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Individual differences and the stress response

Robert M. Sapolsky

Amid the deleterious consequences of prolonged stress, there is tremendous variability in how readily various stressors provoke stress responses in different individuals. This review covers some of the underpinnings of such differences, heavily emphasizing adrenocortical secretion of glucocorticoids during stress, and responsiveness to psychological, rather than physical stressors. Psychological stress is shown to involve loss of control or of predictability, an absence of outlets for frustration, an absence of social support, and a perception of events worsening; some powerful studies show that the physiological and pathophysiological responses to identical physical stressors will vary dramatically as a result of manipulating some of those psychological variables. Those findings are then used to interpret a literature concerning differences in the stress response among individuals of different ranks among a variety of social animal species. In a broad manner, social dominance in a stable hierarchy, with its attendant psychological rewards, is associated with a more adaptive stress response, as measured by a number of physiological endpoints. However, considerable subtleties in this relationship exist, transcending the mere issue of rank. Instead, rank and its physiological correlates are sensitive to the society in which the rank occurs, the individual's experience of both that rank and that society, and personality factors that color the perception of external events. Finally, these primate studies are used to interpret data in the health psychology field concerning individual differences and coping mechanisms in humans.

Key words: stress / glucocorticoids / individual differences / primate social behavior / baboons / coping / stress management / psychological stress

AS SCIENTISTS, we typically abhor variability in our data, as it signals trouble—our measurement instruments are imprecise, our study subjects are heterogeneous, and so on. Yet, when it comes to the topic of this issue, such individual variability is welcome and essential. A theme of many of these papers is the deleterious nature of stress, whether manifested as, for example, increased psychiatric risk,[1] accelerated hippocampal aging,[2] or disruption of development.[3] Despite the general linkings of stress with such dysfunction, there is tremendous variability in the data—stated most simply, bodies and psyches differ tremendously in their vulnerability to stress. It is essential to understand the mechanistic underpinnings of such variability, in order to derive means for minimizing the impact of stress in the most vulnerable of individuals. This paper reviews some of the features of individual variability in the stress response. There will be two biases in the literature covered. The first is a rather heavy emphasis on the adrenocortical axis, an emphasis continued in many of the other papers in this issue. In addition, I focus on individual variability in responses to psychological, rather than physical stressors, and in the context of psychosocial variables such as dominance rank and personality. Naturally, this is not the only framework in which to analyze such variability. For example, some investigators have emphasized the role of genetics,[4] and others, differential perinatal experience,[3] in giving rise to differences in the adult stress response. Obviously, these different orientations do not define exclusive domains—as but one example of this, adult dominance rank in social primates can reflect both genetic and neonatal influences.

Why is psychological stress stressful?

A major physical stressor produces a fairly stereotyped stress response among individuals; for example, few of us would fail to secrete catecholamines or glucocorticoids if happening to be mauled by a lion. In contrast, there is far greater interindividual variability in the magnitude and quality of responses to more psychological stressors—in the realm of our everyday experiences, what might be pathogenically stressful for one individual might be something that a second person would pay to do recreationally. Thus, differences in the psychological context of a physical stressor are important variables in generating individual variability in the physiological stress response. In the face of a consistent physical challenge to homeostasis, what psychological factors

From the Department of Biological Sciences, Stanford University, Stanford, CA 94305, USA

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modulate the magnitude of the resultant stress response? In the absence of an overt homeostatic insult, what psychological factors can independently initiate a stress response?

Arguably, foremost among psychological stressors is a lack of control. This is shown most clearly in rodent studies in which pairs of rats are subjected to intermittent shocks. One rat would have control over the situation, being able to lever press in order to decrease the likelihood of shocks; the second rat is passively 'yoked' to the shock pattern of the first. Over a wide range of shock schedules, the second rat, without control, secretes more glucocorticoids and is more vulnerable to gastric erosions.[5-10] Similar findings have emerged with studies of primates,[11] dogs[12] and humans.[13] As a demonstration that loss of control can cause a stress response itself, rather than merely magnify the response triggered by a physical stressor, removal of such a lever from the cage of a rat trained to press it will trigger glucocorticoid secretion, even in the absence of shocks.[14]

A second and related psychological stressor involves lack of predictability. This has been demonstrated in rats and dogs receiving shocks, in which glucocorticoid secretion is lessened in animals receiving a warning signal preceding the onset of a shock,[8,12] or a warning signaling the end of the shock session.[15] In each of those scenarios, the rat is able to reduce its vigilance when receiving either the explicit (in the second case) or implicit (in the first case) information that the shocks have ended.

Some investigators have emphasized that both loss of control and of predictability combine to cause arousal and vigilance,[16] or represent discrepancy with expectations (i.e. novelty[17]). Others have emphasized that the common theme of the two involves loss of feedback of information.[5-7] One can see the common threads among these various formulations. As an example of psychological stressors most readily interpreted along the lines of novelty, placing an infant monkey into a novel setting provokes glucocorticoid secretion; coupling that with novel individuals worsens the stress response, while coupling that with known individuals attenuates it.[16] As a powerful example of the roles of control and predictability applied to the human experience, individuals with chronic pain syndromes consume less pain medication when they can self-medicate than if they have to rely upon nurses to respond to their requests for medication. The standard explanation given for this is that in the latter case, medication is being requested both for the pain and to quell the stressfulness of the lack of control and predictability.[18,19]

Another facet of psychological stress involves loss of outlets for frustration. Numerous studies have shown that the magnitude of glucocorticoid secretion (or likelihood of ulceration) in response to shocks decreases in rats allowed any of a broad array of unrelated outlets. They include displacing aggression onto a conspecific, being allowed a consummatory event such as eating or drinking, or being allowed access to a running wheel.[17,20-23] Unfortunately, among primates and humans, displacement of aggression is a particularly common and effective outlet; for example, among baboons, individuals who are most likely to displace aggression onto a third following a loss of a dominance interaction have lower basal glucocorticoid concentrations than animals least likely to.[24] On a more optimistic note, also within the primate and human realm, one of the most powerful modulators of the stress response, arguably interpretable within this context, is the outlet of social affiliation. Among humans, the degree of social affiliation is a substantial predictor of disease risk and life expectancy.[25] Medically protective relationships can take the form of marriage, contact with friends and extended family, church membership, or other group affiliations. The magnitude of the effect is as large as for variables such as cigarette smoking, hypertension, obesity and level of physical activity, and people with the fewest social connections have approximately 2.5 times as much chance of dying as those with most connections, after controlling for age, gender and health status. The protective effects of affiliation cannot be attributed merely to factors such as individuals with spouses being reminded to maintain a medication schedule.

Finally, for the same physical stressor, a larger stress response is observed if that event is interpreted as indicating that things are worsening, rather than improving. For example, among numerous social primates, instability of the dominance hierarchy is associated with elevated basal glucocorticoid concentrations among the individuals whose ranks are declining amid the instability, but not among those whose ranks are rising.[26] As an example among humans, one classic study demonstrated near basal glucocorticoid concentrations among parents of children having an approximate 25% likelihood of dying from cancer. Initially, this seems quite surprising, given the presumed stressfulness of such a situation. However, this is explained by

the context of the situation—such children were in remission, having had vastly higher risks a short time earlier.[27,28]

Considerable subtleties have emerged in the study of such psychological stressors. For example, the stress response can vary in a stepwise manner as a function of the intensity of the psychological variables. Thus, increasing degrees of novelty provoke progressively larger glucocorticoid responses,[15-17,29] akin to the studies of physical stressors showing, for example, correlations between the magnitude of the adrenocortical stress response and the rate and magnitude of change of blood volume in response to hemorrhage.[30] Other studies have emphasized that increased senses of control and/or predictability are not uniformly protective against stressors. For example, predictive information is most useful for stressors of intermediate likelihood and with an intermediate time delay (for example, little psychological benefit is derived from the information that there will be only a single occurrence, rather than multiple occurrences, of an extremely unlikely stressor vast years in the future) (discussed in ref 31).

Collectively, differences in the psychological milieu in which a physical stressor occurs accounts for enormous amounts of variability in the stress response. It is in the context of these psychological factors that some of the more robust individual differences in patterns of stress responses can be interpreted. This is particularly applicable to explaining the individual differences that occur as a function of dominance rank among social species.

Social status in dominance hierarchies and the stress response

Regardless of how rich an ecosystem might be, resources are rarely divided evenly among unrelated social animals. In many social species, dominance hierarchies have evolved instead. Pairs of individuals are not equally likely to obtain a disputed resource, and one of the individuals is consistently the winner of such outcomes. Critically, this asymmetry is not re-established through overt aggression at each contested interaction; instead, a *status quo* emerges with a recognition of the inequality of the two, typically signaled with conventionalized gestures of dominance and subordinance. Out of these dyadic asymmetries can emerge coherent dominance hierarchies. Depending on the species and circumstances, they may or may not be linear, involve coalitions, be sex-specific, be static and hereditary or dynamic and fluctuating.

As a general rule, in stable dominance hierarchies, it is the subordinate individuals who have the most stressful of lives. They may be supplanted from feeding sites, resulting in less food consumption and/or more effort that must be expended in obtaining food. They may have their sexual liaisons interrupted or usurped, or may be subject to high rates of unpredictable and injurious displaced aggression. Thus, subordinance not only involves increased rates of physical stressors, but of psychological ones as well, as the scenarios just described all involve marked absences of control, predictability or outlets for frustration. Not surprisingly then, a literature derived from a wide range of species demonstrates that social subordinance in stable dominance hierarchies is associated with elevated basal glucocorticoid concentrations and/or adrenal hypertrophy [mice;[32-38] rats;[39-43] wolves;[44] fish;[45,46] various primate species (to be discussed at greater length)[47-53]].

Some of the underpinnings of the glucocorticoid hypersecretion among subordinates have been uncovered. One of the most detailed studies has been carried out with a population of wild baboons living in a national reserve in east Africa.[52,53] If the basal hypersecretion of glucocorticoids is caused by the stressfulness of subordinance, then such hypersecretion should be initiated at the level of the brain (rather than it being due to some peripheral mechanism, such as different clearance rates of glucocorticoids from the bloodstream). This appears to be the case. Subordinate and dominant individuals do not differ in the half-life of glucocorticoids in the bloodstream,[54] or in adrenal sensitivity to ACTH,[53] implying that the elevated glucocorticoid concentrations must arise from elevated ACTH levels (something not directly measurable under those field conditions). Furthermore, the pituitaries of subordinates not only are not overly responsive to CRF, but are in fact hyposensitive to the secretagog.[55] This implies that if there is hypersecretion of ACTH occurring despite decreased pituitary sensitivity to CRF, then there must be substantial hypersecretion of the latter. Thus, the onus of hypersecretion moves to the brain. As an additional feature, subordinate animals are less sensitive to glucocorticoid feedback inhibition, as manifested by their being relatively dexamethasone resistant.[54] That is to say that subordinates continue

to secrete endogenous glucocorticoids, despite the potent negative feedback signal exerted by the administration of the synthetic glucocorticoid dexamethasone.

The psychosocial explanation of individual hypersecretion by subordinates (i.e. such animals are stressed) and the neuroendocrine explanation (i.e. such animals have impaired feedback regulation) are not mutually exclusive,[56] as the sustained glucocorticoid hypersecretion caused by stress can down-regulate corticosteroid receptors in the brain,[57] desensitizing it to inhibitory negative-feedback signals by circulating glucocorticoids.[58]

The chapter by Nemeroff in this issue[1] reviews some of the adrenocortical abnormalities found in approximately half of depressives, and there are striking similarities between a depressed human and a subordinate baboon—dexamethasone resistance, elevated basal glucocorticoid concentrations, a lack of adrenal hypersensitivity to ACTH (although extremely prolonged incidences of major depression can be associated with adrenal hypertrophy and enhanced sensitivity to ACTH),[59-63] and pituitary hyposensitivity to CRF. To a striking extent, subordinance in a primate society can share many psychological traits with depression as well, insofar as the latter can be viewed as a stress-related disorder[64,65] with components of learned helplessness.[66]

In addition to the rank-related differences in adrenocortical profiles, social subordinance has been associated with other distinctive physiological features; some of them are readily interpreted in the context of stress. The classic work of James Henry demonstrated that subordinate mice have elevated sympathetic tones and an increased risk for hypertension and atherosclerosis.[67] More recent work has shown similar patterns among subordinate primates in stable dominance hierarchies.[68,69] As another example with considerable evolutionary implications, subordinate animals of both sexes also tend towards the reproductive dysfunction typical of chronic stress (reviewed in refs 70-72).

Complexities regarding rank and the psychological context in which it occurs

The preceding studies suggest that social rank can be a powerful predictor of individual differences in the physiology of the stress response. Some of the strongest correlates among male rodents have been summarized as 'higher social status and aggressiveness are associated with elevated testosterone levels, whereas submissiveness and defeat are related to increased output of adrenal corticoids.[11,73] Not surprisingly, far more complexity is encountered when considering the subtleties of primate social dominance—there is far from a monolithic relationship between rank and any particular physiological endpoint. I discuss three examples.

Physiological correlates of rank are also sensitive to the social setting in which the rank occurs

As perhaps the strongest example, already noted indirectly, the physiology of dominance can differ diametrically, depending on whether the dominance hierarchy is stable or unstable.[74] As noted, in certain species, dominance hierarchies are dynamic and fluctuating, and even in the most stable of such hierarchies, there are dyadic pairs in which the direction of dominance is in the process of shifting (for example, in which the dominant individual of that pair is now winning 51% of interactions, rather than 99% of them). Despite such individual foci of instability, hierarchies among Old World primates are typically quite stable, with the dominant individuals winning an average of 90% of the time across all the dyads in the group. However, widespread and prolonged instability can occur on occasion. In feral populations, this most typically follows the transfer into the troop of new and aggressive individuals, or the death or severe injury of someone's coalitional partner. In captive populations, such instability characterizes the period immediately following the formation of the group.

During such instabilities, much of the psychological advantages otherwise typical of dominance are lost. Rather than a milieu filled with social control, predictability and outlets, dominance is now associated with the highest rates of psychological stressors. This is because ranks shift within that cohort frequently and unpredictably, coalitions form and disintegrate regularly, and there are particularly high rates of aggressive interactions.

Not surprisingly then, social instability is associated with physiological correlates very different than during stable times. During the latter, dominant individuals have the lowest basal cortisol concentrations, the largest increases in cortisol secretion during stress, are more sensitive to glucocorticoid feedback regulation, and have the smallest adrenal glands

(talapoin monkeys;[46,47] squirrel monkeys;[49] baboons;[53] macaques[50]). In contrast, none of those traits are correlates of dominance during unstable periods (talapoin monkeys;[47] squirrel monkeys;[73,75] baboons;[53,76] macaques[50,76,77]). Within the testicular realm, in a stable hierarchy, dominant males do not necessarily have the highest basal testosterone concentrations, but they are uniquely able to maintain such concentrations during stress, a time when concentrations plummet in subordinates (macaques;[78,79] baboons[72]). In contrast, during unstable times, that stress-resistance is lost, and dominant males have the highest basal testosterone concentrations (macaques;[80,81] talapoin monkeys;[82] squirrel monkeys;[73,75] baboons[72]). Finally, among macaques, dominance is associated with the least atherosclerotic occlusions in blood vessels in a stable hierarchy, and the most occlusions in an unstable one.[83]

Another example that stress-related physiology is not only a function of rank but the social setting in which it occurs, involves subordinate individuals. As noted, subordinance in stable hierarchies typically is associated with elevated basal glucocorticoid concentrations. Over the course of a decade of study of the same baboon population, higher basal cortisol concentrations occurred among subordinate males during the years in which they were exposed to the highest rates of unpredictable displaced aggression by dominant males.[56] Thus, the hypercortisolism of subordinance does not reflect the abstract psychological state of being low-ranking, but rather reflects, in a very concrete way, the precise impact of such subordinance in everyday life.

Physiological correlates of rank are also sensitive to the individual's experience of that rank and its setting

One example of this was noted earlier—despite the fact that basal cortisol concentrations are, on the average, elevated during periods of social instability, such hypersecretion does not occur among the subset of individuals whose ranks are rising as a result of the instability. This demonstrates that 'instability' is not, in and of itself, automatically a stressor. Instead, the physiological outcome of that condition will depend on the social ramifications of the instability for the individual.[26]

Another example was observed among these baboons during the very stressful period following the transfer into the troop of a highly aggressive male. Over the subsequent weeks, he attacked numerous individuals in the troop unprovoked, and this period of social instability was associated with, among other indices of the stressfulness, a significant decline in circulating lymphocytes among the members of the troop. Remarkably, there was a highly linear relationship between the frequency with which the immigrant male attacked an individual and the extent of suppression of that individual's lymphocyte count, with there being no decline in counts among the individuals never attacked by the male.[84] These data demonstrate that being in a troop containing a new and highly aggressive male does not necessarily provoke the physiological changes typical of the stress response; instead, it depends on each individual's experience of that male.

Physiological correlates of rank are also modulated by personality

Animals other than humans can be highly individualistic, and it is not necessarily an anthropomorphism to discern stable 'personalities' among animals (for a fascinating extreme, see an analysis of shy and bold personalities among sunfish[85]). Within the primate order, the study of personality and stylistic differences in affiliative and coalitional behavior, niche exploitation and alternative reproductive strategies is one of the most exciting of current topics.[86-89]

Within this framework, physiological correlates of rank can, in fact, be more closely yoked to personalities and behavioral styles that co-vary with rank. For example, among these baboons, low basal cortisol concentrations were found among individuals with the following behavioral styles (after controlling for rank as a variable):

(a) a marked capacity to differentiate between threatening and neutral social situations (i.e. specifically, these are animals who assume a vigilant and defensive set of behaviors when threatened by a rival, but whose prior behaviors remain unchanged by the mere neutral presence of the rival. In contrast, the highest basal cortisol concentrations are found among males who are equally likely to assume vigilant behaviors when in close proximity to a rival, regardless of the latter's behavior;

(b) when actually threatened by a rival, a strong tendency to be the initiator of the overt aggression which erupts shortly thereafter;
(c) a capacity to distinguish between winning and losing such an interaction (i.e. where winning typically is followed by some affilitiative behavior, losing by a displacement behavior. In contrast, those with the highest basal cortisol concentrations do not differentiate between having won or lost in terms of their next behaviors;
(d) the preceding set of traits form an intercorrelated cluster. As an additional trait, independent of these, low basal cortisol concentrations are also found among males with the most affiliative behavioral style (i.e. the highest rate of affiliative interactions with females and infants).

Finally, these stylistic features appear to be stable over time, lending credence to the interpretation that they reflect aspects of individual personality.[24,90]

These studies demonstrate that low basal cortisol concentrations are found in the individuals with the greatest skills at predicting and controlling social stressors, and the greatest availability of outlets. These findings resonate with the features of psychological stress and stress management discussed earlier. Moreover, the findings that high-ranking individuals (with a distinctive absence of those personality markers) have elevated basal cortisol concentrations demonstrate that physiology is not only sensitive to rank, its context and the personal experience of it, but also to the capacity of the individual to perceive whatever psychological advantages of dominance there may be. In effect, even non-human primates differ as to whether they view the world as consisting of glasses half full or half empty.

Conclusions: personality, coping and the stress response in humans

It is beyond the scope of this paper to review the subject of individual differences in the quality of any facet of the human stress response, including that of the adrenocortical axis. Nevertheless, a few encouraging points should be emphasized. First, as an obvious follow-on from the preceding section, if the personalities of baboons are sufficiently variable to correlate with differing physiological profiles relevant to stress, those of humans certainly should. Not surprisingly, issues of personality and individual differences in the interpretation of external events dominate the human literature concerning responses to psychological stressors. There have been relatively few studies documenting differences in stress-related physiology or pathophysiology as a function of 'rank' in humans. The few successful examples are among the most artificial of ones, documenting the acute physiological responses to the 'rank' outcome of a sporting event. Far less successful have been attempts to correlate physiology with 'rankings' from more every-day life examples, such as positions in corporations or in a military organization. Instead, the richest physiological correlations have come from far subtler realms, reflecting the interactions between psychological stressors and such profoundly human attributes as rationalization, denial, internalization of standards, and so on. One striking example comes again from the classic studies of parents of children dying of cancer. While that stressful situation was associated with, on average, an increase in glucocorticoid concentrations among parents, there were nevertheless subsets of parents spared the hypercortisolism. Among the factors that predicted low cortisol concentrations was having a structure of religious attributions to explain the cause of the child's cancer (e.g. God chose this family to carry this special burden because of his faith in their strength).[27] Examples such as this make even the complexities of non-human primates pale in comparison.

As a second and final point, the subtle and complex human correlates of the physiological stress response can be extraordinarily plastic. Stated more plainly, we have a heartening capacity to change. This is, of course, the province of stress management. Numerous studies, even of individuals in some of the most stressful of physical or psychological circumstances (for example, chronic pain syndromes, forced placement in a nursing home) have shown that the physiological or pathophysiological sequelae of stress can be changed by manipulating the psychological context of the stressor and the attributes given to it by the individual (for major reviews, see refs 25, 31, 66, 91, 92). Many of the papers comprising this issue will, along with presenting information about the ability of the stress response to solve the adaptive problems of the individual, also outline some of the deleterious consequences of stress. Despite the latter grim news, it strikes me that these last points about the abundant human capacity to become more resilient in the face of stress are grounds for considerable encouragement.

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