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Allostasis: A model of predictive regulation

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ABSTRACT

The premise of the standard regulatory model, "homeostasis", is flawed: the goal of regulation is *not* to preserve constancy of the internal milieu. Rather, it is to continually *adjust* the milieu to promote survival and reproduction. Regulatory mechanisms need to be efficient, but homeostasis (error-correction by feedback) is inherently *in*efficient. Thus, although feedbacks are certainly ubiquitous, they could not possibly serve as the primary regulatory mechanism.

A newer model, "allostasis", proposes that efficient regulation requires *anticipating* needs and preparing to satisfy them *before* they arise. The advantages: (i) errors are reduced in magnitude and frequency; (ii) response capacities of different components are matched – to prevent bottlenecks and reduce safety factors; (iii) resources are shared between systems to minimize reserve capacities; (iv) errors are remembered and used to reduce future errors. This regulatory strategy requires a dedicated organ, the brain.

The brain tracks multitudinous variables and integrates their values with prior knowledge to predict needs and set priorities. The brain coordinates effectors to mobilize resources from modest bodily stores and enforces a system of flexible trade-offs: *from* each organ according to its ability, *to* each organ according to its need. The brain also helps regulate the internal milieu by governing anticipatory behavior. Thus, an animal conserves energy by moving to a warmer place – *before* it cools, and it conserves salt and water by moving to a cooler one *before* it sweats.

The behavioral strategy requires continuously updating a set of specific "shopping lists" that document the growing need for each key component (warmth, food, salt, water). These appetites funnel into a common pathway that employs a "stick" to drive the organism toward filling the need, plus a "carrot" to relax the organism when the need is satisfied. The stick corresponds broadly to the sense of anxiety, and the carrot broadly to the sense of pleasure. This design constrains anxieties to be non-adapting and pleasures to be brief – fast-adapting – to make way for the next anxiety.

The stick/carrot mechanisms evolved early and expanded so that in humans they govern higher level learning and social organization. Correspondingly, the "funnel" widened to allow innumerable activities and experiences to each provide non-adapting anxieties and brief pleasures, their reward values depending partly on the effort expended. But modern life narrows the variety of small pleasures and reduces effort, thereby reducing their reward value and requiring larger portions for equivalent satisfaction – a cycle that generates addictive behaviors.

Homeostasis and allostasis locate pathology at different levels. Homeostasis identifies proximate causes; for example, it attributes essential hypertension to excess salt water in too small a vascular reservoir. Thus it directs pharmacotherapy toward reducing salt and water, expanding the reservoir, and blocking feedbacks that would counteract these measures. Allostasis attributes essential hypertension to the brain. Chronically anticipating a need for higher pressure, the brain mobilizes *all* the low level mechanisms in concert: kidney to retain salt and water, vascular system to tighten, and salt appetite to rise. Correspondingly, allostasis would direct therapy toward higher levels – to reduce demand and increase sense of control – so that the brain can down-shift its prediction and relax all the low-level mechanisms in concert.

For disorders of addiction homeostasis pursues pharmacological treatments: drugs to treat drug addiction, obesity, and other compulsive behaviors. Allostasis suggests broader approaches – such as re-expanding the range of possible pleasures and providing opportunities to expend effort in their pursuit.

1. Introduction

Just as every human society has its own story of where humans originated, each has its own model of what regulates human physiology and behavior. Each model defines a particular concept of health and

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disease, and these determine an approach to therapeutics. Simpler societies attributed regulation to *spirits* – health depended on the spirits' satisfaction, and disease to their lack thereof. Therapeutics involved placating a spirit, sometimes by encouraging an ill person to repair his communal relationships [1].

The Western model of physiological regulation for millennia involved a balance between four *humors*. Patho-physiology was attributed to humoral imbalance, which therapeutics tried to repair. "Sanguinity" was treated by bleeding and other excess humors by purging. Under this model, Dr. Benjamin Rush, a pre-eminent physician at the University of Pennsylvania, treated yellow fever by bleeding and purging with such vigor that in Philadelphia's great epidemic of 1793 he was believed by contemporaries to have killed a great many patients. Survival rates were better with milder treatment based on rest and nutrition [2].

Around mid-19th century a new concept of regulation was proposed by Claude Bernard: "*… All of the vital mechanisms … have always one goal, to maintain the uniformity of the conditions of life in the internal environment*…[3]. A generation later Cannon summarized this concept, naming it "homeostasis" [4]. The concept was eventually formalized with a diagram suggesting that stability is achieved for each vital parameter by a sensor detecting deviations from a "set-point" and feeding back the "error signal" to a controller that restores the value to normal (Fig. 1). In a way, homeostasis remains a theory of humoral balance – only now are recognized, not just four humors, but a multitude.

This model dominated research on normal and patho-physiology over the next century and continues to do so, also setting the primary approach to therapeutics. Thus, a modern physician little inquires into your spirit; rather he studies your *lab values* and, upon identifying a deviation, recommends a drug to correct it. The homeostasis model of regulation is so well established and has been so successful that it needs neither review nor defense.

It seems more useful in this brief essay to first identify key points missing from homeostasis and then consider how they can be integrated in a more comprehensive model. This new model is based on the idea that regulation must be efficient – which requires anticipating needs and satisfying them with minimal error. This model, termed *allostasis* [5–9] assigns a central role to the brain – both for regulating low-level peripheral mechanisms and also for governing behaviors, even to the highest levels, that enhance the organism's capacity to serve its low-level needs.

2. Homeostasis cannot be the primary mechanism for regulation

One must finally acknowledge that Bernard's dictum is flawed. He proposed this idea contemporaneously with *Origin of Species*, but neither he, nor subsequent proponents of homeostasis, ever revised the model to incorporate Darwin's big idea: the goal of all species is *not* constancy of internal parameters but, rather, *survival and reproduction*. Because organisms compete, natural selection drives them toward efficient designs. However, regulation via error-correcting feedback is intrinsically *in*efficient.

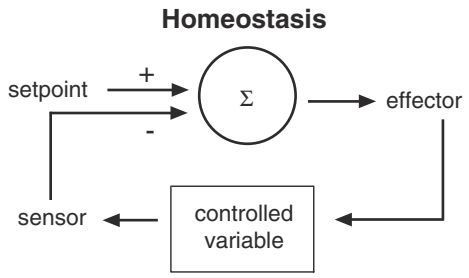

Fig. 1. Homeostasis. This model describes a mechanism for holding constant a controlled parameter by sensing its deviation from a "setpoint" and feeding back to correct the error.

First, if a parameter is held constant (clamped) by negative feedback, it cannot then respond to changes in demand. For example, if a rise in blood pressure were promptly "corrected" by reducing heart rate and stroke volume, an organism could not satisfy an increased need for oxygenated blood. This difficulty tended to go unnoticed in the period when organs were studied *in vitro* or in anesthetized animals – where demand is relatively steady. Yet, for an alert animal in the real world demand fluctuates constantly and requires corresponding changes in response magnitude. A fixed capacity would be excessive for smaller loads (thus wasteful) but insufficient for larger loads (thus dangerous). Of course, Cannon and Selye noted exceptions to meet severe conditions (fight, flight, stress), but these were considered emergency systems superimposed on the basic homeostatic model.

Certain parameters are indeed regulated quite closely. For example, the mammalian brain is designed by natural selection with small safety factors for oxygen, glucose, temperature, and osmotic pressure. An insult that drives any one of these parameters beyond its design limit can trigger cascades of positive feedback that are quickly lethal. But the purpose of such tight regulation is not to defend "constancy" in the abstract. Rather, it is to improve efficiency, partly by conserving energy and space. If the brain were allotted a larger metabolic reserve and space to accommodate changes in volume, it could afford to relax these regulatory requirements, but that would produce a larger, clunkier, fuel-hogging organism – as happens with automobile designs when they are similarly unconstrained.

In fact, mammalian brain tissue, such as retina or a slice of cerebral cortex, functions for hours in a simple medium at *room temperature*. Neuronal sensitivity is lower than for the optimal 37° C by two-fold for each ten degrees, similar to the thermal coefficient of most biochemical reactions [10]. Higher temperature increases conduction velocity and reduces noise in axons by reducing channel open times. It also accelerates ion channel kinetics, which reduces overlap between currents, thus increasing spike efficiency. The combination of increased conduction velocity, reduced noise, and improved energy efficiency might have promoted the evolution of endothermy [11]. In short, close regulation of human brain temperature does not exemplify *the* condition for preserving *all* life – it is just *a* condition that serves efficient design.

A second reason why homeostatic control would be inefficient is that if each organ self-regulated independently, opportunities would be missed for efficient trade-offs. Thus each organ would require its own reserve capacity; this would require additional fuel and blood, and thus more digestive capacity, a larger heart, and so on – to support an expensive infrastructure rarely used. Efficiency requires organs to trade-off resources, that is, to grant each other short-term loans.

For example, resting skeletal muscle uses ~1.2 liters of oxygenated blood per minute, but peak effort requires ~22 l/min, nearly 20-fold more. Cardiac output increases, but that is insufficient, and although muscle can store fuel (glycogen and fatty acids), it cannot store much oxygen. Nor would it help to maintain a reservoir of de-oxygenated blood because at peak demand the lungs operate at full capacity. So a reservoir of de-oxygenated blood would require a reservoir of lung and heart. In turn, these would require increased capacities for digestion, absorption, excretion, and cooling. Consequently, for a non-storable resource subject to variable demand, it is most efficient to *borrow*[12].

Because the loan cannot come from brain, muscle borrows from kidney and viscera, whose individual shares of cardiac output both drop from about 20% to 1% [12]. Skin also contributes but this depends on circumstances, for in a warm environment the skin may need its blood supply for cooling. Gut can also postpone re-oxygenation, but following a meal it may need its blood supply to transport digests into the portal circulation. Clearly, these sorts of trade-offs are key to efficiency, but equally clearly, they could not be managed by local negative feedbacks. They require a higher level mechanism to evaluate needs and set priorities.

A third problem for homeostasis is that it cannot efficiently match capacities across stages that are functionally coupled. For example, during peak exercise lung capacity matches cardiovascular capacity, which matches the oxidative capacity of muscle mitochondria ["symmorphosis"; 12,13]. Because homeostasis would wait for each stage to produce an error signal and follow it with a correction, every initial change in demand would involve serial propagation of errors through the system – slow, awkward, and inefficient.

Pavlov identified a more efficient mechanism for the digestive system. He showed that mere sight of a particular food triggers salivation and gastric secretions with the appropriate composition – amylase for bread, protease for meat. Consequently by the time meat reaches the stomach, the appropriate digestive juices are waiting. This prescient demonstration of anticipatory matching across levels earned Pavlov a Nobel Prize, but the implications of his deep insight were not immediately appreciated [14].

A fourth problem for homeostasis is that it is not designed to minimize error. Although errors are unavoidable, they are bad. They can be acutely catastrophic, for example, a new distribution of blood pressure needs to be established *before* a change in posture, such as standing up, otherwise, the error ("postural hypotension") may cause fainting. Chronic errors can be damaging, for example, cardiovascular pathology due to chronic hypertension, chronic hyperlipidemia, and chronic hyperglycemia (see Fig. 8). An efficient system must not merely correct the errors but also find ways to minimize their magnitude and frequency.

3. An organ for predictive regulation

Given the intrinsic problems of homeostatic regulation, animals have evolved a special organ whose core task is not to clamp the internal milieu but rather to regulate it efficiently. This organ (the brain) monitors enormous numbers of external and internal parameters to anticipate changing needs, evaluate priorities, and prepare the organism to satisfy them *before* they lead to errors. The brain even anticipates its *own* local needs, increasing flow to certain regions – before there is an error signal [15].

Consider the record of arterial blood pressure measured continuously over 24 hours in a normal adult (Fig. 2). Far from holding steady, as expected for homeostatic control, pressure fluctuates markedly around 110/70 mm Hg for two hours. Then, corresponding to specific external stimuli and mental states that predict different needs, it varies more extremely. During a lecture, the subject predicting a low requirement for vigilance, dozes and his pressure falls to 80/50. Jabbed with a pin, his pressure spikes to 150/70; recognizing the prank, he again predicts safety, and pressure sinks to 80/50. During sexual intercourse, pressure spikes to 170/90 and then falls profoundly during sleep to ~70/40, including one hour as low as 55/30. Next morning, anticipating a stressful day, pressure steps up nearly to its level during sex and remains high for hours.

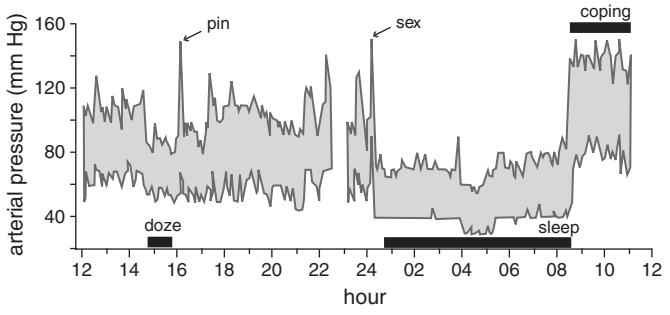

Fig. 2. Arterial pressure is not regulated to a set-point but shifts to meet predicted demand. Pressure was plotted in a normal adult at 5 minute intervals over 24 hours. Note that pressure spends about equal time above and below the steady daytime level. This pattern suggests, not defense of a set-point, but rather responsiveness to rising and falling demand. Upper trace, systolic; lower trace, diastolic. Redrawn from [47]; reprinted from [6].

This record contains no hint that blood pressure is defended at particular set-point. Quite the contrary, it fluctuates markedly and over multiple time scales – seconds, minutes, and hours. There are elevations, both brief and sustained, above and below the most frequent level. If this level represented a "set-point", it should fluctuate only mildly except when a particularly challenging signal would drive it higher (fight-or-flight).

That the pressure spends about as much time *far below* the most frequent level as above it is not predicted by a model of set-point + arousal-evoked elevation. If fluctuations were caused by poor control, for example by excessive or insufficient loop gain (Fig. 1), the deviations would show characteristic temporal patterns, such as "ringing" or lag. Thus the varied temporal patterns, plus their exquisite matching to particular behavioral states, imply that fluctuations arise not from poor control but from *precise* control.

The record suggests that pressure is regulated to match anticipated demand, rising to certain signals and falling to others. This implies that the most frequent value, 110/70, occurs, not because pressure is clamped there, but because that value satisfies the most frequent level of demand (Fig. 4). Indeed, were pressure actually clamped at an average value, it would match some specific need only by sheer accident. This is true for all states and all parameters: the goal is not to clamp a parameter at the average value, but to anticipate demands that depart from the average and move flexibly between them. But how could this occur, given local negative feedback mechanisms that do tend to resist fluctuations?

Once the brain predicts the most likely demand for oxygen, it resets various parameters to achieve the needed flow rate. Pressure here plays the same role as in a shower: for a given resistance, set by the caliber of all the channels, pressure sets the flow. To adjust the pressure, the brain directly modulates all three primary effectors: nerves signal the heart to pump faster, some blood vessels to constrict and others to dilate, and kidneys to retain salt and water. These direct neural messages are reinforced by additional signals acting in concert (Fig. 3). For example, the neural system that excites the primary effectors also releases multiple hormones that send the same message. Hormones signaling the opposite message are suppressed. This pattern: multiple, mutually reinforcing signals acting on multiple, mutually reinforcing effectors, overrides the various feedbacks that oppose change.

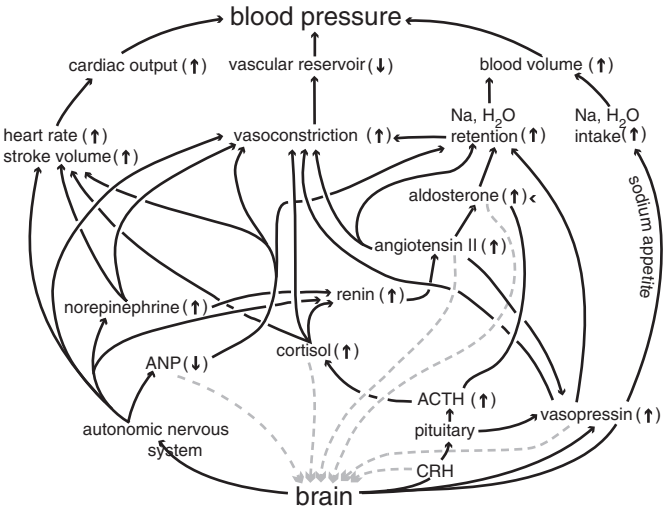

Fig. 3. Brain sets blood pressure via multiple, mutually reinforcing mechanisms. Negative feedback mechanisms are acutely overridden. When demand persists, all mechanisms are reset to operate at the new level. Most hormones illustrated here are also sensed by brain (dashed arrows) in specific regions that control behaviors that support increased pressure. Thus, aldosterone and angiotensin II are sensed by brain regions that enhance salt appetite and drive salt-seeking behavior. CRH, corticotrophic releasing hormone; ACTH, adrenal corticotrophic hormone; ANP, atrio-natiuretic peptide. Reprinted from [6].

The same is true for essentially *all* parameters: temperature, blood distribution, hormone levels, and so on. All change with different amplitudes and time constants, and these fluctuations all share a single goal. However, the goal is not constancy, but coordinated variation of broad patterns to optimize performance at the least cost. This is the core idea of predictive regulation, whose essential design principles are addressed next.

4. Design of predictive regulation

4.1. Efficient regulation uses broad, complementary patterns

The variations in blood pressure illustrated in Fig. 2 reflect complementary neural mechanisms for which we use the self-explanatory terms "arousal" and "relaxation".

During the 1960s John W Mason and colleagues studied monkeys during mild arousal accompanying a task that required focused attention over hours. Measuring multiple hormones, they found broad, complementary patterns: elevations of cortisol, epinephrine, norepinephrine, antidiuretic hormone, and growth hormone – all associated with catabolism – and suppression of other hormones, such as insulin and testosterone, associated with anabolism [16]. Prolonging the task caused sustained elevations of blood pressure resembling essential hypertension [17]. Mason concluded that the broad metabolic patterns over short and long time scales – even under mild conditions – are controlled by the brain.

Subsequently, myriad studies of neuroendocrine control confirmed and extended this concept [reviewed by 1,5–7,18]. Thus the changes in blood pressure illustrated in Fig. 2 are merely the tip of an iceberg – essentially every physiological parameter follows these broad patterns.

It seems obvious in retrospect why so many physiological parameters should be correlated, either negatively or positively. First, efficiency requires *matching* across components, so while muscles are being prepared for action, it is efficient to simultaneously prepare the heart, lungs, and liver. This explains the numerous positive correlations. Second, efficiency requires *reciprocity* – the body cannot effectively mobilize fuel and oxygen to meet catabolic demands while it is simultaneously siphoning them off for growth, repair, and immune surveillance. This explains the need for two complementary patterns – arousal and relaxation – alternating in time.

Third, to the extent that responses of different organs are correlated, they can be called by the same neural routine and can thus share some of the same signals. For example, cortisol activates many components of the broad catabolic pattern. Since the brain is an expensive organ [19], it is efficient to coordinate and execute broad patterns at the lowest possible level, saving space and energy for the more difficult computations which can then be used to modulate lower level routines. This strategy is used also in the somatic motor system, which organizes low-level, reciprocal motor patterns such as flexion/extension and stepping, and then modulates them from higher levels.

4.2. Peripheral mechanisms adapt locally to match predicted loads

Sensors typically use a sigmoid response curve with the midpoint matched to the statistically most probable load (Fig. 4). This assigns the curve's steep, linear region (most sensitive to small changes of load) to bracket the most probable loads and assigns the flatter, less sensitive regions to loads that are fairly *im*probable (either very weak or very strong). This design embodies "prior knowledge", derived from natural selection, regarding the natural distribution. Of course, load distributions can vary dramatically and thus require corresponding shifts in the curve. For example, as mean light intensity shifts over 24 hours by ten billion-fold, the photoreceptor's response curve, whose linear range spans only ten-fold, must shift correspondingly (Fig. 4).

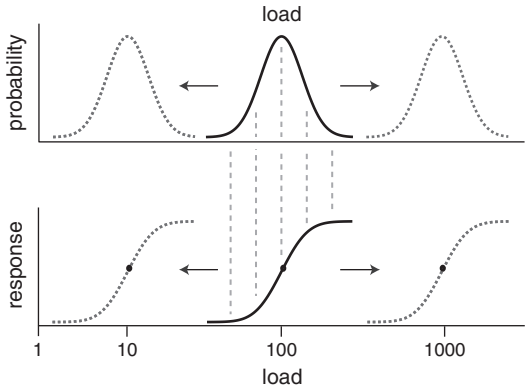

Fig. 4. Regulatory mechanisms adapt to keep the response curves centered on the most probable loads. Upper panel. Every system confronts some distribution of probable loads (bold curve). As conditions shift, so does the distribution (dashed). Lower panel. The response curve (bold) is typically sigmoid with its most sensitive region (steep part) matched to the most probable loads. As a sensor detects a statistically reliable change in predicted load, it signals effectors to prepare by shifting their response curves to match (dashed). The sensor also resets its own sensitivity. See [48]. Reprinted from [6].

The time course of predictive adaptation differs for each sensor and depends on how rapidly, how often, and how regularly the statistics change. For example, a baseball player awaiting his turn at the plate, takes a few minutes to swing several heavy bats. This promptly shifts the sensitivity curves of his mechano-receptors to anticipate a heavy load. When he steps up to the plate gripping a single bat, it feels unexpectedly light and thus can be swung with greater force. Adaptive shifts that occur rapidly also decay rapidly and rely on cellular mechanisms within the sensory receptors. Although such resetting is certainly based on feedback from an error signal, it is not homeostatic. That is, the error is not used to maintain constancy of a physiological parameter. Rather, it is used to predict what the parameter is most likely to be – thus preparing the system to match it more effectively.

Efficiency is enhanced by two levels of prediction: (i) most likely state in the next moment – generally best captured by the current state and its rate of change; (ii) probable time course of the new state. Calculating this second factor, *persistence,* improves efficiency because each adjustment has a cost – which can be reduced by anticipating regular shifts in demand. For example, circadian predictions of probable metabolic need exchange catabolic patterns for anabolic ones on a daily cycle, and prove so advantageous that they are used by every cell in the body to regulate the expression of innumerable different genes. The brain's circadian sensor (suprachiasmatic nucleus) resets to a shift in day length within one cycle, but the liver, which synthesizes many gene products under circadian control, resets over six days.

On a longer time scale, seasonal variations in day length predict average environmental temperature and food availability, performing much more reliably than local temperature. Furthermore, for migratory species day length predicts the most likely temperature thousands of miles away. Consequently, predictions based on day length have been built into the brains of many species as "prior knowledge" that profoundly regulates their physiology. This includes expansion and contraction of brain structures involved in territorial defense and mating, for example song nuclei in certain birds.

All cells regulate via diverse molecular sensors on their surfaces to meet predicted demands. Moreover, the receptors themselves adapt in number and sensitivity to match shifting expectations. Typically, prolonged exposure to high levels of a natural ligand (signaling molecule) reduces receptor number and sensitivity. This is another case of negative feedback that is not caused by an "error". Rather, this down regulation is an adaptive response to the anticipation of a higher level of the ligand.

Thus, when blood glucose is persistently elevated and triggers persistent secretion of insulin, insulin receptors eventually anticipate high insulin and down-regulate. The system learns that blood glucose is *supposed* to be high. Similarly, sustained demand for elevated blood pressure teaches all peripheral effectors to expect it, and gradually adapt: arterial smooth muscle cells hypertrophy to contract against higher pressure; the carotid sinus wall thickens to reduce baroreceptor sensitivity; secretory cells hypertrophy to support the pressure rise with more renin, norepinephrine, and cortisol. In short, it seems inevitable that the sustained elevation of blood glucose would gradually reduce insulin sensitivity; i.e. cause "insulin resistance" and thus type 2 diabetes; it seems equally inevitable that sustained elevation of blood pressure would gradually cause essential hypertension. Such changes are the appropriate adaptations to predicted demand (Fig. 4).

4.3. Signals that regulate the periphery are monitored by brain

Where efficient control needs sharp localization in space and time, direct innervation is used. Thus blood vessels and various peripheral endocrine cells, such as insulin-secreting cells in pancreas and renin-secreting cells in kidney, are all directly innervated. But the hormones so modulated, for example, insulin, renin, angiotensin, and aldosterone, are monitored centrally.

In fact most peripheral effector substances, such as catecholamines, peptides, steroid and protein hormones, are monitored by low-level mechanisms in brainstem and hypothalamus and even higher level sites, such as the amygdala and hippocampus. Some effector substances penetrate the blood brain barrier and others, though impermeant, are sampled at special sites (circumventricular organs) where the barrier opens to allow direct contact between blood and central sensors. For example, this allows, the subfornical organ to directly monitor blood sodium levels while also monitoring angiotensin and aldosterone, key hormones that regulate sodium, water and blood pressure [20].

The information gathered from neural sensors in the periphery (e.g., pressure at carotid sinus, heart, and aorta) is integrated with information gathered from the central monitors and used in two ways. First, the brain continuously re-computes anticipated needs for blood distribution and re-sets priorities, including immediate needs to "spend" and longer range needs to "save". For example, a well-hydrated hiker on a cool day may empty his bladder regularly, but if the day is hot, he may not void a drop because his kidneys have been conserving salt and water. The kidney cannot predict what will be needed – but the brain can – and sensing temperature, need to sweat, and blood levels of sodium, aldosterone, and angiotensin – it authoritatively shifts renal mechanisms into "conservation mode".

Second, the brain uses its sensing of peripheral signals to continually update its "shopping lists". For example, the hormones aldosterone and angiotensin that drive the kidney to conserve salt and water also drive the *appetites* for salt and water and support behaviors to replenish them. The same is true for many (possibly most) regulatory signals: whatever their action in the periphery, they simultaneously drive corresponding central appetites. Therefore, when arousal releases peripheral catabolic hormones, such as cortisol and orexin, to mobilize glucose and fatty acids, these hormones also increase hunger. Moreover, efforts to restrict food intake by "dieting" are treated by the brain as threatening and thereby intensify arousal, raising cortisol, and driving the sense of hunger all the harder [21].

4.4. Internal regulation requires foraging behavior

It is efficient, of course, to keep inventories and shopping lists, but what gets us up and out the door? Consider our hiker. While his subfornical organ monitors blood sodium, aldosterone, and angiotensin, other sensors monitor air and body temperature to help set a sweating rate for cooling. At a certain moment the brainstem mechanisms that integrate all these data may conclude that, despite reduced urine formation, an external source of water will be needed and that the hiker should start looking for it. With time this message intensifies, and to the growing sense of thirst is added a sense of anxiety. This serves as a "stick" to arouse and focus both body and mind: "Find water, damn it!" The sense of anxiety persists until the need that triggered it is satisfied.

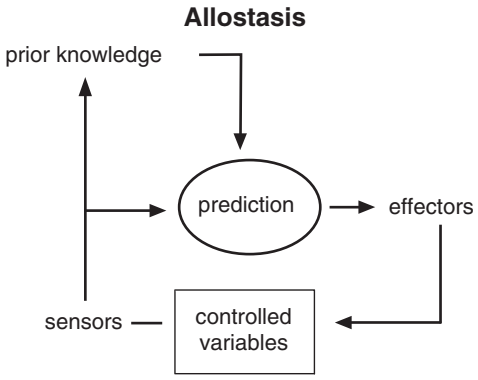

Fig. 5. Allostasis model. The brain integrates prior knowledge with sensory data to predict what resources will most likely be needed. The brain then directs effectors to optimize the distribution of resources in space and time. An arrow leads from "sensors" to "prior knowledge" because the brain integrates – and stores in compressed format – lessons from today's sensing – so that they can become tomorrow's "prior knowledge.

With any luck the hiker finds water *before* his internal milieu has deteriorated. And to the extent that he felt endangered, the negative feelings (anxiety, fear) are used to mark the memory of this event to prevent its repetition. Next time, he will start at dawn and carry Gatorade. In short, the anticipatory mechanisms that use anxiety and fear to drive us forward toward a goal, also drive efficient learning mechanisms that attach stable warning labels to threatening events, smells, sounds, and tastes.

In summary, efficient regulation depends on the brain's sensing the current state, integrating this information with its prior knowledge to optimize its regulatory decisions. By also relaying current messages to higher levels, today's "lessons" become tomorrow's "prior knowledge". This is the allostasis model (Fig. 5).

5. Allostasis uses high-level brain mechanisms

A key brain locus of the "stick" component of anticipatory regulation is the amygdala, a forebrain structure that integrates myriad lower level physiological signals: (i) steroid hormones and peptides that regulate blood pressure, mineral and energy balance; (ii) neural signals from the brainstem visceral areas, such as nucleus of the solitary tract and the hypothalamus; (iii) signals from brainstem raphé neurons that modulate levels of arousal and mood via the neural transmitter, serotonin [22–24].

Certain neurons in the amygdala's central nucleus are excited by cortisol (which in the periphery is a key component of the arousal response) to release the hormone CRH (corticotrophin-releasing hormone) whose levels correlate with anxiety [18]. The central nucleus connects reciprocally with the hippocampus, to which it is adjacent, thus allowing efficient storage and retrieval of anxious memories [25]. The amygdala reports its "concerns" to prefrontal cortex (Fig. 6B), a region concern with planning and deciding [26]. So this pathway allows insistent signals regarding incipient needs and past dangers to shape the plan. The stick may suffice to get us moving and warn us of danger, but the environment presents many possibilities for foraging, and how is an organism to calculate which

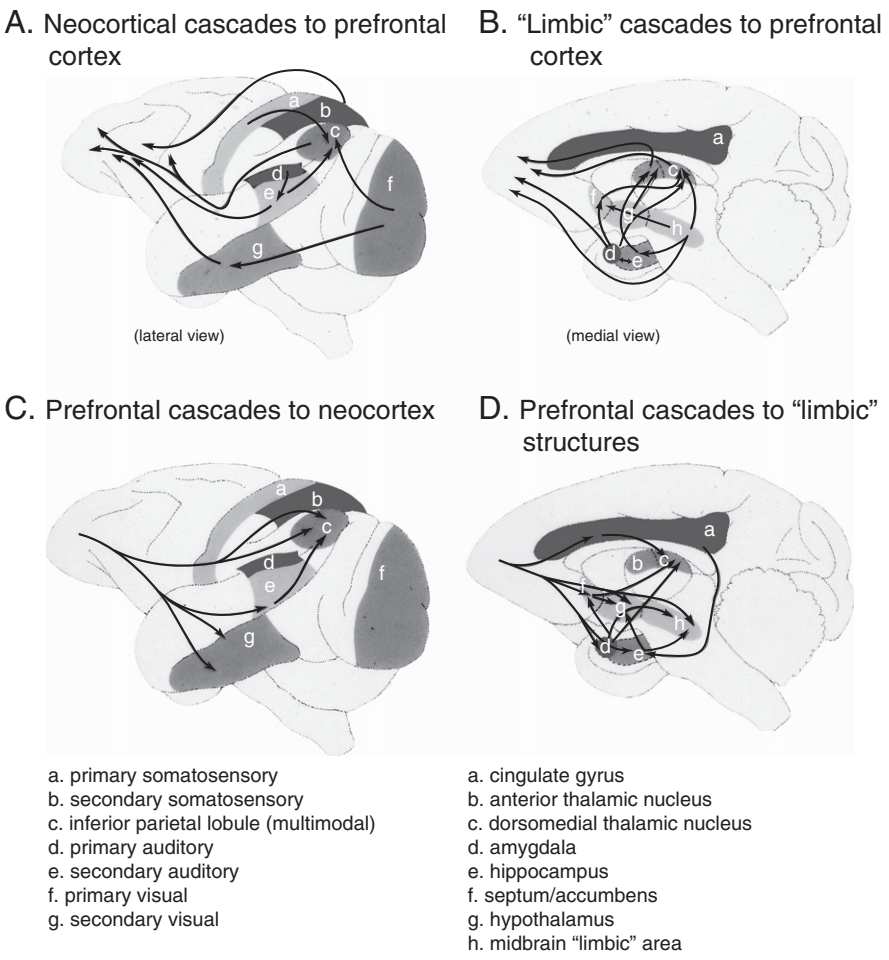

Fig. 6. Prefrontal cortex integrates cascaded inputs from neocortical and "limbic" structures - and feeds back to both. This arrangement serves two functions: to imbue intellectual calculations with urgency and focus, and to modulate emotional expression by perceptual and cognitive context [49]; see especially [50]. Diagram shows the brain of macaque monkey. Modified from [6].

is best? This core problem is addressed by the midbrain reward system, which to the amygdala's stick, serves the role of "carrot".

6. What neural signals optimize foraging?

Foraging decisions can be complicated. Should an animal search first for water or food? If the latter, *which* food? Where to search? Should it search where food is plentiful, drawing competition? If so, how much competition should it tolerate before moving to a sparser, less competitive spot? How much danger should it tolerate, and how much effort should it expend?

The answers depend partly on signals from the internal milieu, as communicated through the "stick" system. If an animal is profoundly hungry, it will tolerate higher than normal risk and expend greater than normal effort to obtain a morsel, even though it may be of less than normal quality. One can easily observe these calculations at a bird feeder, where a normally meek bird, momentarily hungry, will stand up to a more aggressive one and feed, until being sated, its natural timidity again rules. Or a bird will feed near to the best cover (foliage) – unless food is only in available the open, and hunger supersedes caution. These calculations depend, of course, on a great deal of prior knowledge, some of it genetically programmed, some of it taught by parents, and some of it learned from life experience.

Carrot delivery follows a well defined economic calculation, termed "reward prediction error" [reviewed by 27,28] Neural mechanisms calculate how much reward should be anticipated for a particular effort and then delivers when the result is *better* than predicted. The central representation of "reward" is a brief burst of spikes in neurons of the ventral midbrain that release a pulse of dopamine to the nucleus accumbens and prefrontal cortex. The precise correspondence between a "feeling" and a specific neurotransmitter is difficult to establish and is probably oversimplified, since many chemicals change in concert. Yet, one imagines that the dopamine pulse evokes momentary relief from flagellating anxiety and a brief sense of satisfaction/pleasure – at last, the carrot.

This calculation of "reward prediction error" implies that, as the nominal reward (such as food or water) is delivered repeatedly following a signal, its surprise value declines and so, therefore, does the amount of dopamine. Moreover, *sensitivity* to dopamine also declines because dopamine receptors, anticipating high levels have down-regulated (Fig. 4). This may explain Goethe's famous remark, "*Nothing is harder to bear than a succession of fair days.*"

The pulse of dopamine seems to evoke a feeling that we associate with an object of desire, but actually as a signal repeatedly predicts a reward, e.g., a tone that reliably predicts food, the pulse of dopamine shifts earlier in time, associating with the predictive signal rather than the external reward. This counterintuitive feature belongs to the algorithm for reward prediction and supports the hypothesis that the system is actually performing an optimal calculation [reviewed by 27,28].

This reward system has two additional advantages. First, by establishing a final common pathway for optimally calculating *many* peripheral regulatory needs (water, salt, sugar, protein, temperature), the brain can avoid redundant parallel circuits. This could only work if the dopamine

pulse and the satisfaction that it delivers were brief – so that the system can reset to reward the next priority. Second, because the pulse *is* brief it can be associated temporally with a repeated signal, allowing an organism to learn quickly which signals are important and which can be ignored. Were pleasure prolonged, we would be hard put to correlate it with the critical signal rather than with some earlier or later event.

One downside of this push-pull design seems evident. The list of needs that cause anxiety is at least as long as the list that might give pleasure. Moreover, the anxiety mechanisms are designed to be prolonged and non-adapting; whereas the pleasure mechanism is designed to be brief and adapting. Consequently, *we* are designed to experience substantially more anxiety than pleasure. Freud captured this painful conundrum in a way that now seems to map remarkably onto its neural substrate:

> *One feels inclined to say that man should be 'happy' is not included in the plan of 'Creation'. What we call happiness in the strictest sense comes from the (preferably sudden) satisfaction of needs which have been dammed up to a high degree, and it is from nature only possible as an episodic phenomenon. When any situation that is desired by the pleasure principle is prolonged, it only produces a feeling of mild contentment. We are so made that we can derive intense enjoyment only from a contrast and very little from a state of things. Thus our possibilities of happiness are already restricted by our constitution" Unhappiness is much less difficult to experience. We are threatened with suffering from three directions: from our own body, which cannot do without pain and anxiety as warning signals; from the external world, which may rage against us, and from our relations to other(s). Suffering which comes from this last source is perhaps more painful to us than any other* [29, my underscore; edited for brevity].

7. Efficient design: "A" for effort

Success at any difficult task requires some investment of effort without expectation of short-term external reward. Sometimes one must even *prefer* a harder task to an easier one. This has obvious selective advantage for basic neurobiological reasons. Proficiency requires practice: it is essential to training control circuits, for example, in cerebellum for both motor and non-motor tasks [30].

But, if effort promises no immediate external reward, how can be sustained? Apparently, the reward system is designed to deliver some level of satisfaction for effort alone. Of course natural talent – athleticism, musicality, verbal or mathematical abilities – have their own distributions in a population. But these talents only flourish when conjoined with high levels of effort – which initially are rewarded from within.

This intuition is supported by animal studies suggesting that effort toward a goal uses dopamine mechanisms [31]. For example, rats raised to work for their food were more willing to search for a hidden reward than were "trust-fund" rats, reared to feed without effort. Moreover, human fMRI shows activity in dopaminergic midbrain areas during a task of greater effort (identifying shapes vs. colors) when neither success nor failure are rewarded [32]. The "stick"component also appears to contribute in that serotonin release from the dorsal raphé neurons to amygdala and prefrontal cortex sustains effort when rewards are delayed [22–24].

Reward for effort and practice might be triggered by neural projections downward from prefrontal cortex to the reward structures (Fig. 6D). These might well initiate serotonin and dopamine pulses to sustain such key efforts as the early manufacture of stone tools. Consistent with this brain expansion of apes, especially the frontal lobe, correlates with tool use [33]. Reward-prediction experiments typically attribute activity in midbrain reward regions to the reward-predicting properties of the stimulus – but, some of the dopamine might well arise from the required cognitive or physical effort. These factors are hard to separate [32]. However, we hypothesize that both are relevant to the regulatory disorders of modern society.

8. Reproductive success often depends on social cooperation

Homeostasis proposes that all is steady except for emergencies, when resources are sharply mobilized for acute "fight or flight" and/or to cope with more prolonged "stress". But allostasis notes that the blood pressure record shown in Fig. 2 is typical and that pressure is regulated continually – 24/7 – to match even mild changes in demand. Mason made the same point for hormones, based on his finding that a monkey set to a mild laboratory task shifts its hormones in broad patterns: catabolic as part of the arousal response to increased demand; and anabolic as part of a growth and repair response to periods of relaxation.

But what happens outside the laboratory? Do these endocrine shifts belong to normal life? If so, are they "adaptive" i.e., do they demonstrably improve chances of survival and reproduction? Myriad human studies support this hypothesis [reviewed, 6,7,9], but they rely on statistical correlations in large samples, rather than on direct observation and experiment. This lends special interest to long term studies of baboon troops in the wild – where social relationships were closely followed and matched to cortisol levels in fecal samples of known provenance [34,35].

Membership in a troop demonstrably improves baboon survival. The key advantages lie in better detection of predators (90 animals are more likely to spot a predator) and defense: when a troop encounters a leopard, *everyone* attacks it, including females and juveniles as well as adult males. Because predation is a major cause of mortality among females and young, a female's membership in the troop measurably improves her reproductive success. On the other hand, a female may lose her infant to infanticide committed by a newly dominant male – in his impatience to return her to sexual cycling. So a mother allies herself with other females and with a male "friend" who help protect the infant.

But, since her allies also compete with her for food and shade, it is tricky to hold the balance between cooperation and antagonism. The mother needs to recognize every troop member by voice, know their social ranks and her position in the overall structure. This allows her to calculate how to treat each group member: ignore, acknowledge, give way, groom, or threaten. Each male needs comparable information to track and update his opportunities for mating. Moreover, social structure shifts constantly, as female alliances form and dissolve, and as males move up or down their dominance hierarchy. So there is a constant stream of data from "social sensors" to update the individual's "social register".

Perceptual streams flow from integrative areas of neocortex to prefrontal areas (Fig. 6A), which in different species of monkey are proportional to group size [33]. Given the evident survival value of their complex social structure, this seems like a good investment. What is required in the way of physiological support? It turns out that shifts in social structure are accompanied by changes in cortisol excretion, which is a reliable marker for the broad catabolic/anabolic patterns [35].

For example, high ranking males normally have somewhat lower cortisol than low ranking males, but during a power shift within the upper ranks, all high ranking males excrete more cortisol; those of lower rank, who are unaffected by this shift, do not change. A female, bereaved by loss of an ally, shows a rise in cortisol excretion. Then, as she extends her network of social connections by adding more grooming partners and spending more time at it, her cortisol relaxes [36,37]. In short, the arousal mechanisms that modulate broad response patterns are not reserved for emergencies: they are quotidian mechanisms for managing the soap opera that is life in the troop.

9. Social cooperation exploits stick/carrot mechanisms

For a baboon to reliably and safely obtain its groceries (food, salt, and water) requires the cooperation and forbearance of others;

therefore, the animal must invest in and maintain its social connectedness. Probably because it is efficient, the push-pull mechanism of anxiety and pleasure that optimize low-level foraging also serves as a final common pathway for social needs. To find a grooming partner can be as urgent and as satisfying - as finding a ripe fruit. Social needs and satisfactions widen the variety of experiences and behaviors that funnel into the reward system. And as its needs for social connection are satisfied, the individual's level of arousal declines.

From baboons to humans, the funnel widens enormously. For example, baboons lack *empathy*, the ability to imagine what another might be feeling. But its appearance in humans allows innumerable pleasures to be obtained from *shared* experience – of nature, religion, music, art, literature, and sports. These shared pleasures support a sense of connectedness that seems essential to human cooperation. Yet, civilization now shrinks the possibilities for small, effortful pleasures, and with this loss seems to arise a sense of 'alienation' – disconnectedness – that sustains arousal and leads to chronic disease (Fig. 7).

This occurs partly from reduced environmental variation. How much pleasure can be obtained from a sip of cool water – in an air-conditioned office? And where is the satisfaction in moving from one warm room to another? Modern social organization also reduces the pleasure of direct experience – for example, the pleasure of eating what we grow or kill. Primary experience is replaced by vicarious experience – which lacks authenticity and requires less effort. In general, music from a compact disk is less satisfying than live performance; fast food is less satisfying than home cooking; and watching sex is less satisfying than doing it. Both factors – reduced authenticity and reduced effort – probably contribute to reduced satisfaction.

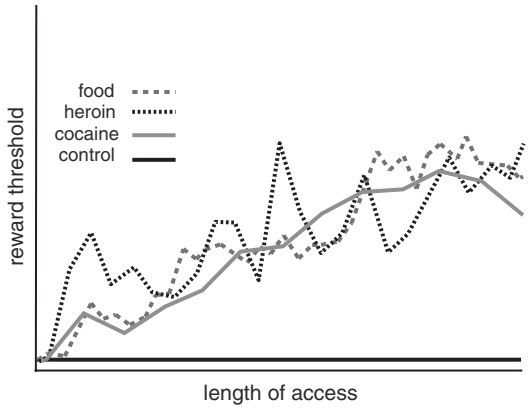

Fig. 8. Reward thresholds rise similarly with extended daily access to palatable food, cocaine, or heroin. Elevated reward thresholds reflect decreased sensitivity of the brain reward system, suggesting that daily consumption of rich food induces deficits in brain reward systems comparable to those induced by regular consumption of addictive drugs. Reprinted with modifications from Fig. 3, [38].

As the range of possible satisfactions narrows, people concentrate on a few that are readily available and cheap. But of course, pleasure from a single source declines with repetition, because of adaptation in the reward pathway. Therefore, an equivalent degree of satisfaction requires progressively larger doses from that source. This may initiate the addictive cycle that operates as powerfully for food as for drugs [Fig. 7; 38].

This might explain why modern disorders of regulation take the form of compulsive behaviors – addictions. These do not arise from intrinsic

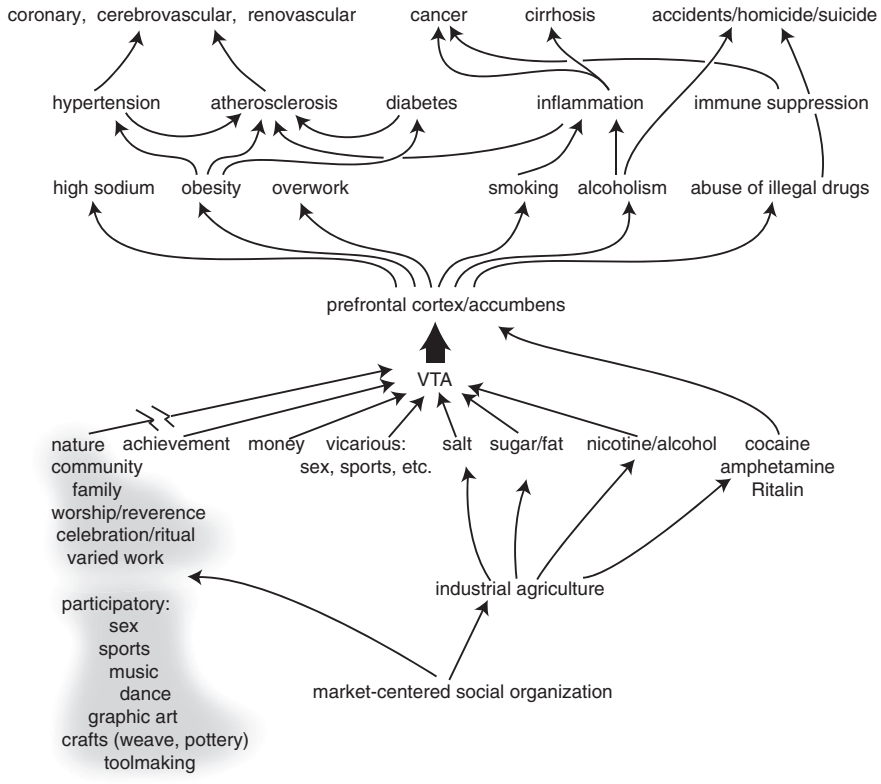

Fig. 7. Market-centered social organization requires hypervigilance but narrows the sources of satisfaction. This causes disorders from chronic arousal, such as hypertension and atherosclerosis, which are exacerbated by disorders from addictive behaviors that try to maintain reward levels in key brain regions. Each potential satisfaction (shaded on left) can cause neurons in the ventral tegmental area (VTA) to deliver a pulse of dopamine to the nucleus accumbens and prefrontal cortex and provide a brief sense of well-being [50,27,28]. By design, satisfaction from each source adapts, thus requiring either a new source or higher levels of input from the same source. Chronic arousal elevates appetites for salt, amino acids, fats and sugars, which "industrial agriculture" provides cheaply [51] and with attenuated demand for physical effort, which itself increases reward. This leads to a panoply of pathogenetic mechanisms including obesity and type 2 diabetes. When the cerebral reward system is unsatisfied by natural inputs, people use "recreational" drugs to stimulate it directly [52]. Reprinted from [6].

low-level defects. For example, essential hypertension is not caused by any identifiable "broken" connection or defective process; nor in general is obesity. Rather, they seem to arise from the difficulty of finding a rhythm and balance that provides stable reward values [39,40]. This means maintaining sufficient variety to reduce adaptation and requiring sufficient effort that some value is gained from that source as well.

10. What *is* "health"?

The allostasis model defines health as *optimal predictive fluctuation*. Increased demand calls for increased response capacity, so the latter shifts until the most common response occupies the mean and the effectors are prepared to increase or decrease as needed (Fig. 9A). When the prediction reverses, so should the response. A system is *un*healthy when its effectors adapt so tenaciously that, reversing the prediction fails to alter the response range (Fig. 9B). Pharmacotherapy acting at low levels can force the response back toward the original level, but this compresses the responses and narrows their range (Fig. 9C).

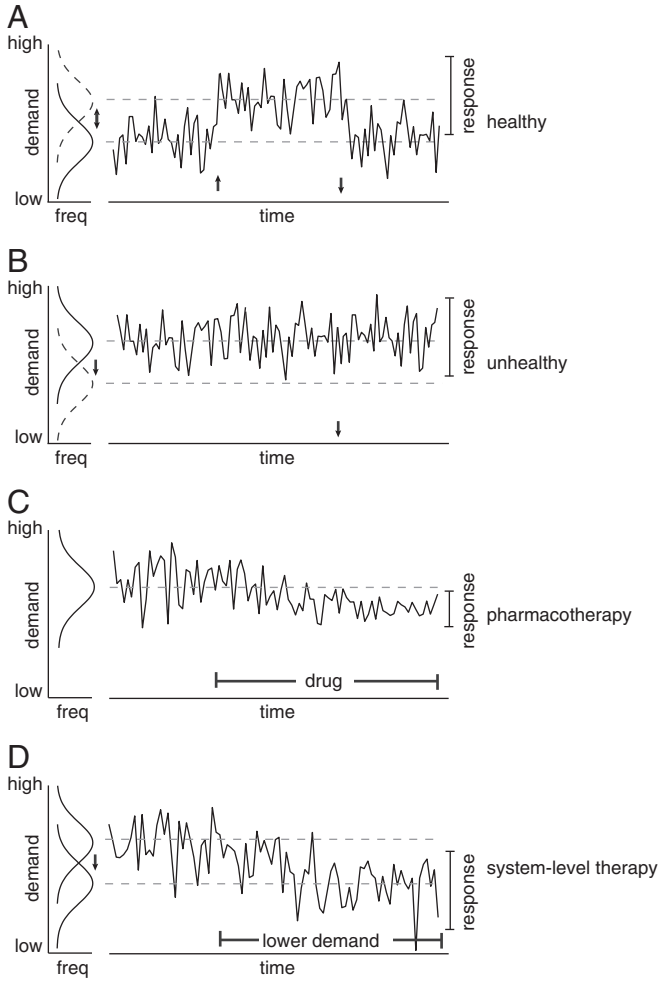

Fig. 9. Where to intervene? A. Healthy system. Demand distribution rises briefly (solid curve =>dashed curve), and response distribution follows to keep it centered on most probable demand. Demand distribution falls, and response distribution follows. B. Unhealthy system. Demand rises for long times, and system adapts to this expectation. When demand falls briefly, system does not follow. C. Pharmacotherapy. Homeostasis model targets low levels. Under high demand, antagonists of key effectors can force the response distribution downward. But this reduces responsiveness, forcing the organism to meet elevated demand with fewer and weaker effectors. D. Systems-level therapy. Allostasis model targets higher levels. When demand is reduced for longer periods, the system gradually re-adapts to the initial demand distribution while maintaining responsiveness. This process may be facilitated by restoring earlier sources of small pleasures and finding new ones. Reprinted from [6].

For example, pharmacotherapy for essential hypertension, a disease substantially attributable to chronic arousal [reviewed, e.g., 41,6] targets the primary effectors: diuretics to reduce blood volume via renal loss of sodium and water; antagonists to dilate the vascular tree; and antagonists to reduce cardiac output. But these mechanisms are set by concerted signals from the brain (Fig. 3), so when one is suppressed, the brain compensates by driving the others harder. The compensatory responses can be blocked by additional antagonists, but adding more drugs to a complex system frequently becomes iatrogenic. Furthermore, clamping a parameter by blocking all its effectors, renders it unable to respond to predicted need (Fig. 9C).

Similar problems are faced by drug therapy for obesity, a disorder that certainly looks like an addiction (Fig. 7). As experts acknowledge,

> *Theoretically, drugs that target neuronal receptors for leptin, insulin, ghrelin, melanocortins, NPY, etc. have potential, but therapeutic breakthroughs have yet to emerge. One obstacle is the integrated nature of energy homeostasis neuronal systems, which predicts that efficacy of targeting one neuronal subset or pathway is limited by compensatory responses elsewhere… effective prevention or treatment of obesity may therefore require drug combinations that target discrete components of energy homeostasis, satiety or food reward systems…* [42, edited for brevity and emphasis].

Allostasis suggests a different therapeutic goal: to restore *flexibility of response capacity* so that it can again shift according to predicted demand and thus preserve the range of responsiveness (Fig. 9D).

This seems to work for hypertension. Recent authoritative recommendations for treatment are no longer drugs but: (i) weight loss; (ii) exercise; (iii) moderation of alcohol consumption; (iv) diet reduced in sodium and fat and increased in calcium, potassium, and fiber; (v) cessation of smoking [43]. Weight loss, strongly correlated with reduced blood pressure, is considered to be the most effective of all nonpharmacological treatments. Moderate exercise, such as brisk walking or bicycling thee times per week, may lower systolic pressure by 4–8 mm Hg. The "DASH" study found overall reductions in blood pressure of 11.4/5.5 mm Hg to a diet rich in fruits, vegetables, and low-fat dairy products, with further pressure reductions to reduced sodium. These reductions appear "comparable to or greater than those usually seen with monotherapy (i.e., 1 drug) for stage 1 hypertension" [44].

To the extent that regular exercise reduces chronic arousal, it reduces the hormones that drive the hungers for salt and fat. This facilitates conscious efforts to reduce these dietary components. Whereas dieting alone increases arousal hormones (e.g., cortisol) and stimulates hunger [21], exercise can be a small pleasure and contribute independently to shifting the prediction.

The most successful interventions acknowledge the sense of need and try to satisfy it by enlarging positive social interactions that restore the sense of connectedness. Outstanding examples are "therapeutic communities", such as the "twelve-step" programs. Self-help works too [38], including efforts to expand sources of pleasure: a hobby; new friends; a pet; cook an authentic meal; bake authentic bread. Baboons teach, after all, that bereavement is treated effectively by efforts to expand social connections [34].

The allostasis model hints that large improvements in health might be achieved by enhancing public life. The guiding principle would be: invest in anything that promises to reduce hypervigilance and expand possibilities for small, effort-requiring satisfactions. Enhance contact with nature by building more parks and by providing communal opportunities to garden – i.e. not just to look but to grow flowers and vegetables. Enhance opportunities to walk and cycle by restricting automobile traffic. Encourage broader participation in sports especially among youth – by constructing public facilities for gymnastics, skating, skate-boarding, climbing, and swimming. Improve work. No human can

be satisfied to perform an unvarying task for eight hours a day, 40 hours per week, 50 weeks per year.

11. Conclusions

One subtext of the homeostasis model is that close, automatic regulation of the internal milieu has allowed the great expansion of the human brain with its infinity of higher faculties, such as language, literature, and art. These faculties, as Darwin realized, must have evolved by natural selection and therefore must have promoted reproductive success. But the homeostasis model offers no framework for understanding this. It does not try to explain what these higher faculties are *for*, and thus it fails to ask what the *brain* is for. In this sense the homeostasis model is essentially pre-Darwinian.

Regarding this question, the allostasis model is specific. It claims that the brain is fundamentally an organ for predictive regulation of the internal milieu. Predictive regulation is efficient for numerous reasons mentioned in this essay, and these efficiencies have justified, through natural selection, a dedicated organ for this purpose. Even tiny organisms, such as the worm, C. elegans, invest hugely in a brain (one-third of its total cells). Thus for the allostasis model it is not regulation that enables the brain – but rather the opposite: it is the brain that enables efficient regulation.

If the brain is indeed an organ for predictive regulation, it follows that our higher faculties must also serve this function. The baboon studies support this claim because they connect, for individual animals in the wild, patterns of arousal (via its marker, excreted cortisol) to fluctuations in social interaction. Certain situations and interactions evoke a pattern of arousal – which supports the animal as it works to improve its social connections. Then, when they *do* improve, the arousal pattern resolves. The capacity to function in this social network is shown to require mental abilities that we easily recognize as "higher". Finally, the studies document that the ability to maintain and manage these social connections improves the individual's longevity and reproductive success [45,46].

In short, these studies connect across levels: individual physiology to social behavior to survival. It then seems obvious that humans, being intensely social, will need similar mechanisms – but elevated and elaborated in the extreme. Our unique capacities for love, deception, and treachery; plus our needs for apology and reassurance, must far exceed those of baboons. When we attend to our social relationships – through play and celebration, confession and atonement, we reduce our needs for vigilance that require arousal with its catabolic pattern, and thus allow relaxation and anabolism. These anabolism-promoting behaviors are ancient components of human culture. In short, the allostasis model recalls the early idea that health is intimately connected with placating spirits (including our own) through maintaining communal relationships.

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