



Mobile madness: Electronic gadgets like smartphones and the associated culture of always being online have added to the stress of modern life. Psychologists warn that multitasking can diminish the attention we can devote to an important task, which can be particularly dangerous when driving. (Photo: Christopher J. Mills.)

our psychology and our natural environment. He organises the Blue Mind conference series, the fourth instalment of which takes place at Bedruthan Steps, Cornwall, UK, 10–12 June 2014, and will be live-streamed on the web (www.bluemind.me). As Nichols describes it: “over the past several years I’ve brought together an eclectic group of scientists, psychologists, researchers, educators, athletes, explorers, businesspeople, and artists to consider a fundamental question: what happens when our most complex organ — the brain — meets the planet’s largest feature — water?”

He has also explained these ideas in a new book, called *Blue Mind: How Water Makes You Happier, More Connected, and Better at What You Do*, which is also due to appear in June. In his book, Nichols discusses a spate of recent psychology papers showing that the proximity of “blue nature” can improve people’s physical and mental health and counterbalance the damaging effects of the chronic stress and the permanent engagement of the red mind. While the opportunity to exercise plays a part, several studies have shown that the positive effect of being near water can be separated from that aspect.

Water has also proven beneficial for people with specific problems beyond chronic stress. Nichols cites as examples organisations that offer kayaking excursions for war veterans with PTSD and/or physical injuries, such as Rivers of Recovery (ROR). Children with autism are also widely reported to have a natural affinity for water and to benefit from the calming effect of being near or on the water.

“Practising Blue Mind is no silver bullet solution,” Nichols concludes, “but when understood and used in conjunction with indoor relaxation practices we find it to be widely useful. By describing and assigning the full value of the cognitive and emotional benefits and services to healthy waterways and oceans we provide a compelling additional argument for restoration, protection, maintenance and access.”

Whether you decide to reduce stress by walking to work, by doing yoga on the beach, or by jumping out of planes, it all boils down to finding the natural balance between the highly alert red mind and the relaxed blue mind.

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Primer

Stress and life history

Pat Monaghan and Karen A. Spencer

In his book on behavioural endocrinology, Randy Nelson describes ‘stress’ as a ‘notoriously ethereal concept’. Yet, despite this lack of clarity, studies of the consequences of stress across different time scales, life history stages, taxa and levels of biological enquiry form a large part of modern biology and biomedicine. Organisms need to recognise and respond to environmental challenges. Being able to do so appropriately, and with minimal costs, is an important physiological attribute, with great adaptive value. The costs and benefits of different mechanisms that enable organisms to cope with unpredictable environmental changes can be manifest to different degrees at different life stages. Accordingly, the level of stress experienced in the environment can act as a strong selective pressure that drives the evolution of life histories.

Though tight definitions have certainly proved problematic, there is considerable consensus about what stress is and why it plays such an important part in shaping life histories. The more challenging the environment, the more important is the stress response system. The concept of stress is closely related to the concept of homeostasis. Both are best viewed as biological states, the latter representing the optimal physiological state or ‘comfort zone’, and the former the state that arises when homeostasis is disrupted.

We can think of organisms as occupying a multi-dimensional physiological space, in which they have optimal zones or set points for key body parameters, such as temperature, metabolic activity, energy balance, blood flow, water balance and so on. When internal or external circumstances give rise to a situation that takes, or threatens to take, the individual out of its zone of tolerance for one or a number of parameters, or cause it direct harm,

comfort zone (homeostasis) vs. disrupted homeostasis (stress)

the organism has to do the following: recognise the danger, mount a stress response that facilitates evasive action, restore homeostasis, repair any resulting damage, and, if appropriate, recalibrate the homeostatic set points and tolerance zones in the light of the new environmental circumstances.

The factors that cause significant deflection from homeostasis are termed stressors. Most studies that try to link stress exposure and life histories have focussed on environmental stressors, such as predators, weather, food shortage and such like — indeed any environmental challenge to homeostasis that the individual might face. However, stressors can be generated internally by system malfunction. The ‘stressor’ might even be generated by the brain itself, for example by the recall or imagination of threatening circumstances creating a state of stress, usually termed ‘anxiety’ in humans where it has been most studied. In fact, the stressor need not in itself be the danger. Associative learning can result in a benign factor, which presents no direct threat, being perceived as noxious because the individual has learned that it signals the arrival of something harmful. Recent studies even suggest that such associations can be transmitted across generations — the offspring and grand offspring of mice trained to associate a particular odour with foot shocks were more behaviourally sensitive to the odour their parents had learned to fear even though they had not themselves experienced the association. This apparent ‘inheritance of fear’ was transmitted by epigenetic changes to parental gametes.

What constitutes a stressor for one individual might not do so for another, as inheritance, age, life history stage, current condition, experience and developmental history are all involved in the regulation of stress responses. The disruption of homeostasis that results from exposure to stressors, or anticipation of their effects, puts the organism in a state of stress in which it will remain until homeostasis has been restored. The stress response activates appropriate avoidance, coping and then restorative

processes. Restoring homeostasis has been termed ‘allostasis’, and the physiological effort expended in doing so ‘allostatic load’ (Figure 1).

This representation of the state of stress in a homeostatic and tolerance zone framework (Figure 1) allows us to encapsulate within- and between-individual differences in the level of a stressor that triggers a stress response. The tolerance zones, that is the range of values for a particular parameter outside of which a stress response is generated, may be narrowed or broadened with seasonal or circadian rhythms, early life experience, acclimatisation and so on, either permanently or temporarily. Where the zone of tolerance is broader, the individual will be less sensitive to stressors, and where it is narrower, more sensitive. Changes in tolerance levels can occur slowly and in response to predictable environmental change. Such changes enable the organism to make appropriate physiological responses at different times of day or year, and, in some cases, to acclimate to a gradual environmental change.

Stress responses generally occur when an unpredictable challenge is encountered, and serve to increase the likelihood of survival in the short term. Unpredictable changes effectively put the physiology of the animal into an ‘emergency’ state. Survival is prioritised over other less essential activities. This has been well studied in vertebrates, and involves a complex interaction between the environment, the brain and the endocrine system (Figure 2). A key component of the system is the Hypothalamic-Pituitary-Adrenal axis in mammals, birds and reptiles, and the Hypothalamic-Pituitary-Interrenal system in amphibians and fish. On encountering a stressor, there is an almost instantaneous release of stored catecholamines (adrenaline and noradrenaline) from the adrenal medulla triggered by the sympathetic nervous system as a consequence of the action or perception of the stressor. This activates the so-called ‘fight or flight’ reaction, which enables the animal to alter its physiology and take rapid action. Energy is mobilised, respiration rate, alertness, blood

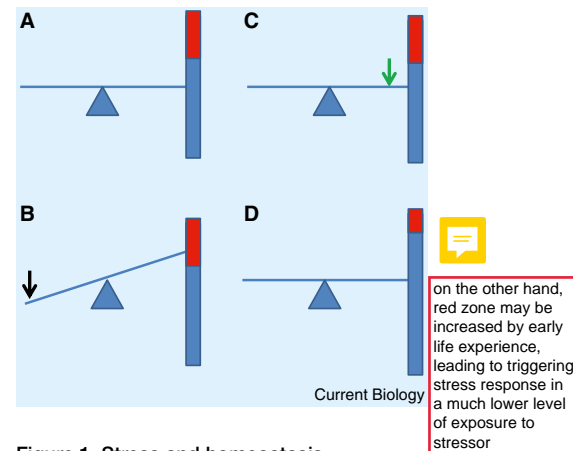


Figure 1. Stress and homeostasis.

(A) The blue line resting on the fulcrum illustrates the state of homeostasis. When the line is horizontal, the animal is in a state of homeostasis with respect to a particular physiological parameter. The vertical column represents the tolerance zone for this parameter. (B) Only when a stressor, shown as a black arrow, deflects the animal into the red zone will a stress response be triggered. (C) The stress response serves to restore the state of homeostasis. The green arrow represents the degree of effort required to do so, and thus represents the allostatic load. (D) The tolerance zones can shift seasonally, as a result of programmed seasonal changes or individual experience. In the situation illustrated here, a much higher level of stressor will be required to trigger a stress response. Equally, the red zone might be increased by early life experience and the animal is less tolerant of deflections from a homeostatic set point for this parameter, in which case a stress response will be triggered at a much lower level of exposure to the stressor.

pressure and flow to muscles are increased, while pain perception and blood flow to areas not necessary for movement are decreased.

Within minutes, the hypothalamus releases corticotrophin releasing factor (CRF), which initiates the release of adrenocorticotrophin (ACTH) from the pituitary. ACTH then stimulates the synthesis and release of glucocorticoid hormones (GC) from the adrenal cortex (Figure 2), mainly corticosterone in rodents, birds and reptiles and cortisol in fish and most mammals. The initial exposure to a stressor triggers a surge in glucocorticoid production, termed the acute stress response, which in many vertebrates reaches its peak in the peripheral vascular system within 5–30 minutes (Figure 3). These elevated levels, often many multiples of the basal condition, serve to promote physiological and behavioural activities that either remove the animal from

glucocorticoid = a kind of corticosterone (anti-inflammatory)

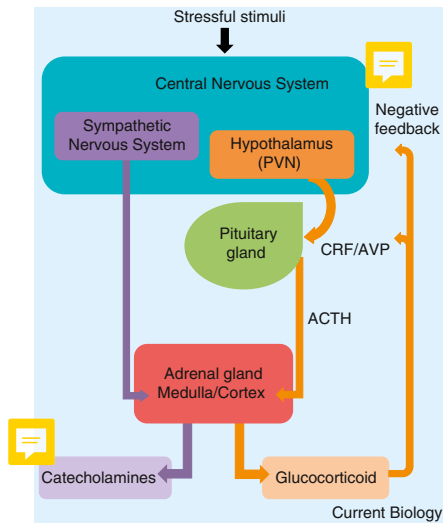


Figure 2. Overview of the physiological response to stress.

Stressful stimuli initially trigger the sympathetic nervous system to produce noradrenaline and adrenaline from the adrenal medulla. Within minutes the HPA axis is activated. The paraventricular nucleus (PVN) in the hypothalamus releases corticotrophin releasing factor (CRF) and arginine vasopressin (AVP; vasotocin (AVT) in birds), which initiates the release of adrenocorticotrophin hormone (ACTH) from the anterior pituitary. This stimulates the release of glucocorticoid hormones from the adrenal cortex. Glucocorticoids also act via intracellular receptors and negative feedback to stop the stress response.

the stressful situation or facilitate coping. This stress response is shut down via intracellular receptors within the paraventricular nucleus of the hypothalamus and the hippocampus (glucocorticoid (GR) or mineralocorticoid (MR) receptors), which act as the main regulators of HPA axis functioning via classical negative feedback mechanisms that gradually return glucocorticoid concentrations to basal levels (Figure 3).

Glucocorticoid hormones act over a longer time frame than adrenaline to prepare the organism to face adversity. It has been assumed that the two main glucocorticoids in vertebrates (cortisol and corticosterone) do essentially the same job in suspending non essential activities (such as digestion, growth, reproduction and tissue maintenance/repair and promote those important for short term survival (e.g. gluconeogenesis, increased locomotor activity); consequently, usually only one of

these two hormones is measured depending on the species. However, recent studies in ungulates, in which cortisol and corticosterone levels were shown to be differentially affected by the environment, suggest that both may be important. Many invertebrates have analogous systems. Insects, for example, release octopamine in response to stressors, which has a similar effect to noradrenaline, followed by adipokinetic hormone, akin to glucocorticoids in its effects. Even single-celled animals show some kind of stress response.

Vertebrate glucocorticoid hormones play an important role in the regulation of homeostasis, particularly energy balance, and so are always present at a baseline level. These baseline levels can change in response to predictable changes in the environment, and such changes in glucocorticoid levels are not usually considered stress responses, but rather evolved coping strategies. For example, birds in temperate regions modulate the production of corticosterone in response to seasonality, whereas in environments where seasonal changes are minimal baseline corticosterone varies little. During reproduction, baseline levels rise in amphibians, reptiles and birds, but apparently not in mammals. In amphibians, baseline glucocorticoid levels have also been shown to rise at metamorphosis. Such strategic changes in baseline levels presumably maintain a state of homeostasis. Development too can be affected in an adaptive manner. In environments where predators are present, levels of corticosterone in developing tadpoles are higher, and they also develop larger tails, thought to be a direct effect of the greater exposure to corticosterone and to assist in predator evasion. Protracted or repeated exposure to unpredictable stressors can also cause rises in baseline corticosterone above what the level would otherwise be, for example inclement weather, food shortage or high social stress or predation risk. However, it has proved difficult to demonstrate the expected link between variation in baseline corticosterone levels and fitness. The unanswered question is whether a relatively high baseline level

indicates an individual who is finding the environment very challenging, and thus likely to have low fitness, or an individual who is more effectively rising to the challenge, and thus likely to have a higher fitness. Similar problems arise with the acute stress response, variability in which has also proved difficult to link to fitness. The strength and direction of such links may very much depend on the environmental circumstances or the timescale over which fitness is measured. This may explain why some studies find a clear link and others do not. It is important to remember that long-term effects on health and longevity are not the same as fitness effects, as individuals might still have a higher lifetime reproductive success than they would have had without the physiological changes induced by the environmental circumstances they experienced.

There is a substantial body of work which shows that having high concentrations of circulating glucocorticoid hormones induced by protracted or repeated exposure to stressors can be extremely costly to long-term health. Remaining 'ready for the worst' for a lengthy period of time depletes resources and the body will suffer from the absence of maintenance. It is well known that chronic exposure to stressors is associated with reduced longevity. High acute stress responsiveness has been linked to reduced body condition and reduced survival in several species across a range of taxa (e.g. in zebra finches, cane toads, marine iguana and white storks). The mechanisms that underlie this are varied and include increased oxidative stress and reduced repair of oxidative damage, decreased immune function and increased telomere attrition. Unlike adrenaline and noradrenaline, glucocorticoid hormones can pass through the blood-brain barrier, and as such can directly influence neuronal activity. Prolonged exposure to glucocorticoids can drive elevated programmed cell death in several brain regions, including those important for HPA axis functioning, such as the hippocampus, as well as suppressing the production of proteins that enhance neuronal growth. This has been shown to

rise of baseline Corticosterone level due to repeated exposure to stressful situations

Glucocorticoids during stress response suspend growth, reproduction, tissue maintenance/repair and promote locomotor activity by increasing sugar level for energy

have significant implications for learning and memory. Chronic stress also alters the receptor expression (both GR and MR) within the HPA axis, inducing dysregulation of the axis. This can result in changes to basal and/or stress-induced levels of stress hormones and a decreased speed of return to baseline after the exposure to the stressor (Figure 3). These neuroendocrine changes are linked to altered behavioural responses, particularly under novel circumstances. For example, artificial selection experiments have provided a link between the magnitude and duration of the acute stress response and exploratory behaviour, where animals with attenuated responses show reduced fear and increased exploration. Interestingly, the acute response appears to be linked to personality traits (or consistent behavioural phenotypes) in avian species, such as the great tit. Individuals exhibiting 'shy' personalities also exhibit higher acute glucocorticoid responses. In some cases, chronic stress can dampen the acute stress response, but we know little about what determines whether responses are heightened or dampened.

Certain periods of life, when significant body development or reorganisation takes place, appear to be very important in determining or 'programming' the levels of stressors required to trigger a stress response. Repeated exposure to stressors during pre- and post-natal growth in birds and mammals seem to result in a narrowing of tolerance zones and increased stress sensitivity. Pre-natal exposure can be influenced by maternal state, and glucocorticoids transmitted to the developing embryo through the egg or placenta. In amphibians, the environment experienced at the time of metamorphosis has also been found to have long-term effects in shaping the response to future stressors. Puberty may also be an important life-history stage in this context, but much less is known about this. Most commonly, baseline levels are not affected, but in response to a stressor, glucocorticoids in the plasma rise faster and to a higher peak, then taking longer to return to baseline. The subsequent higher exposure to glucocorticoid hormones has

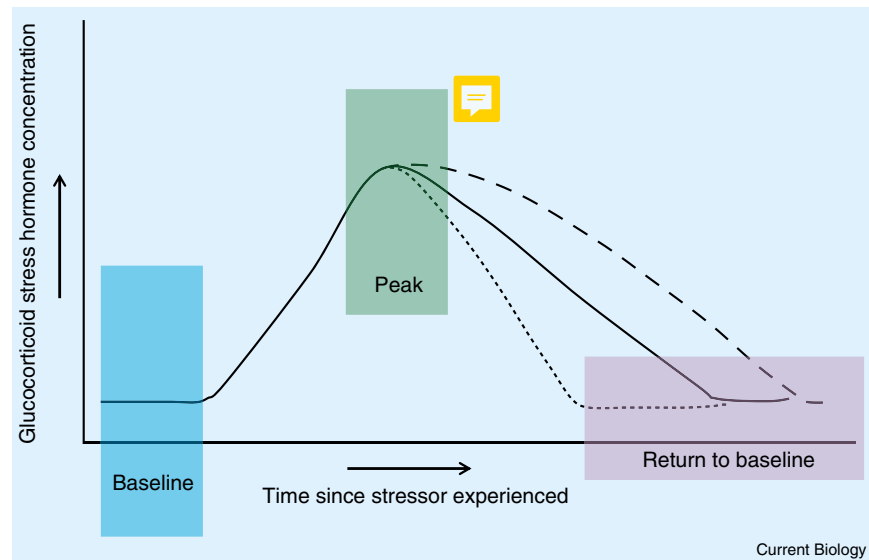


Figure 3. The acute stress response.

The baseline glucocorticoid levels are indicated by the blue box. When an animal encounters a stressor the release of glucocorticoids (solid line) from the adrenal cortex cause a sudden increase in levels, which reach a peak several minutes after the stress exposure (green box). Negative feedback mechanisms act to steadily reduce levels within the vascular system back to baseline levels (purple box). The diagram also shows how this response can vary depending upon the efficiency of the feedback mechanisms (amount of intracellular receptors). Larger populations of receptors result in an attenuated response (dotted line), whereas reduced numbers of receptors result in a prolonged stress response (dashed line). Baseline levels of glucocorticoids tend to remain constant, though several factors can cause fluctuations over the long term, such as seasonal changes or age. However, chronic exposure to stressful stimuli causes an increase in basal levels.

negative consequences later in life. Mammalian studies were the first to demonstrate that differential glucocorticoid exposure during early development results in differences in HPA-axis activity and behaviour and that these effects are associated with differences in glucocorticoid receptor gene expression. In rats, early maternal separation results in increased HPA-axis activity in response to stress associated with a decrease in cognitive performance. Conversely, early handling of pups results in reduced stress responsiveness and enhanced negative feedback of the HPA axis, and is associated with enhanced spatial cognition later in life. However, more recent studies using non-mammalian models have also confirmed the powerful effects of early life exposure to glucocorticoids on the brain and HPA axis functioning. Japanese quail exposed to pre-natal glucocorticoids exhibit attenuated stress responses, which facilitates enhanced exploratory behaviour in a novel environment. There is a substantial literature, mainly from

work on rodents and birds, which shows that changes to the acute stress response and at least some of the behavioural changes persist into adulthood. An additional layer of complexity is added by the fact mild stress exposure in early life can actually make organisms less sensitive, by broadening the zone of tolerance, improving defence mechanisms and/or dampening the stress response itself. It has been shown, for example, that exposure of zebra finches to a mild heat stress makes them more able to withstand heat stress later in life.

Why such environmentally induced programming occurs, why there appear to be particularly sensitive periods for this and how reversible are the induced changes are key questions to which we do not yet have answers. It is possible that there are constraints imposed by developmental pathways, or that reversibility is very costly, and that these constraints or costs are reduced at times when significant physiological changes are occurring. We also know relatively little about the adaptive significance of these

induced changes to the HPA axis; it is clear that there can be long-term costs, but we need to know much more about the benefits at different life history stages in different environments. The extent to which the environment at one life history stage is predictive of the subsequent environment is likely to be of crucial importance in determining fitness outcomes.

Understanding how unpredictable environmental challenges shape life histories is a very active, interdisciplinary research field. Clearly, organisms would be expected to benefit from adjusting their physiologies in response to reliable cues that provide information on future environmental conditions. More experiments are needed in which environmental conditions

at different life history stages are manipulated. Many challenges remain for researchers — why should stress responses sometimes be elevated and sometimes dampened, under what conditions is high stress reactivity good or bad, and over what time scales do these costs and benefits occur?

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