. However, when the situation remains unclear fear potentiation may take place via a GR mechanism [48,121].

Returning to the Hawks–Doves, the above mentioned findings fit with the observation that Doves, with a higher HPA axis reactivity and corticosteroid output, immediately freeze via a non-genomic MR-mechanism after warning signals that make them very alert to environmental changes. Without any doubt the hippocampus plays an important role in these corticosteroid-mediated effects. It is speculated that Hawks, with their higher HPG-axis activity but lower HPA axis activity, are more aggressive and bold but are less impressed by or less aware of environmental changes. Interestingly, the differences in HPA axis may also causally be related to high aggression in the Hawks at the start of the dark active period. The low corticosteroid levels in Hawks may produce high aggression because experimentally induced glucocorticoid hypofunction in rats increases aggression [177]. Especially, total MR occupancy at the beginning of the dark active period is a prerequisite for the expression of aggressiveness, because MR antagonists inhibit this type of aggressive behavior in rats [178,179]. Thus, these data suggest the binding of corticosteroids to MRs is a prerequisite for the stimulation of aggression, whereas GRs are involved in the suppression of high aggression.

Differences in HPG-axis reactivity and consequently testosterone levels may influence territorial aggression in

males during the breeding season, the correlation of plasma testosterone and aggression appears to be limited to periods of social instability when a male is challenged for his territory by another male, or when mate-guarding a sexually receptive female [180]. From songbirds it is reported that in the winter non-breeding season, when plasma testosterone is basal, exogenous dehydroepiandrosterone (DHEA) which is converted into active sex steroids by steroidogenic enzymes in the brain, increases male–male aggression and increases territorial song and the size of an associated brain region in a male songbird [181,182]. This is consistent with the hypothesis that DHEA increases territorial behavior.

In summary, it can be concluded that at the start of an active day, relatively low levels of corticosteroids stimulate exploratory behavior and food-seeking and exert permissive (tonic) effects via central MRs to facilitate aggression (Hawks) or induce freezing (Doves). During freezing, a MR action makes it possible that Doves can detect sensory signals at significantly lower levels, which may be functional because at feeding time they are more vulnerable to predation. Later during the day, at higher corticosteroid levels, suppressive actions via central GRs inhibit aggression. After detection of a predator or rival, high levels of corticosteroids via central GRs promote processes underlying contextual fear conditioning and fear potentiation, consolidation of acquired information, episodic, and spatial memory. Since GRs are widely distributed throughout the brain, including hypothalamus and brainstem nuclei, it is expected that energy metabolism is also affected.

3.4.3. Allostasis and energy metabolism

Glucocorticoids, so-named because of their ability to promote conversion of protein and lipids to usable carbohydrates, serve the body well in the short run by replenishing energy reserves after a period of activity, like running away from a predator. Thus, glucocorticoids play an important role in energy metabolism. Phasically activation of GRs in the hypothalamic paraventricular nucleus (PVN), arcuate nucleus or locus coeruleus (LC) is required for the natural surge in carbohydrate ingestion and metabolism that is essential at the onset of the active feeding cycle [183–185]. At this time-point glucocorticoid levels are high, the body's glycogen stores are at their nadir, and gluconeogenesis is needed to maintain blood glucose levels. During situations when food is unavailable or exploring for food is too dangerous, GR receptor activation may also cause the breakdown (catabolic) and utilization of body fat and protein to produce the essential carbohydrates [185]. In contrast, glucocorticoids via MRs located within the PVN tonically stimulate fat intake and fat deposition that occurs during most meals of the feeding cycle [185].

Storing food as abdominal fat is extremely functional. The stored fat can be used for migration, hybernation, during periods of starvation or it can be mobilized in females for breastfeeding. We still carry the so-called thrifty (or greedy) genes which enable fat storage when food is plentiful [186,187]. This can clearly be observed in Australian aborigines, some native Americans, Pima indians and other recently westernized populations. We still react to a psychological challenge with an increase in cortisol, which is followed by greater food consumption, especially of sweet things (carbohydrates) [188]. In normal rats glucocorticoid infusion favors anabolic processes, such as feeding behavior, body weight gain, and insulin output, while promoting muscle insulin resistance, probably via the parasympathetic system [189]. In principle, abdominal fat is a wonderful way of securely storing fuel for times of need. It is speculated that Doves, because of their higher HPA axis activity, more easily store fat (Table 2).

In summary, tonic activation via MRs (in PVN) stimulates fat intake and fat deposition during most meals of the feeding cycle, while phasic activation of GRs (e.g. in PVN) is required for the natural surge in carbohydrate ingestion and metabolism when the body's glycogen stores are low. During situations when food is unavailable, GR receptor activation causes the breakdown and utilization of body fat and protein to produce essential carbohydrates. Although fat deposition is an adaptive trait for hibernation or migration it can be a risk factor for cardiovascular disease in an overweight person (see Sections 4.2 and 4.3).

3.4.4. Allostasis and the cardiovascular system

Exploring for food, freezing to avoid detection, or showing fight or flight during a conflict are all behaviors that need their own specific autonomic changes that favour redistribution of blood to vascular beds. It is important to realize that complete behavioral strategies can be evoked by chemical stimulation of the midbrain, which is associated with specific autonomic changes favouring redistribution of blood to vascular beds with increased metabolic needs [190]. At least four different activation patterns can be distinguished.

First, the layers of the superior colliculus (SC) receive direct input from the retina and indirect input from the visual cortex, and they respond better to the movement (looming or fluttering) of a stimulus than its form [191,192]. The SC is functionally involved in the orienting reflex that is characterized by turning the head and eyes toward sudden changes in the environment to visually identify a potential threat or prey [193]. Orienting is often followed by freezing behavior and is associated with a relatively slower heart rate (bradycardia) and hypertension [194,195]. Interestingly, from the SC two different anatomical pathways have been identified, the ipsilateral tecto-cuneiform descending projection that is involved in freezing and fleeing behavior and the contralateral descending pathway that mediates contralateral movements that are involved in tracking or pursuit, sometimes in association with biting [192].

Second, stimulation rostrally within the dorsolateral periaqueductal grey (PAG) and lateral PAG evokes fight/confrontational defence associated with hypertension and tachycardia that is characterized by hind limb and renal

vasoconstriction, decreased blood flow to skeletal muscle and viscera, but increased extracranial blood flow to vasculature supplying skin and muscle of the oral–facial region [196].

Third, stimulation caudally within the dorsolateral PAG and lateral PAG evokes flight associated with hypertension and tachycardia that is characterized by hind limb vasodilatation with increased blood flow to the skeletal muscles, but extracranial and renal vasoconstriction with decreased blood flow to viscera and extracranial vasculature [196].

Fourth, stimulation ventrolaterally with the PAG evokes quiescence/immobility without orienting and is associated with hypotension and bradycardia. This conservation–withdrawal type of response, first described by Engel and Schmale in 1972 [197], is thought to support recovery and healing [196]. It is important to remember that freezing behavior reflects reactive coping [30], whereas conservation–withdrawal is a more passive coping style [197].

From the PAG and the cuneiform nucleus descending projections go to brainstem nuclei (e.g. vagal complex and adrenergic cell groups) where they regulate, respectively, parasympathetic and sympathetic activity to induce the necessary cardiovascular responses. The rostral (rVLM) and caudal ventrolateral medulla (cVLM) are especially involved in sympathetic activity [194,196]. According to Porges in 1995 [198] two vagal components have evolved in the brainstem to regulate parasympathetic functions. The phylogenetically old 'reptilian' part is the dorsal vagal complex (DVC), which consists of the nucleus tractus solitarius (NTS) and the dorsal motor nucleus of the vagus (DMNX). It was hypothesized that the DMNX-induced bradycardia may have evolved from an ancient gustatory response, i.e. the primary method for identifying prey and other food sources in aquatic environments [198–201]. In line with this hypothesis the DVC plays an important role in energy conservation, apnoea, sphincter relaxation and gastrointestinal activation. In mammals, however, bradycardia during orienting should be of short duration because of their high oxygen need. The phylogenetically younger 'mammalian' ventral vagal complex (VVC) consists of the nucleus ambiguus (NA) and nucleus retrofacial (NR). The VVC is involved in vocalization and in bronchial contraction in favour of high oxygen need and energy utilization. The VVC also provides a vagal brake that mammals combat instantaneously (as shown by increased heart rate and decreased heart rate variability) to increase metabolic output in favor of fight–flight [198–201].

There is accumulating evidence that Hawks adopting the fight–flight response are characterized by a shift to sympathetic dominance, while Doves often show the orienting reflex and freezing–hide responses associated with increased parasympathetic activity [30,44,202].

3.4.5. Allostasis and the immune system

The risk of being wounded is greater in Hawks because they are more aggressive and bolder than Doves. We have already shown that they differ in sympathetic and parasympathetic activation and glucocorticoid secretion, but how does this affect immune functioning? From an evolutionary viewpoint it is important to realize that the central nervous system, circulating adrenal hormones, behavioral processes and the immune system influence each other in ways that are central to the survival and well-being of the organism in its natural environment [203–209]. This was first recognized by Bob Ader in 1975, who showed that both an antibody response to antigen [210] and the immunosuppressive effects of a drug can be classically conditioned [211]. Now, we know that 'hard wiring' links exist between nerve fibers of both the sympathetic and the parasympathetic nervous system and the immune system. Sympathetic noradrenergic nerve fibers innervate the vasculature and parenchymal fields of lymphocytes and associated cells in several lymphoid organs, including the thymus, spleen, lymph nodes, gut-associated lymphoid tissue and bone marrow, in a variety of mammalian species [212]. However, the parasympathetic system, with its neurotransmitter acetylcholine, also innervates the immune system [213]. Perhaps the best known immune mediators, circulating glucocorticoids, have now been recognized as having biphasic effects upon immune function [208,209]. Remarkably, glucocorticoids may produce a Thelper1/Thelper2 (Th1/Th2) shift, from cellular towards humoral immunity because Th1-related cytokines (e.g. IL-2, IFN-gamma) stimulate cellular immunity Th2-related cytokines (e.g. IL-4) and enhance humoral immunity [205,214,215]. The Th1 response protects against infections (viruses, m. tuberculosis, etc.) and tumors, while the Th2 response protects against gastrointestinal parasites (e.g. helminths).

Communication in the other direction, i.e. from immune system to brain, also takes place. The immune system communicates with the brain via a neural and a humoral pathway [216]. Recently, it became clear that cytokine receptors also exist in the brain [217]. Previously, it was shown that interleukin-1 (IL-1), IL-6 and TNF stimulate HPA axis activity via an increase in CRF in the PVN [218,219]. Interestingly, the immune system also evokes changes in hypothalamic noradrenergic neurons and in hippocampal serotonergic neurons [220]. Finally, the brain itself can produce cytokines. Further, IL-1beta gene expression is increased in brain cells and is specifically related to hippocampal long-term potentiation (LTP), a process related to learning [221].

With the above mentioned findings it becomes much easier to understand why differences in immune responses between Hawks and Doves have been observed [222]. Due to their different behavioral strategies Hawks and Doves are confronted with different pathogens and Hawks are at greater risk of wounding because of their aggressiveness and boldness. It is speculated that increases in the levels of catecholamines in Hawks result in elevated leukocyte numbers in the blood, because it is known that catecholamines recruit the body's soldiers, especially NK cells

and granulocytes [205]. Thus, this enhanced trafficking of immune cells to places where they are needed to heal wounds and fight infections might be a very functional response in Hawks. Interestingly, humoral immunity (via Th2) was higher in Doves than in Hawks [222,223]. It is speculated that Doves, because of their high exploration in the search for new resources, incure a higher risk of infection by parasites in the food, than the Hawks. Therefore, from an evolutionary viewpoint a higher humoral immunity (e.g. IgE) in Doves, directed against parasites, can be seen as adaptive.

Previous experiments displayed consistent individual behavioral and physiological Hawk–Dove differences between aggressive-active and non-aggressive-passive pigs [222–224]. The Hawks responded with a cell-mediated immune activity, especially the Th1 response to non-specific and specific antigens [222,223], and a higher natural killer (NK) cell activity [225]. However, after aversive stimulation, cellular mediated immunity was reduced to a greater degree in the Hawk than Dove pigs [222]. This can be explained as follows: catecholamines drive a Th2 shift at the level of both antigen presenting cells (APCs) and Th1 cells (via beta2-adrenergic receptors, which are not present on Th2 cells) [214]. Furthermore, glucocorticoids act through their GRs on APCs to suppress the production of the main inducer of Th1, IL-12 [214]. Thus, such mechanisms may be involved in the prevention of a cellular mediated immune overshoot. A shift from Th1 to Th2 may counter the tissue-damaging effects of macrophages and Th1 cells.

Both Doves and Hawks respond to inescapable threat with HPA axis activation resulting in the release of glucocorticoids that, in turn, induce a decrease in circulating leukocytes. The specific GR agonist RU38362 caused a rapid decrease in blood lymphocytes, monocytes and NK cell numbers whereas a MR agonist failed to do so, suggesting that glucocorticoids via GRs are involved in the decrease in leukocytes [226,227]. This is not due to immunosuppression, a widely spread dogma, but rather to the redistribution of leukocytes, i.e. leukocytes exit from the blood and take position at potential 'battle stations', such as skin, lymph nodes, etc. [206]. Once immune cells have begun to enter the tissue, other factors become involved as local mediators of further activation of immune function. For instance, IFN-gamma is known to induce expression of antigen-presenting and cell-adhesion molecules on endothelial cells and macrophages and cell adhesion molecules on leukocytes. It is also significant that glucocorticoids induce IFN-gamma receptors on monocytes [207]. Thus, after perception of an acute threat, release of the above-mentioned mediators of allostasis prepare an organism for potential immunologic challenges (i.e. wound or infection inflicted by attacker). It is thought that peripherally released cytokines act on the brain via a fast transmission pathway involving primary afferent nerves innervating the bodily site of inflammation and a slow transmission pathway involving cytokines originating from the choroid plexus and circumventricular organs and diffusing into the brain parenchyma by volume transmission [216,228]. It is well accepted that cytokines may produce '*sickness behavior*', which is not a maladaptive response, but rather an organized, evolved behavioral strategy to facilitate the role of fever in combating viral and bacterial infections [229]. It is thought that immune overstimulation, which may lead to septic shock, can be prevented through the vagus nerve pathway, also named '*cholinergic anti-inflammatory pathway*'. Via this parasympathetic route rapid inhibition of release of the macrophage TNF, IL-1beta, IL-6 and IL-18 takes place [230–232].

In summary, the Th1 dominated cellular immune response of Hawks and the Th2 dominated humoral immune response of Doves are very adaptive and biologically sensible because Hawks are at greater risk of wounds and infections during fighting, while Doves with their exploratory nature and greater intake of new resources are more likely to be contaminated with parasites. However, a shift towards Th1 can also incur other disadvantages and costs to the body such as autoimmune disease, whereas a shift towards Th2 is known to increase vulnerability to viruses. Now that we have discussed one side of the coin, '*the benefits of allostasis*', we will continue with the flip side, '*the costs of allostatic load*', because together they produce trade-offs in health and disease. We will discuss how different personalities, such as the aggressive Hawk and the non-aggressive Dove, each with associated differences in underlying physiology and behavior, differ in their allostatic load and vulnerability to stress-related diseases.

4. The costs of allostatic load

4.1. Allostatic state, allostatic load and the emotional brain

Mediators of allostasis (e.g. adrenal hormones, neurotransmitters, and immuno-cytokines) act on receptors in various tissues and organs to produce effects that are adaptive in the short term but that can produce an allostatic state which may be damaging if the mediators are not shut off. Allostatic state refers to a state of chronic deviation of the regulatory system from its normal mean operating level [9]. As a result, the effects of the different mediators on target cells are prolonged and may produce receptor changes [233,234]. Four types of allostatic states leading to allostatic load have been identified: (a) repeated challenges; (b) failure to habituate with repeated challenges; (c) failure to shut off the response after the challenge is over; and (d) failure to mount an adequate response [7,234]. All changes are not necessarily irreversible; an increasing amount of data suggest that the body and the brain have a huge capacity for adaptive plasticity. Below it will be shown that social conflicts between males, involving high aggression and threat (psychosocial conflicts), produce both an

allostatic state and allostatic load. The costs for the aggressors (Hawks) and victims/losers tested under semi-laboratory conditions, without the possibility of escape, are quite different.

4.1.1. Aggression, anti-social behavior and violence

Several hormones are involved in the expression of aggression. It is speculated that Hawks, with their higher HPG-axis activity but lower HPA axis activity, are more aggressive and bold but are less influenced by or less aware of environmental changes than Doves. It is noteworthy that testosterone does not cause aggression, it simply exaggerates the pre-existing pattern and response to environmental triggers of aggression [235]. Prolonged high levels of circulating testosterone and low levels of corticosteroids may incur costs that can potentially reduce lifetime fitness, e.g. exposure to predators, increased risk of injury, loss of fat stores and possibly altered immune system function [236]. However, Hawks with their higher testosterone levels have an advantage when food is stable and abundant; consequently they produce more offspring. Accordingly, it has been shown in a population of mice, that males with high testosterone outnumbered those with lower levels , but that eventually the presence of too many aggressive mice resulted in a collapse of the population [41]. In humans, especially male offenders, plasma testosterone correlated positively with aggressive acts, whereas the 5-HT function was inversely correlated with impulsivity [237]. Several animal studies suggest the involvement of tonic low 5-HT neurotransmitter levels in aggression. For example, chronic anabolic–androgenic steroid treatment during adolescence facilitated offensive aggression in male hamsters, probably via significant reductions in the number of 5-HT immunoreactive varicosities and fibers in anterior hypothalamus, ventrolateral hypothalamus and medial amygdala [238]. Conversely, loss of serotonin reuptake function in 5-HT transporter knock-out mice causes reduced clearance of extracellular 5-HT causing reduced aggression, increased anxiety-like behaviors, and exaggerated hormonal responses [239]. Thus, increased tonic 5-HT neurotransmission may have contributed to reduced aggression in these knock-outs [240].

Interestingly, lower corticosteroid levels may be causally related to high aggression in Hawks because at the start of the dark active period experimentally induced glucocorticoid hypofunction in rats increased aggression [179,241]. Decreased threat (attack signalling) and dramatically increased targeting of attacks towards vulnerable parts of the opponent's body (mainly the head) were observed under these conditions [241]. Thus, it is speculated that total MR occupancy at the beginning of the active period, with low GR occupancy, is a prerequisite for the expression of violence [177–179]. In agreement, increased aggressive behavior in adolescent boys with low resting cortisol may be strongly associated with lack of self-control [242]. Decreased morning cortisol levels also appear to be most strongly associated with antisocial behavior in girls [243]. In addition to cortisol, the hormone dehydroepiandrosterone (DHEA) may also be involved. In prepubertal boys suffering from severe aggression and antisocial behavior, DHEA levels were significantly positively correlated with the intensity of aggression [244].

In summary, in Hawks low corticosteroid levels, high DHEA and testosterone levels may be risk factors for high aggression, anti-social behavior and violence. Low tonic 5-HT neurotransmission may lessen anxiety and increase impulsivity thereby worsening the situation. Confrontations with such aggressors are a source of allostatic load in the opponents and the victims of violence.

4.1.2. Psychosocial challenge in mice

Exposure to high levels of aggression, threat and/or violence (psychosocial conflict or defeat) produces an allostatic state in numerous species. The individual's personality, for example Dove or Hawk, has a major impact. For example, non-aggressive mice showed a significant and much stronger corticosterone release and body weight reduction than aggressive mice after sensory contact with aggressive opponent for 5 and 25 days [245,246]. Furthermore, the depressed seminal vesicle weight after psychosocial challenge in the non-aggressive mice (Table 4) suggests a lowered testosterone action on target cells [245–247]. The non-aggressive mice also had lower thymus weights, lower MR mRNA expression and less 5-HT_{1A} binding in hippocampal CA1 ([245,246]; Table 4). Interestingly, GR mRNA was increased in the dentate gyrus of non-aggressive mice after sensory contact with an aggressive opponent for 5 days. Importantly, the aggressive mice showed no such neuroendocrine effects [245,246]. In addition, chronic sensory contact with an aggressive opponent for 25 days induced a decrease in hippocampal gene-expression in conserved helix–loop–helix ubiquitous kinase (CHUK) in the dentate gyrus (DG) of non-aggressive mice [248]. CHUK is a kinase that is involved in the translocation of NFκB to the nucleus [249]. Moreover, several genes belonging to ras-family members and members of the Bcl-2 family are down-regulated in these non-aggressive mice [248]. These findings suggest that NFκB signalling is downregulated; NFκB plays a crucial role in neuronal survival and synaptic plasticity [250–252].

In summary, aggressive mice do not respond to sensory contact with another aggressive animal, whereas non-aggressive ones do! This is consistent with the notion that non-aggressive Doves are much more aware of danger in their environment than bold Hawks (see also Table 1). Thus, Doves are more responsive to threats, which in turn have deleterious consequences, including decreased hippocampal NFκB signaling and the resultant increase in neuronal vulnerability.

4.1.3. Psychosocial defeat in isolated rats

It is becoming increasingly noticeable that it is primarily Doves that are used in social defeat experiments because

Table 4
Psychosocial challenges in various animal models produce an allostatic state reflected by temporal changes in hormone levels, neurotransmitters, receptor numbers, etc

Sensory contact with dominant in non-aggressive mice		5 days		25 days
Plasma corticosterone levels in mice		↑		↑
Testosterone action on target cells		↓		n.m.
5-HT_{1A} receptor or mRNA in CA1		↓		↓
MR mRNA in CA1		↔		↓
GR mRNA in DG		↑		↔
NFκB signal transduction pathway genes		n.m.		↓
Psychosocial defeat in isolated non-aggressive rats	1 day	7 days		21 days
Sensitivity of the postsynaptic 5-HT_{1A} receptor–effector system	↓	n.m.		↓
5-HT_{1A} receptor or mRNA in hippocampus	↔	n.m.		n.m.
MR receptors in hippocampus and septum	n.m.	↔		↓
GR receptors in hippocampus and hypothalamus	n.m.	↓		↔
Feedback resistance	n.m.	↓		↓
Psychosocial challenge in the visible burrow system with rats			14 days	
Plasma corticosterone levels in dominants and subordinates			↑	
Plasma CBG levels in subordinates			↓	
Plasma testosterone levels in subordinates			↓	
5-HT_{1A} receptor in DG and CA1 in dominants and subordinates			↓	
5-HT_2 receptor in layer IV of parietal cortex in subordinates 5-HTT expression in CA3 in dominants and subordinates			↑	
CA3 dendritic remodeling in dominants and subordinates			↓	
MR mRNA and GR mRNA in CA1 in subordinates			↑	
Tyrosine hydroxylase mRNA and protein in LC in subordinates			↓	
CRF mRNA in PVN in the hypothalamus in subordinates			↑	
CRF mRNA in CeA in subordinates			↑	
Psychosocial challenge in tree shrews	2 days		10 days	28 days
Plasma cortisol levels	↑		↑	↑
Testosterone action on target cells (55 days*)	n.m.		n.m.	↓*
5-HT_{1A} receptor in DG, CA1 and parietal cortex	↔		↔	↓
CRF receptors in anterior lobe of the pituitary, DG, CA1–CA3, SC	n.m.		n.m.	↓
CRF receptors in frontal cortex, cingulate cortex, CeA, LA	n.m.		n.m.	↑
MR mRNA in CA1, CA3, dentate gyrus: posterior part of hippocampus	n.m.		n.m.	↑
MR mRNA in CA1, CA3, dentate gyrus: anterior part of hippocampus:	n.m.		n.m.	↓
GR mRNA in CA1 and CA3	n.m.		↓	↓
GR mRNA in dentate gyrus	n.m.		↔	↓
$Alpha_2$-adrenoceptor in LC	↓		↓	↓
$Alpha_2$-adrenoceptor in prefrontal cortex	↔		↓	↑
CA3 dendritic remodelling	n.m.		n.m.	↑
Neurogenesis in DG	n.m.		n.m.	↓
Hippocampal volume	n.m.		n.m.	↓

Definitions of acronyms: CeA, central nucleus of the amygdala; LA, lateral amygdala; LC, locus coeruleus; DG, dentate gyrus; CA1, cornu ammonis 1 (both DG and CA1) are part of the hippocampus; PVN, paraventricular nucleus of the hypothalamus; MR, mineralocorticoid receptor; GR, glucocorticoid receptor; CBG, corticosterone binding factor; SC, superior colliculus. ↑, increase; ↓, decrease; ↔, no difference; n.m., not measured.

the aggressive Hawk type personality is missing from the Wistar populations prevalent in such studies [34]. This might explain why similar responses are observed in non-aggressive mice and in Wistar rats [34]. For example, in defeated rats, plasma testosterone levels were decreased for several days [47]. GR-binding was also decreased in the hippocampus and hypothalamus 1 week after social defeat though no changes were observed in GR-binding in the pituitary or in MR-binding in any of the regions analysed [253]. Three weeks after defeat, GR-binding recovered in the hippocampus and hypothalamus, but MR-binding in septal and hippocampal tissue was markedly decreased [253]. Furthermore, the ACTH response to CRF following dexamethasone was significantly higher in defeated rats than controls at both 1 and 3 weeks after defeat, suggesting the development of feedback resistance in the defeated animals [253]. Additionally, decreased HPA axis activity after 5-HT_{1A} receptor challenge was observed 24 h after defeat, reflecting subsensitivity of the 5-HT_{1A} receptor–effector system [254]. In addition, rats that had been defeated once showed a gradual increase in immobility over a period of 3 weeks in response to sudden silence. Chronic treatment with the antidepressant clomipramine abolished the long-term behavioral effects of social defeat [255]. Recently, an attenuated induction of hippocampal CA1 long-term potentiation (LTP) was observed after social defeat that lasted for more than 3 months [256] (For more details see Dr Bauke Buwalda's chapter elsewhere in this

issue). Remarkably, when familiar rats are housed together several of the effects of social defeat are greatly reduced, suggesting that social support can alleviate its negative consequences [257]. In other more complex social models such as the visible burrow system the animals' social status, (dominant or subordinate), can have different consequences.

4.1.4. Psychosocial challenge in the visible burrow system with rats

The advantage of the visible burrow system as a social conflict model is that an unstable social hierarchy can produce different allostatic states depending on the social status of the animal [258]. In this model five males and two females are placed in an apparatus that has an open chamber connecting with tunnels and compartments. A male usually becomes dominant after some days and then controls access to the food and water cups and to the females. The most striking effects have been observed in the subordinates, including progressive weight loss; strong thymic involution; decreases in corticosterone binding globulin (CBG); testosterone, insulin and glucose, whereas both subordinates and dominants showed elevated plasma corticosterone levels; adrenal hypertrophy and thymic involution [259,260]. Furthermore, hippocampal 5-HT concentrations were increased in subordinate rats [261]. Both subordinates and dominants showed increased CA3 dendritic remodeling; decreased 5-HT_{1A} receptors in the hippocampus and increased CRF mRNA in the PVN of the hypothalamus. At the hippocampal level the dominants showed somewhat more dendritic remodeling and somewhat greater down-regulation of 5-HT transporter (5-HTT) in the hippocampus [262], whereas subordinates also showed increased tyrosine hydroxylase mRNA and protein in the LC; increased 5-HT_{2A} receptor binding in layer IV of parietal cortex; downregulation of MR mRNA and GR mRNA in hippocampal CA1 and increased CRF mRNA in the CeA ([259,260,262]; Table 4). Thus, an unstable hierarchy produces robust changes in allostatic state depending on the social status of the animal. Remarkably, subordinate males sometimes die within 2 weeks of being exposed to such an unstable social system [263].

4.1.5. Psychosocial conflict in tree shrews

Psychosocial conflict also elicits very robust changes in allostatic state in primates, such as the tree shrew. Tree shrews are very social animals and psychosocial conflict in a resident–intruder paradigm produces dramatic effects [264,265]. For instance plasma cortisol levels were chronically elevated in the intruder and hippocampal 5-HT concentrations were increased during conflict [265,266]. The 5-HT_{1A} receptor system reacts relatively slowly as shown by the decreased number of hippocampal and cortex 5-HT_{1A} receptors. Also, hippocampal GR expression is down-regulated 12 days after chronic social conflict [267]. The numbers of CRF binding sites are reduced in the anterior lobe of the pituitary, the dentate gyrus, the CA1–CA3 areas of the hippocampus, and in both the stratum griseum superficiale and the stratum opticum of the superior colliculus, while CRF binding sites are increased in the frontal cortex, cingulate cortex, claustrocortex, CeA and the lateral nucleus of amygdala 24 days after psychosocial conflict [268]. It has been suggested that high local concentrations of norepinephrine (NE), released from terminals originating from the locus coeruleus (LC), transiently down-regulated beta 1-adrenoceptors after 2 days of psychosocial conflict in the prefrontal cortex and the olfactory area but that they were decreased after 28 days of conflict in the parietal cortex and the hippocampus, while apha2-adrenoceptors in the prefrontal cortex were transiently downregulated after 10 days then upregulated after 28 days [269]. These results indicate that the noradrenergic system adapts to social conflict by counterbalancing its receptor numbers relatively rapidly.

Repeated exposure of tree shrews to psychosocial conflict for 28 days also induced remodelling of dendrites of CA3 neurons, which could be prevented by daily treatment of the intruders with phenytoin, a drug that blocks the actions of excitatory amino acids [270]. Chronic exposure to conflict also resulted in a more substantial inhibition of neurogenesis in tree shrews than did a single acute encounter [271,272]; moreover, the dentate gyrus was much smaller in the chronically exposed tree shrew and hippocampal volume was reduced [273,274]. Such reduction in neurogenesis can be prevented by daily treatment with the antidepressants tianeptine [273] or clomipramine [274]. Recently, it was reported that the tianeptine reduced apoptosis (probably of non-neuronal cells) in the temporal cortex and dentate gyrus [275]. Furthermore, anhedonia and reductions in exploratory activity are prevented by treatment with antidepressants [276].

In summary, social challenges can produce an allostatic state as observed by the changes ranging from hours to days or weeks (Table 4). The temporal dynamics of these changes may be very important in order to understand where the fine line lies between the benefits of allostasis (adaptation) and the potential costs of this adaptation (allostatic load).

4.1.6. Temporal dynamics

It is possible to suggest a sequence of changes in the production of the allostatic state and allostatic load after a social challenge. First, activation of the HPA axis, leading to increased plasma corticosteroid levels, may negatively affect gonadal function. As a consequence testosterone secretion is significantly lowered in the (psychologically) defeated individuals. Similar decreases in testosterone levels have been observed in human patients [277] and primates [278]. Decreases in testosterone concentrations may be responsible for a general decrease in activity and motivation, often associated with low self-esteem. The global situation in which an organism is best off withdrawing and decreasing its effort is one in which that effort would be wasted or would make a situation worse.

A confrontation with a dominant is wasted effort that is likely to result in injury [279,280]. Thus, depressive-like feelings (and low self-esteem) are part of a normal defense [12]. There is some evidence that Doves more readily show decreases in testosterone concentrations than Hawks. For instance, high ranking male (by reproductive criteria) wild olive baboons show a transient increase in testosterone concentrations in the first hour after rapid capture and immobilization, probably because of the high sympathetic activity in these males and their lesser sensitivity to the suppressive effects of glucocorticoids. In contrast, low ranking males show a continuous decline in testosterone levels [278].

4.1.7. Altered MR–GR balance in the limbic system

Social conflict-induced HPA axis stimulation may also produce dramatic differences in central MR–GR balance (Table 4). These observations agree with earlier findings that MRs rather than GRs are reduced in number when corticosteroid levels are elevated [281,282]. It has been shown that glucocorticoid downregulation of the GR requires extensive and prolonged exposure to extremely high levels of corticosteroids [283]. In contrast, MR may rather easily tonically inhibit GR biosynthesis in dorsal hippocampus [282] by way of binding to glucocorticoid response elements present in the GR promotor region [284]. Thus, as a consequence of downregulation of the MRs after a dangerous encounter GR numbers may increase. The initial MR downregulation and GR upregulation may be functional. Corticosteroids via MRs prime the different elements of allostasis, and bring it to peaks of readiness for action (e.g. increased orientation and freezing, lower sensory detection thresholds, higher alertness), which is no longer of use after the threat has disappeared [121]. The role of GRs is especially important after a dangerous encounter. There is a growing body of evidence that glucocorticoids via hippocampal GRs promote the organization of incoming sensory information (e.g. predator's appearance, location, smell and sound) according to relevant relationships among them [86,121,167,285–287]. The benefit of a more active hippocampus is an increased survival because a second confrontation may be anticipated. There are costs of such an adaptation: a reduction in the population of MRs presents a risk of reduced fear-extinction, whereas elevated numbers of GRs may increase contextual fear conditioning and fear potentiation as well as strenghtened consolidation of traumatic memories, thereby, making the organism vulnerable to the development of psychopathologies [121]. In agreement, it has been shown that the time course of antidepressant actions on corticosteroid receptors closely follows that shown by clinical signs of reduced depression [288,289], and antiglucocorticoid therapy (e.g. metyrapone, RU38486) appears to be an effective tool in the treatment of major depression [290,291, 292–295], especially when it is associated with psychotic features [296–298].

4.1.8. Increased CRF mRNA expression in the amygdala

The above mentioned disturbances in MR–GR balance, especially the downregulated MRs which were observed in all animal models shown here (Table 4), occur at the beginning of a cascade of events that ultimately connect anxiety with depression. The psychopathology may develop as follows: a decrease in central MRs (and GRs) may result, respectively, in elevated baseline plasma corticosteroid levels (due to decreased MR function) and prolonged increases corticosteroid levels after exposure to threat (due to decreased GR function: feedback resistance) [299]. Such feedback resistance was also observed in defeated isolated rats. As a consequence, the chronically elevated corticosteroid levels affect the central amygdala (CeA). Indeed, corticosterone implants (for 7 days) led to increases in both the basal level of CRF mRNA per neuron and the number of neurons with CRF hybridization signal in the CeA, which produced a concomitant enhanced anxiety state in the elevated plus-maze [300,301]. In agreement, that stereotaxic delivery of corticosterone to the CeA elicited fear-potentiation in the elevated plus-maze as well as colonic hypersensitivity, probably via descending neuronal pathways from the CeA [302]. Rapid increases in CRF mRNA levels have also been observed in the rostral CeA region after acute restraint [303,304]. These findings support the idea that chronic elevation of glucocorticoids may increase anxiety by inducing CRF expression in the amygdala. A large body of evidence indicates that high levels of corticosteroids can facilitate the expression of CRF mRNA in the CeA, in the lateral part of the bed nucleus of the stria terminalis (BNST), and in the hypothalamic paraventricular nucleus (PVN) [305–312]. These effects are in agreement with the observed increased concentrations of CRF mRNA in the PVN and CeA of subordinate rats in the visible burrow system ([259,260,262]; Table 4). There is general agreement that CRF, via its CRF_1 receptors in the amygdala [313], is involved in the regulation of fear, anxiety and depressed mood [313,314]. Further, elevated concentrations of cerebrospinalfluid CRF-like immunoreactivity have been observed in depressed patients [315]. It has been suggested that activation of the CeA mediates stimulus-specific (e.g. lights, tones, touch) fears, whereas somewhat less explicit information, such as that produced by exposure to a threatening environment for several minutes, may activate the BNST [316]. Because the nature of this information may be less specific than that produced by an explicit cue, as well as of much longer duration, activation of the BNST may be more akin to anxiety than to fear [316,317]. Remarkably, in circumstances where attentional resources are limited, or even in the absence of attention, processing of emotional stimuli in the amygdala proceeds [318,319]. Thus, a corticosteroid-induced CRF mRNA increase in BNST and in CeA can produce an allostatic state of enhanced anxiety and fear, respectively [121,320,321]. This phenomenon might again increase the likelihood of

survival because the animal may respond earlier with fleeing or freezing/hiding. In agreement, monkeys with high cortisol levels showed longer durations of freezing when exposed to frightening stimuli than those with lower levels [322]. Similarly, shy children showed relatively high morning levels of salivary cortisol and were more behaviorally inhibited [323,324]. Remarkably, it has been reported that adults who had been categorized as inhibited infants showed greater functional MRI signal response within the amygdala to novel versus familiar faces than did uninhibited controls [325]. Additional support comes from the finding that in rats high (but not low) doses of corticosterone potentiated freezing to an explicit auditory cue that had been previously been paired with footshock [163]. However, the costs of an enhanced state of fear and anxiety make the organism more vulnerable to the development of psychopathology. For example, chronic elevation of central CRF levels produced a depressive-like state [326], HPA axis dysregulation ([327] and autonomic activation [328]). Accordingly, depressed patients have left amygdala hyperactivity, even when processing stimuli outwith conscious awareness, and this increased amygdala activation is normalized with antidepressant treatment [329]. Interestingly, glucose metabolism in the left amygdala of depressive patients correlates positively with cortisol levels [330]. Also, the larger amygdala volumes in patients with first-episode depression suggest that a hyperactive amygdala is one of the first steps in the psychopathological cascade [331,332]. Sustained (left) amygdala activity is observed in depressed individuals [329,333,334] and may be due to higher neuronal amygdala activity and blood flow [333]. Because the amygdala integrates information related to fear and strong emotions and also sends outputs via the CeA for autonomic arousal and via the basal nucleus for more active aspects of coping [168], the elevation of amygdala activity may be a first step that leads to overactivation of systems involved in physiological and behavioral coping. Recent findings suggest that the amygdala has a pivotal role in negative affect as a specific effect of its more general role in recruiting and coordinating vigilant behavior towards stimuli with undetermined (uncertain) contingencies [335]. Therefore it was speculated that hyperactivation of the amygdala in major depression may bias initial evaluation of and response to incoming aversive and emotionally arousing information [335].

4.1.9. Increased noradrenergic feed-forward

Once the amygdala has become hyperactive, as described in Section 4.1.8, an organism is ready to enter '*the wild roller coaster*' stage. CRF, originating from the CeA, activates brainstem noradrenergic activity in the locus coeruleus (LC), which in turn activates forebrain CRF activity in the CeA and the BNST, where norepinephrine (NE) stimulates CRF release. This view is supported by reports that danger induces NE release in the CeA [336] and that this stimulates release of CRF [337]. Evidence that CRF originating from these NE terminal areas innervates the LC region [338–340] suggests that this last projection effectively closes the loop, making it a powerful '*feed-forward loop*'. An increased level of the rate-limiting enzyme tyrosine hydroxylase in catecholamine biosynthesis in the LC of subordinate rats and the decreased alpha$_2$-adrenoceptors in the LC of psychosocially challenged tree shrews supports the existence of such a mechanism (Table 4). Mounting data also suggest that there is a second positive '*feedforward loop*'. Thus, elevated corticosteroid levels also increase CRF levels in the hypothalamic paraventricular nucleus (PVN) [305–310]. From here a specific PVN CRF pathway projects to the brainstem NE LC region, which in turn innervates the PVN and closes the loop [341]. In agreement, the amount of CRF mRNA was increased in hypothalamic neurons of depressed patients who had committed suicide, especially in those CRF neurons that projected to brainstem NE nuclei [342]. According to George Koob [313] such feed-forward CRF–noradrenaline–CRF systems may be especially important for making behavioral adjustments in anticipation of changing demand. It is speculated that such a feed-forward circle, with the hyperactive LC at its center, produces a state of high arousal and high attention. The benefit is heightened awareness of possible threats in the environment. However, the costs of such a feed-forward mechanisms may include greater vulnerability to dysfunction, especially stress-sensitization [313]. In agreement, a positive correlation between hypercortisolism and increased cerebrospinalfluid NE has been observed in patients suffering from melancholic major depression [343]. Once the LC has become hyperactive this core system may enter a vicious circle, because the LC can inhibit the prefrontal cortex [344,345]. It has been suggested that inhibition of the left medial prefrontal cortex (or left sided defect) in melancholic depressed patients and disinhibition of the right prefrontal cortex, causes activation of the HPA axis and sympathetic system [346,347]. Moreover, there is some evidence that also the hippocampus is impaired (see Sections 4.1.11 and 4.1.12). Although the neural design of such a system favors rapid instinctual responses over more complex ones to service survival strategies in acute life-threatening situations (168), the costs of allostatic load are dramatic. Indeed, it is hypothesized that it can lead to psychopathological conditions such as melancholic depression, which is characterized by a state of pathological hyperarousal and feelings of anxiety, worthlessness and helplessness associated with decreased food intake and insomnia ([347]; see Table 5). A hyperactive CRF system may be partially responsible for these effects, including loss of appetite, weight loss and diminished activities of the growth hormone and reproductive axes ([341,348,349]; see Table 5).

4.1.10. Altered 5-HT$_{2A}$ receptor, 5-HT$_{1A}$ receptor and 5-HT transporter expression

In parallel to the noradrenergic mechanisms outlined above, substantial data suggest that 5-HT is also involved in mood disorders. Social conflict increases the release of the neurotransmitter 5-HT, and increased 5-HT levels may produce an enhanced 'anxiety state'. This notion is supported by reports that anxiolytic drugs that reduce 5-HT release in dorsal hippocampus, lateral septum and cortex concomitantly decrease anxiety [350]. Psychosocial challenge in mice, rats and tree shrews induced a robust decrease in expression of the inhibitory 5-HT$_{1A}$ receptor in the hippocampus (especially CA1 and smaller effects in DG) after some weeks (Table 4). Decreased HPA axis activity after 5-HT$_{1A}$ receptor challenge has been observed 24 h after social defeat in rats, reflecting hyposensitivity of the 5-HT$_{1A}$ receptor–effector system [254]. In patients with mood disorders decreased numbers of 5-HT$_{1A}$ receptors or hyposensitivity of the 5-HT$_{1A}$ receptor–effector system have been observed in different cortex areas and sometimes even in the raphe nucleus [351–354]. There is mounting evidence that the above-mentioned decrease in 5-HT$_{1A}$ receptor densities in the hippocampus is mediated by corticosteroids via a MR-dependent mechanism [355,356]. However, other mechanisms may also be involved. For example, testosterone can enhance 5-HT$_{1A}$ receptor expression so the opposite effect. i.e. a reduction in 5-HT$_{1A}$ receptor expression due to a social conflict-induced decrease in testosterone, cannot be excluded [357]. Exposure to a visible burrow system produces up-regulation of 5-HT$_{2A}$ receptors in the cerebral cortex of subordinate rats [262]. This also has relevance for depressive illness, since the deactivation of the 5-HT$_{2A}$ receptor by antisense induces an antidepressant-like effect in mice [358]. In human patients variability in the 5-HT$_{2A}$ receptor gene is primarily associated with suicidal behavior and with the seasonal pattern in major depression [359,360]. Furthermore, in depressed patients dysfunctional attitudes were positively associated with cortex 5-HT$_2$ binding potential, suggesting that low levels of 5-HT agonism in the brain cortex may explain the severely pessimistic, dysfunctional attitudes associated with major depression [361]

Moreover, in the visible burrow model of psychosocial challenge in rats, both dominants and subordinates showed downregulation of 5-HT transporter (5-HTT) expression in the CA3 region, indicating either a reduced density of serotonin terminals or a reduced expression of the transporter [362]. This downregulation in 5-HTT expression plays a crucial role in the role of 5-HT in anxiety disorders and depression. In humans 5-HTT promoter polymorphism, which is associated with anxiety-related traits has been observed [363]. Remarkably, individuals with one or two copies of the short allele of the 5-HTT promoter polymorphism, a phenomenon associated with reduced 5-HTT expression and function and increased fear and anxiety-related behaviors, exhibit greater amygdala neuronal activity in response to fearful stimuli compared with individuals homozygous for the long allele [364]. Thus, this polymorphism increases 5-HT levels in the amygdala and produces an enhanced anxiety-state. A major breakthrough was made recently in a longitudinal–epidemiological study, where clear gene-by-environment interactions led to psychopathology. It was shown that individuals with one or two copies of the short allele of the 5-HTT promoter polymorphism exhibited more depressive symptoms in relation to stressful life events than individuals homozygous for the long allele [365].

In summary, the above findings suggest that, both in animals and humans, an increase in 5-HT levels in the amygdala is associated with greater amygdala neuronal activity, fear and anxiety disorders, depression and suicide. The evidence for a causal connection between anxiety and depression becomes stronger.

4.1.11. Decreased neurogenesis in the hippocampus

The proposed corticosteroids–amygdala relationship in depression is relatively new, while the involvement of the corticosteroids–hippocampus link in emotional behavior goes back at least 30 years [176]. Recently, it is also becoming clearer that the hippocampus has a very high plasticity in response to environmental changes. For instance, production of new cells (neurogenesis) in the dentate gyrus (DG) of rats was increased by housing in an enriched environment [366], by learning [367] and by voluntary exercise [368]. Birds that use the space in their environment to hide and locate food, and voles and deer mice that traverse long distances to find mates have larger hippocampal volumes than closely related species that do not show these behaviors. Moreover, there are indications that hippocampal volume may change during the breeding season [369,370], indeed, the rate of neurogenesis in male and female prairie vole varies according to the breeding season [371]. Also, neurogenesis has been found in the hippocampus of adult humans [372]. Remarkably, environmental challenges, such as psychosocial conflict, can affect hippocampal plasticity, which in turn impacts on the animals' ability to adapt to environmental demands (Table 4).

Exposure to both acute and chronic frightening experiences, as observed in intruder tree shrews (Table 4), can suppress ongoing neurogenesis [272,373]. Different mediators of allostasis can explain this. For example, glucocorticoids participate with excitatory amino acids in the inhibition of neurogenesis whereas serotonin, via hippocampal 5-HT$_{1A}$ receptors and insulin-like growth factor-1 [374,375], stimulate neurogenesis [376]. The administration of a specific 5-HT$_{1A}$ receptors antagonist blocks this hippocampal cell-proliferation [377]. Thus, the observed increases in plasma cortisol levels may lead to an inhibition of neurogenesis in the intruder tree shrews, while serotonin is less able to stimulate neurogenesis due to decreased numbers of hippocampal 5-HT$_{1A}$ receptors.

Recently, it was shown that popular antidepressants, serotonin selective reuptake inhibitors (SSRIs), produce their anti-anxiety effects partly by stimulating hippocampal neurogenesis via the 5-HT_{1A} receptor, because 5-HT_{1A} receptor null knock-out mice were insensitive to the neurogenic and anxiolytic effects of SSRIs [378]. It is quite conceivable that the above effects are involved in fear-related learning and emotional memory because of the anatomic and functional connections between the dentate gyrus and the amygdala [379]. It was also recently hypothesized that therapeutic interventions for depression that increase 5-HT neurotransmission act, at least in part, by augmenting DG neurogenesis and thereby promoting recovery from depression [380].

Returning to the Hawks and Doves argument, it is known that aggressive mice (Hawks) have higher hippocampal 5-HT_{1A} recepor expression and binding [54,55] as well as higher hippocampal 5-HT_{1A} responsiveness [56] than non-aggressive ones (Doves). Consistent with the role of serotonin, via 5-HT_{1A} receptors, on neurogenesis cell proliferation in the DG of adult non-aggressive mice (Doves) was suppressed by stressful stimuli, probably though a corticosterone-mediated action, while cell proliferation in aggressive mice (Hawks) was resistant to this downregulation [54]. Thus, Doves are more vulnerable to stress-induced decreases in hippocampal neurogenesis than Hawks.

4.1.12. Increased dendritic remodeling in the hippocampus

The plasticity of the hippocampus is not only affected by neurogenesis but also by dendritic remodelling. In both tree shrews and rats sustained adrenal hormone release, due to psychological challenge, was accompanied by dendritic remodelling, i.e. decreased length and branching of apical dendrites of CA3 pyramidal neurons (Table 4). There is mounting evidence that glucocorticoids are involved in this dendritic remodelling. For instance, daily exposure of rats to elevated corticosterone levels produced dendritic remodelling [381–384] remodelling which was reversible [382,385]. The involvement of glucocorticoids was also confirmed by the use of an adrenal steroid synthesis blocker, cyanoketone, which blocked dendritic remodelling [386,387].

Glucocorticoids do not act alone, and their effects can be blocked by agents that interfere with excitatory amino acids, such as glutamate [383,384]. As shown in tree shrews, dendritic remodelling can be blocked by phenytoin which inhibits glutamate release and antagonizes the sodium channels and possibly also T-type calcium channels that are activated during glutamate-induced excitation. *N*-methyl-D-aspartate (NMDA) receptor blockade is also effective in preventing stress-induced dendritic remodelling [388]. Moreover, involvement of the γ-aminobutyric acid (GABA)–benzodiazepine receptor system is revealed by the ability of a benzodiazepine, adinazolam, to block dendritic remodelling [382].

The neurotransmitter serotonin (5-HT) is also involved in dendritic remodelling; 5-HT release is stimulated by social conflict [261], and tianeptine, an atypical tricyclic antidepressant that enhances 5-HT reuptake and thus reduces extracellular 5-HT levels, prevents dendritic remodeling of CA3 pyramidal neurons [382]. There is also evidence of interaction between serotonin and NMDA receptors, indicating that serotonin potentiates NMDA receptor binding as well as the activity of NMDA receptors [389], and that it may do so via 5-HT_2 receptors [390]. Following upon the widespread activation of NMDA receptors, the increased levels of intracellular calcium may cause the dendritic cytoskeleton to become depolymerized or to undergo proteolysis, thus accounting for the dendritic remodeling [381].

However, serotonin also binds to astroglial 5-HT_{1A} receptors to release S-100 beta; this is a major neurite extension factor that protects microtubule-associated proteins from phosphorylation and stabilizes and promotes the extension of dendritic processes [391]. Thus, reduced astroglial 5-HT_{1A} receptor stimulation may result in a collapse of cellular morphology, e.g. dendritic retraction. Dendritic remodeling in CA3 apical dendrites is an example of adaptive plasticity (i.e. resilience), since it is a reversible process that may protect nerve cells from permanent damage [383]. To understand this phenomenon, it is important to consider some key features of the CA3 region. In terms of circuitry, there are a series of recurrent feedback loops within the CA3 region that reactivate the mossy fiber system and sustain CA3 excitation [392]. The CA3 region has an intrinsic instability that can be driven by stimulation via the perforant pathway, and the CA3 apical dendritic remodeling might be a protective adaptation to limit the increased excitatory input via the recurrent feedback loops. Down-regulation of GRs in response to repeated exposure may be another example of a protective response [393], since glucocorticoids exacerbate permanent damage to hippocampal nerve cells [394,395]. It has been suggested that remodelling of dendrites provides one potential explanation of the hippocampal shrinkage reported in a number of disorders such as recurrent major depression [396]. In some depressive patients hippocampal apoptosis only contributes to a minor extent to volume changes [397]. Remarkably, the duration of depression but not age predicts hippocampal volume loss in medically healthy women with recurrent major depression [398]. This suggests that repeated stress during recurrent depressive episodes may result in cumulative hippocampal injury as reflected in volume loss. In primates hippocampal degeneration can be observed after sustained social conflict, with consequent ulceration and hyperplastic adrenal cortices indicative of sustained glucocorticoid release [399]. It has been suggested that chronic activation of GRs located in the hippocampus can damage hippocampal neurons, potentially leading to more severe hypercortisolism [400].

It is important to note that other brain regions besides the hippocampus are affected in depressive illness and undergo structural changes. One region is the prefrontal cortex which loses volume in depressive disorder [401], autopsy studies also revealed loss of volume and glial cells as well as neuronal density in both unipolar and bipolar depression [402–404]. Left prefrontal cortex volume reductions are already present in young women in early onset depression [405] and chronic glucocorticoid treatment induced loss of dendrites in the rat prefrontal cortex [406]. However, much more work is required on this brain region. In male Wistar rats, pyramidal and stellate neurons in the basolateral complex of the amygdala exhibited enhanced dendritic arborization in response to chronic immobilization [407]. Conversely, in the same study, chronic immobilization induced dendritic atrophy and debranching in the hippocampal CA3. The authors suggested that chronic immobilization leads to an imbalance in HPA axis function through a gradual loss of hippocampal inhibitory control as well as a gain in excitatory control exerted by the amygdala [407]. Finally, depressive illness is also associated with shrinkage of the amygdala with increased duration of depression [408].

There may, however, be a fine line between circumstances that can cause permanent damage and the conditions that lead to reversible remodeling of neurons [6,260]. Therefore, the challenge for future research is to understand what triggers the transition from adaptive plasticity to permanent damage. More research is needed to investigate whether Doves with their larger mossy fiber system, lower 5-HT_{1A} expression and higher HPA axis reactivity are at greater risk of hippocampal degeneration.

4.2. Allostatic load and energy metabolism

It is well known that in animals and humans social conflict not only affects mood and brain functioning but also food intake. Exposure to high levels of glucocorticoids inhibits food intake and evokes body weight loss (see Table 5), probably via increased hypothamic CRF levels which may act as catabolic signals [409]. In agreement, it was shown that chronic corticosteroid elevations increased CRF expression in the PVN [259].

However, if the animals can choose between different diets a more complex picture emerges. Socially defeated rats preferred carbohydrate intake during the first 2 weeks after social defeat but thereafter they favoured fat intake [410]. Following social defeat, high fat intake normalizes the suppression of body weight gain and speeds recovery of the body temperature increase relative to control animals and suppresses home cage locomotor activity [411]. The serotonergic 5-HT_{1A} receptor hyposensitivity observed for 2 weeks after defeat is absent in rats given a high fat regimen [411]. There is no doubt that eating high fat and carbohydrate comfort foods cheers people up and may make them feel and function better [188,412]. Recently, Dallman and colleagues [413] suggested that people or animals eat comfort food in an attempt to reduce the activity in the ‘chronic stress-response network’ with its attendant anxiety. They suggested the following mechansism: first, in the periphery, glucocorticoids stimulate accretion of mesenteric energy stores; second, as the abdominal energy-generated (unidentified) signal increases, the negative input to catecholaminergic cells in the NTS reduces the synthesis of enzymes required for norepinephrine synthesis; third, the decreased noradrenergic signal to the PVN, in turn, decreases CRF synthesis and secretion [413]. Thus, there is a powerful metabolic feedback control of CRF in the PVN, which may indirectly decrease glucocorticoid-action in the CeA and thereby lower anxiety.

Eating comfort food, however, is not the solution because diets rich in saturated fat and refined sugar reduce hippocampal levels of brain-derived neurotrophic factor (BDNF), a crucial modulator of synaptic plasticity and a predictor of learning efficacy [414]. Animals maintained on such a diet showed a decrease in levels of cyclic AMP-response element-binding protein (CREB) mRNA; this protein CREB is required for various forms of memory formation and is under the regulatory control of BDNF [415]. A decrease in CREB is assumed to produce negative mood effects because a genome-wide linkage survey for genetic loci showed that genes whose products participate in cellular signaling pathways that converge on CREB, as well as the target genes whose expression they regulate, may also harbor alleles that affect the development of recurrent early-onset major depression [416]. Fortunately, it is now clear that voluntary exercise can increase levels of BDNF and other growth factors, increase CREB phosphorylation, neurogenesis, resistance to brain insult and fat intake, and improve learning and mental performance [414,417,418]. Thus, exercise could provide a simple means of maintaining brain function and promoting brain plasticity.

From an evolutionary standpoint, one could argue that drives to conserve energy by preferential selection of calory-dense foods would favor survival and fitness. For instance, a negative mood or a ‘thrifty–greedy’ genotype that stimulates food intake and the storage of abdominal fat is beneficial in hunter-gatherers, because the surplus of energy is necessary for survival in hard times (e.g. survival at times of shortage, or during migration to an environment that has more food or is safer). However, the ‘thrifty–greedy’genes that were adaptive in promoting food intake and the storage of abdominal fat in the remote past have now become maladaptive [419–421]. Especially, in our modern individualistic societies with a lack of strong social support networks, the effect of corticosteroids is less buffered. Abundant high calorie food together with inactivity and the lack of energy expenditure creates a situation where chronically elevated glucocorticoids can impede the action of insulin to promote glucose uptake [420,421]. One of the results of this interaction is that insulin levels increase, and, together, insulin and glucocorticoid elevations promote

the deposition of body fat. The role of obesity as a factor speeding up other pathologies requires separate reviews. It is known that high levels of glucocorticoids produce an allostatic load which may result in obesity, that, if combined with inactivity, increases the risk of the metabolic syndrome or syndrome-X ([422]; Table 5). Syndrome-X is a new term for the cluster of conditions, including insulin resistance, high blood sugar levels, high triglycerides, decreased HDL ('good') cholesterol, abdominal obesity and raised blood pressure. When occurring together, this cluster of conditions may indicate a predisposition to diabetes type II, hypertension and cardiovascular disease. Since Doves predominantly respond with high HPA axis activation leading to increased plasma corticosteroid levels it is speculated that they are more vulnerable to these metabolic diseases. On the other hand, Hawks have low HPA axis reactivity but their high sympathetic system activivity and reduced parasympathetic counteraction result in other cardiac risks (see below).

4.3. Allostatic load and the cardiovascular system

Meyer Friedman and Ray Rosenman [32] were the first to point out that a relationship exists between cardiovascular disease and one's behavioral strategy, which they described as type A behavior. They observed that humans with a Type A personality are more aggressive and hostile, extremely competitive, impatient and always in a hurry whereas Type B individuals show more social behavior, are non-aggressive, non-hostile and seldom become angry or irritable. Personality type A closely resembles the Hawk type (see Table 1). Several investigators did not show a relationship between type A personality and increased cardiovascular risk but one explanation for this seeming inconsistency is that type A behavior is an especially strong predictor of when incident coronary heart disease (or a coronary event) may occur rather than if it will occur [423]. Another explanation may be the component hostility, rather than Type A behavior in general, is the predictor for coronary heart disease and atherosclerosis [424,425]. Several mechanisms may be responsible for differences in cardiovascular disease development between Hawks and Doves. First, Hawks are characterized by high levels of testosterone. These increased testosterone concentrations in Hawks may play a negative role because coronary atherosclerosis was found to be approximately twice as extensive in testosterone-treated female cynomologus monkeys as in untreated controls [426]. Second, increased sympathetic activity in Hawks is a risk factor for cardiovascular disease. Jim Henry showed that in colonies of mice dominants that experienced threat to control developed aortic arteriosclerosis and myocardial fibrosis [427,428]. In these studies, '*threat to control*' was induced by housing the mice in an intercommunicating system of cages (at least six containing both females and males) that were connected in a circle by plastic tubes around a central supply of food and water; thus, the multiple entrances to each box made defence of territory extremely difficult. These conditions could cause the sudden death of dominants or sustained elevation of blood pressure with arteriosclerotic lesions in the heart and blood vessels [428]. Clinical, experimental and pathological studies strongly indicate that hypertension is a major factor in coronary heart disease, sudden death, stroke congestive heart failure and renal insufficiency [429]. Similar sustained high blood pressure has been observed in aggressive male rats (Hawks) but not in non-aggressive ones (Doves) [430]. The more aggressive males generally reacted with higher blood pressure and catecholamine responses than more passive rats and they had higher baseline levels of norepinephrine [431]. Increased sympathoadrenal activation can also be observed in dominant male monkeys when they are housed in unstable social groups and these animals suffer more extensive atherosclerosis than subordinates [432,433]. In rabbits it was shown that such profound sympathetic activation induced endothelial injury and abnormal increases in platelet accumulation that could be blocked by beta-adrenoceptor blockade [434]. Moreover norepinephrine stimulated apoptosis in ventricular myocytes via activation of the beta-adrenergic pathway [435]. Third, a shift of autonomic balance toward sympathetic dominance, poorly antagonized by vagal rebound, is associated with the occurrence of cardiac tachyarrhythmias in rats (see Dr Andrea Sgoifo's contribution elsewhere in this issue). These effects were particularly severe in the aggressive wild-type strain of rats compared to non-aggressive Wistars [30,436,437]. In agreement, a weaker parasympathetic antagonism of sympathetic effects on the heart [438] and chronic sympathetic nervous system activation have been observed in Type A men, which could account for epidemiological findings of increased coronary risk in this group [439]. Thus, Hawks with their high sympathetic reactivity and relatively low parasympathetic counteraction are more vulnerable to developing tachyarrhythmias than Doves. It is speculated that shift of autonomic balance toward sympathetic dominance makes Hawks vulnerable to sudden death once apoptosis has developed in the heart.

Although Doves are not characterized by high sympathetic activation, they do develop cardiovascular disease. The mechanism, however, differs from the one described above for Hawks. As reviewed in earlier sections, Doves are more vulnerable to the development of depression-like syndromes. In humans it is widely accepted that depression increases the risk of coronary artery disease [440,441]. Hypercortisolism and a deficiency of sex steroids in depressive patients each contribute to increases in the visceral fat mass, leading to increases in free fatty acids. Hypercortisolism and the increases in free fatty acids both contribute to insulin resistance, which exacerbates the increase in visceral fat mass and promotes activation of the sympathetic nervous system and hypertension [442]. These observations provide a partial explanation for why Doves are also vulnerable to artheriosclerosis. They may also be more vulnerable to bradyarrhythmia due to parasympathetic dominance of the dorsal vagal complex.

Table 5
Different costs of adaptation in Hawks and Doves reflecting inefficient management of mediators of allostasis (e.g. decreased tonic 5-HT neurotransmission; decreased negative feedback by blunted HPA axis reactivity; low parasympathetic counteractivation) and a too frequent release of mediators of allostasis (e.g. increased 5-HT neurotransmission; increased glucocorticoid positive feedforward; high parasympathetic counteractivation), respectively

Costs of adaptation (allostatic load)	
Hawk	Dove
Mediators of allostasis inefficiently managed	Mediators of allostasis released too often (surplus)
Violence/impulse control disorders	Anxiety disorders
Hypertension/cardiac arrhythmias/sudden death	Weight loss/metabolic syndrome
Atypical depression	Melancholic depression
Chronic fatigue states/hypersomnia	Psychotic states/insomnia
Inflammation/autoimmune disease	Infection

The massive increase in vagal tone slows the heart and constricts the bronchi thereby contributing to the conservation of available oxygen [198]. This originally adaptive 'reptilian' response was useful for diving in aquatic environments or during freezing or tonic immobility (i.e. feigning death) in terrestrial environments [198]. In mammals, however, this phylogenetically old strategy may be maladaptive under certain conditions. Based on Porges' Polyvagal Theory [198], it has been proposed that fetal distress and sudden death, including sudden infant death syndrome, due to lethal bradycardia and apnea, are potential examples of the harmful impact of the 'reptilian' vagal surge.

4.4. Allostatic load and the immune system

Sympathetic system hyperactivity affects not only the cardiovascular system but also the immune system. Allostatic load can be produced by a hyperactive sympathetic system and a hyporeactive HPA axis. A growing number of animal findings strongly suggest that a hyporeactive HPA axis may be pathologically significant through a shift to Th1 cytokines that increases susceptibility to chronic inflammation [214]. For example, a defect in the biosynthesis of CRF and the resultant reduction in HPA axis activity was associated with high susceptibility to streptococcal cell wall-induced *arthritis* in Lewis rats as compared to the virtually syngenic Fischer rats [443]. Thus, Lewis rats are vulnerable to inflammatory and autoimmune disturbances that are not found in Fischer rats, and yet these can be overcome by the administration of exogenous glucocorticoids [444]. In addition, it is known that rheumatoid inflammatory T-cell clones express mostly Th1 [445]. Other examples of '*lower-than-needed cortisol disorders*' are *fibromyalgia* [446], *asthma* [214,447], *atopic dermatitis* [448,449], *Chronic Fatigue Syndrome* [450] and *burnout* [451]. Patients with this atopic skin disease showed a significant attenuation of the cortisol response to free speech and mental tasks, whereas catecholamines were significantly elevated in comparison to healthy controls [449]. In humans suffering from *Chronic Fatigue Syndrome* a lower cortisol response to awakening, heightened negative HPA axis feedback, increased GR function and impaired cortisol responses have all been observed [450,452–454]. Improvement in some patients during low-dose hydrocorticosterone therapy has been reported and this also reversed the blunted cortisol response to CRF [455].

Moreover, in atypical depression and chronic fatigue it has been shown that corticosteroid (prednisone) augmentation may be useful [456]. There are some data suggesting that hypoactivity of the HPA axis and hypofunction of CRF neurons results in hyperimmune fatigue states such as chronic fatigue syndrome and atypical depression, e.g. seasonal affective disorder [341]. Atypical depression is characterized by excessive sleepiness (hypersomnia; see Table 5), increased food intake and weight gain; patients also often feel walled off from themselves and they find social contact too demanding and tiring [347]. Atypical depression can be conceptualized as an allostatic state of HPA axis hypoactivity with strong counter-regulatory restraints. Theoretically, in patients with atypical depression the left prefrontal cortex could be hyperactive leading to excessive restraint of the right side (or defect in the right side) and consequently hypoactivity of amygdala and LC [347]. A more active prefrontal cortex may also be involved in the lessening of anxiety. It was suggested that the dorsal region of the medial prefrontal cortex produces a general decrease in fear reactivity (freezing responses) in response to fear conditioning during both the acquisition and extinction phases [457], and that the medial prefrontal cortex may also be involved in the extinction of conditioned freezing in rats, via the formation of a memory of safety [458]. It is thought that the medial prefrontal cortex gates impulse transmission from the basolateral amygdala to central amygdala (CeA), thereby gating the expression of conditioned fear via feedforward inhibition [458]. The above mentioned mechanisms produce a hypoactive amygdala and LC and this may lead to lower central CRF anxiety levels but also to a hyperimmune system [341,347].

Recently, the possible involvement of cytokines in depression and in chronic fatigue syndrome has drawn the attention of many researchers. This is because the administration of the cytokines interferon-alpha (IFN-alpha) and interleukin-2 (IL-2) which are used for the treatment of various viral illnesses, such as hepatitis C and various forms of cancer in humans, induce neuropsychiatric

effects, including depression, fatigue, anorexia and anhedonia [217,228,459]. In animals it is generally accepted that proinflammatory cytokines, such as IL-1beta, IFN-alpha, IFN-gamma and tumor necrosis factor-alpha (TNF-alpha) induce '*sickness behavior*' which might resemble the vegetative symptoms of depression in humans [216,217]. Direct activation of neurons by slowly diffusing IL-1beta takes place in the basolateral amygdala and nucleus parabrachialis, which both project to the CEA to mediate '*behavioral depression*' [228]. It has been suggested that repeated immune stimulation also makes the brain more sensitive to other classes of stimuli, a phenomenon known as cross-sensitization [216].

Growing evidence suggests that cytokines produce the above mentioned effects via changes in the neural 5-HT system. Cytokines like IFN-gamma and IFN-alpha induce the enzyme indoleamine 2,3-dioxygenase which has various negative consequences for the brain [217,228,459–460]. First, this enzyme converts tryptophan along the kynurenine pathway into several neuroactive intermediates and then into kynurenine; this chain of events results in reduced levels of tryptophan, the precursor of 5-HT, and thus to reduced central 5-HT synthesis. Second, kynurenine metabolites such as 3-hydroxy-kynurenine and quinolinic acid have toxic effects on brain function; The former metabolite can lead to oxidative stress by increasing the production of reactive oxygen species, while quinolinic acid may produce overstimulation of hippocampal *N*-methyl-D-aspartate (NMDA) receptors and thereby lead to apoptosis and hippocampal atrophy [216,228]. Indeed, hippocampal atrophy can be caused by NMDA overstimulation and this has been associated with depression [461]. Accumulating evidence suggests that the above mechanisms take place in humans because lower tryptophan values, associated with significantly higher IFN-gamma secretion, have been observed during major depression [462]. Moreover; (a) antidepressants (especially selective serotonin reuptake inhibitors such as paroxetine) are effective in reducing IFN-induced depression [463] and (b) in major depression reductions in tryptophan correlate with depressive, anxious, and cognitive symptoms but not with neurovegetative or somatic ones [464].

In summary, returning to our central theme, in Hawks with their hypoactive HPA axis there is evidence that a Th1 cellular immune response dominates, while in Doves a Th2 dominated humoral immune response is observed. Therefore, it is assumed that although they are more resistant to infections, the trade-off in Hawks is that they are more vulnerable to autoimmune diseases, atypical depression and chronic fatigue. The lower parasympathetic reactivity found in Hawks also suggests that they are less well equipped to inhibit the release of macrophage TNF, IL-1beta, IL-6 and IL-18 via the vagal parasympathetic route; the release of these cytokines may then produce sickness behavior and chronic fatigue. In contrast, Doves are better equipped to combat parasites, but the trade-off for them may be a higher vulnerability to infections. In agreement, it has been shown in male cynomologus monkeys that animals with lower social status (greater elevated cortisol responses to social reorganizations, lower body weight, and less aggressive behavior) are at higher risk of infection with (adenovirus) that causes a common-cold-like illness than are animals with higher social status [465].

5. Conclusions

With the exception of the past few thousand years, a drop in the bucket of evolutionary time, humans and animals have evolved in natural habitats and are therefore intricately tied to nature. It has become clear that natural selection maintains a balance of different traits, e.g. preserving genes for high aggression (Hawks) and low aggression (Doves) within a population. The existence of the Hawk–Dove strategy is widespread in the animal kingdom, not only between males and females, but also within the same gender across species. Both behavioral strategies can be successful, but under different environmental conditions. Bold Hawks preferentially adopt the fight–flight strategy when attempting to establish a new territory or to defend an existing territory, while cautious Doves adopt the freeze–hide strategy to avoid to threats in their environment. The fitness of Hawks is increased when the population density is high and food availability is stable and abundant. In contrast, Doves have an increased fitness during food scarcity and low population density because they explore their environment more thoroughly for new resources and they have greater behavioral flexibility. Hawks and Doves have their own specific underlying physiological characteristics that lead to differences in the trade-offs between the various benefits of allostasis and costs of allostatic load (Table 5).

The cost benefit analysis of the Hawk and Dove strategies is summarized below (A to D).

(A1) Bold Hawks with their relatively low corticosteroid levels, high testosterone and high DHEA concentrations have a higher motivation to express aggressive behavior, but the trade-off is an increased incidence of antisocial and violent behavior. The presence of low tonic 5-HT neurotransmission in Hawks may produce less anxiety but it increases the risk of impulse control disorders.

(A2) In contrast, cautious Doves with their high levels of HPA axis reactivity, corticosteroids, and tonic 5-HT neurotransmission have a higher motivation to express orienting and freezing behavior. Freezing behavior itself may reduce the likelihood of detection and attack from an attacker or predator. Further, if caught, freezing or tonic immobility responses may result in the predator or attacker losing interest and moving away [466]. In combination with their

morphologically better developed hippocampus, Doves are very well able to organize contextual information and incoming sensory input (e.g. predator's appearance, location, smell and sound, avenues of escape, shelter) according to relevant relationships among them. Doves are therefore more aware of danger and safety signals in their environment than are the bold Hawks. However, the trade-off is a higher risk that Doves will develop anxiety disorders.

(B1) In Hawks, the high sympathetic reactivity and relatively low parasympathetic counteraction favors redistribution of blood to muscles, speeds up heartbeat, dilates bronchi, blocks the digestive process, activates adrenal glands, etc. thereby preparing the body for vigorous emergency action during fight–flight responses. The trade-offs, however, are an increased risk of hypertension and cardiac arrhythmias due to a shift of autonomic balance toward sympathetic dominance. Once apoptosis has developed in the Hawk's heart, cardiac arrhythmias may cause sudden death.

(B2) In Doves, negative mood stimulates food intake (in order to lower anxiety via a powerful metabolic feedback to control CRF in the hypothalamus which may indirectly decrease glucocorticoid-action in the central amygdala) and the storage of abdominal fat. This surplus of energy is beneficial for survival in hard times. However, the costs if the fat stores are not used is an increased risk of developing syndrome-X, a metabolic syndrome leading to diabetes type II, hypertension and cardiovascular disease.

(C1) Hawks have an increased risk of wounds and infections because they are more aggressive and bolder than Doves. Not surprisingly therefore, the Th1 dominated cellular immune response in Hawks is very adaptive in the fight against infections. However, this hyperimmune state together with a blunted HPA axis activity incures costs such as the risk of inflammation and autoimmune disease.

(C2) Conversely, Doves with their higher motivation to explore the environment for new resources are at greater risk of being contaminated with parasites. Therefore, their Th2 dominated humoral response is very adaptive for dealing with parasites. However, the trade-off may be an increased vulnerability to infections such as the common cold, etc.

(D1) The lower parasympathetic reactivity of Hawks suggests that they are less well equipped to inhibit the release of macrophage cytokines via the vagal parasympathetic route. The increased release of cytokines can lead to a chronic fatigue state. It is speculated that the hypoactivity of the HPA axis in Hawks combined with hypofunction of CRF neurons may cause atypical depression.

(D2) In Doves, the higher HPA axis reactivity may represent the start of a 'stress-sensitization cascade'. Corticosteroids increase CRF levels in central and extended amygdala and paraventricular hypothalamus. These areas make feed-forward loops with the locus coeruleus producing a state of high arousal and high attention. The benefit is high awareness of potential dangers in the environment. The costs of such a feed-forward mechanisms, however, may be particular vulnerability to dysfunction and the development of melancholic depression and psychotic states. Recurrent depression itself may become a source of allostatic load through initial hypertrophy giving way to atrophy of limbic brain structures.

We hope to have demonstrated that a Darwinian approach to the concept of stress leads to a more refined understanding of the factors underlying differential vulnerability to stress-related diseases. In the past, stress-induced behavioral and physiological changes have been too easily interpreted in terms of pathology. The Darwinian concept of stress requires a detailed analysis of not only the costs of allostatic load, but also of the benefits of stress-induced changes, especially allostasis.

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