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Proximate and evolutionary studies of anxiety, stress and depression: synergy at the interface

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Abstract

While enormous progress has been made in unraveling the proximate physiological mechanisms that account for anxiety, stress, and low mood, these states continue to give rise to considerable conceptual confusion. This is, in part, because proximate studies have neither been adequately distinguished from, nor integrated with, evolutionary explanations for the adaptive functions of anxiety, stress, and mood. A complete biological explanation that incorporates both proximate and evolutionary explanations will be of great value to better define the border between normal and pathological, to help to explain why pathological anxiety and depression are so common, and to provide a much-needed basis for sensible decisions about when different pharmacological manipulations are likely to be helpful or harmful. Ideally, evolutionary considerations should provide a conceptual framework within which the biological significance of the proximate mechanisms can be better understood, and the proximate findings should provide tests of evolutionary hypotheses. Studies at the interface between evolutionary and proximate explanations will be difficult, but important to better understand individual differences in vulnerability and the etiology of diseases that result from dysregulation of anxiety and mood. © 1999 Published by Elsevier Science Ltd. All rights reserved.

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1. Introduction

The extraordinary efforts we humans have made to understand anxiety disorders and depression are entirely understandable. After all, the related states of fear and sadness are two of the most common and severe kinds of human suffering. They are, like pain, aversive in their very essence. To one degree or another, we all experience them and they are thus very different from diseases like cancer or stroke, which only affect some people. The proportion of people who experience depression or anxiety of clinical severity—about one out of five people—is astounding, and is, in and of itself, an important fact about these disorders [1]. Even more disturbing, their prevalence in the prime of life for reproductive-aged women in developed societies results in combined morbidity and mortality estimates, as reported by the WHO, far greater than that of any other illness [2]. Other than conditions related to reproduction, few common diseases have their peak prevalence in the prime of reproductive life.

Approaches to the problem have changed dramatically. During the past century, millennia of philosophical investigations of fear and sadness [3] were displaced by psycho-

logical approaches that have become progressively more objective. In the past generation, traditional psychology has been displaced by cognitive neuroscience, with its new ability to unravel the responsible brain mechanisms [4]. We now know the brain sites that regulate and express aversive emotions [5]. We know enough about the responsible neurotransmitters to assist in designing new drugs (although much of this knowledge has come, in fact, from clinical observation drug effects). In addition, we are starting to find out how the genes and brains of people who are prone to anxiety and depression differ from those of other people.

All this breathtaking progress has revealed, however, some major gaps in our understanding. Arguments about nature vs. nurture, psychology vs. physiology, social vs. physical causes of mental disorders, and psychotherapy vs. drug treatment, continue unabated, thus revealing that the problem that is not just a lack of facts, but the absence of a satisfactory conceptual framework that can incorporate knowledge from different sources. Some of the difficulty arises from the difficulty of distinguishing and integrating work at different levels of organization—the molecule, the cell, anatomic loci and the whole organism. However, much of it arises at the awkward boundary between the proximate and evolutionary halves of biology.

As so eloquently described by Mayr, the entire history of

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biology can be seen as two intertwined but separate threads addressing proximate and evolutionary questions [6]. The proximate component of biology describes the body's mechanisms and their ontogeny. The evolutionary part studies the functions of those mechanisms and their phylogeny. For instance, a full proximate explanation of rat attack behavior would include a description of the behavior, the situations that elicit and inhibit it, the brain locations that mediate and regulate the behavior, the neurons and neurotransmitters involved, the genes that create this system and that account for its individual variations, and the development of the system from the zygote to the adult organism.

Even if we knew every detail of this complete proximate explanation, however, we would still also need a separate evolutionary explanation for why the system is in the way it is. At base, such evolutionary questions are about why the DNA code has the sequence it has. To answer them, one must understand why the DNA that gives rise to one kind of phenotype tends to have higher Darwinian fitness than phenotypes from other DNA sequences. Disembodied DNA has no fitness, of course, so we must study the adaptive significance of a trait in a particular environment, and we must try to understand how this trait evolved from its precursors. In the case of rat attack behavior, there are clues in the situations in which it is expressed—the sex, age and reproductive strategy of rats showing the display, the effects of the display on other organisms, and the competitive ability of rats with artificially (or naturally) increased or decreased tendencies to display the threat.

Both proximate and evolutionary studies have succeeded far beyond what anyone could imagine just 50 years ago, but the task of building strong bridges between them has yet to be accomplished. On the evolutionary side, the field of ethology has been transformed into modern behavioral ecology where the adaptive significance of every behavior is considered [7]. On the proximate side, early forays into biochemistry have resulted in a deep understanding of metabolism and now the chemistry of genes and how they give rise to bodies. However, neurobehavioral mechanisms are just now penetrating ethology [8], and evolutionary perspectives are just beginning to influence neuroscience and psychology [4,9]. The results of the genome project will no doubt provide the impetus for new efforts at integration. Once we know the basic code and some of its variations, we will be able to address, with far more specificity, the evolutionary explanations for why certain genes have been selected for, especially some with deleterious or apparently deleterious effects. We may even be better able to understand which allelic variations are maintained by selection, and which are explained only by mutation and drift. In the meanwhile, there are still many other good reasons to emphasize the benefits of trying to integrate evolutionary and proximate studies.

The thesis of this article is that much progress will come from work at the interface between proximate and evolutionary studies of anxiety, stress and mood. Knowledge

about proximate mechanisms can provide crucial evidence to support or refute evolutionary hypotheses about why traits are in the way they are. An evolutionary perspective can help to unravel why the mechanisms are there in the first place, why the regulation systems work as they do, and why we are so vulnerable to depression, anxiety disorders, and the adverse effects of stress.

The strongest evidence in support of synergy between these perspectives is the major benefits this strategy has provided for the field of animal behavior. Most studies of animal behavior now incorporate both proximate and evolutionary explanations, while the rest are explicit about the specific proximate or evolutionary questions at issue [8]. Before similar benefits can be realized from integrating studies of function and mechanism in emotional disorders however, several obstacles need to be overcome:

1. The distinction between proximate and evolutionary explanations needs to be clarified, along with their complementary roles in a full biological explanation.
2. The different methods for formulating and testing proximate and evolutionary hypotheses need to be recognized.
3. A modern understanding of how natural selection works must be incorporated.
4. Explanations of individual differences need to be recognized as quite different from explanations of why all members of a species are vulnerable to a disease.
5. Special strategies need to be pursued for the study of pathology that results from dysregulation of a defense as compared to primary pathology that does not involve defenses.
6. The tendency to equate aversive experience with pathology must be tempered.

1.1. Separate, complementary questions

While most scientists know the basic distinction between proximate and evolutionary explanations, an outline of some details will lay the groundwork for further exposition. Proximate approaches are about structures or systems and the mechanics of the organism, from molecules to cells, tissues, organs and behavior. Even if the reductionist's dreams were realized, however, even if we had a complete model of how the organism develops from DNA to an adult, and the location of every cell and its regulation and interconnections, this would still not offer a complete biological explanation.

As Tinbergen pointed out so clearly, a complete biological explanation has four components: (1) mechanism, (2) development, (3) function, and (4) phylogeny [10]. Together, mechanism and development offer a complete proximate explanation, but they cannot explain why a trait or mechanism is in the way it is. That requires an evolutionary explanation. A complete evolutionary explanation is as elusive as a complete proximate explanation because it

would require knowing (1) the precursor trait, (2) its minor variations, (3) the genes responsible for those variations, (4) how those variations increased or decreased fitness in response to the selective forces of earlier environments, and (5) the random effects of drift and other chance factors. A partial explanation is usually possible, however, based on what we know about ancestral traits, comparative data, and about the selection forces that are likely to have shaped the observed trait [11,12]. Testing these explanations requires methods different from those used for proximate studies; so misunderstanding is easy. Probably the most common and serious misunderstanding, however, is the failure to recognize that both evolutionary and proximate explanations are needed, and that they are not competitors, but two halves of a whole.

1.2. *Natural selection*

The basic notion of natural selection is widely understood—the gene pool changes over the generations because certain genes give individuals an advantage and thus become more common. Outside of evolutionary biology, however, some subtleties are often missed. The advantage given by successful genes has entirely to do with reproduction, not health or longevity. If individuals with a genetic variation tend to have more children than other people, that genetic variation will likely become more common, even if it causes health problems or early death. The notion that natural selection shapes individuals for health and longevity is a common misconception. The simplest example is one with manifold consequences for human health. In most populations, men die about 7 years earlier, on the average, than women. A proximate explanation can be based on the presence of testosterone, its deleterious effects on health and its tendency to induce men to do dangerous things. Why, then, are not high testosterone levels selected against? It is almost certainly because that would decrease ability to compete for mates, a hypothesis that is supported by comparative studies that show increasing sex differences in life-spans associated with increased reproductive pay-offs for mate competition [13]. Put in other terms, an investment in competitive ability early in life at the expense of ability to repair tissues give a greater reproductive pay-off for males, while for females, the pay-off is greater for investments in tissue integrity. This is the evolutionary explanation for why natural selection has made males the frail sex.

This is an example of sexual selection. It is not a different kind of selection, but a subset of natural selection in which traits are preserved if they give a reproductive advantage either by increasing ability to compete for mates, or making the individual more attractive as a mate [14]. There is, of course, a trade-off between the advantages of increased reproduction, and the costs of not being able to attend adequately to other needs, often with dire results for the individual's health. Some sexually selected traits are

apparently extreme and specifically because they are expensive and thus provide a hard to fake signal that the individual has surplus resources [15].

Group selection is also still frequently misunderstood. In the first half of the 20th century, biologists uncritically accepted the notion that natural selection could be shaped for the good of the species or the group. It seemed sensible. After all, if individuals did not help the group, the entire group would die with all the individuals in it. More recently, however, nearly all biologists have recognized that a gene that gives an individual a reproductive advantage will usually be selected even if that hurts the group, while a gene that is costly to individuals will be eliminated even if it benefits the group [16]. Attempts to resurrect a neo-group-selectionism [17] do not undermine this basic conclusion. Thus, explanations of hierarchies based on benefits to the group, or submissive displays for group harmony, or suicide of some individuals for the good of the group are inconsistent with basic evolutionary theory.

Finally, there is the matter of selection ending at a certain point in life. Since the discovery of kin selection [18], it has been clear that a post-reproductive individual can do things that benefit copies of his or her own genes that reside in kin. Menopause, far from being a barrier to further effects on gene frequencies, has been suggested to be a strategy to maximize reproductive success [19], although there is much controversy about this suggestion [20].

1.3. *Explaining differences vs. explaining similarities*

Another major source of misunderstanding arises because much clinically based research aims to explain the etiology of diseases by finding individual differences, while most evolutionary research tries to explain why all members of a species have a trait in common. Evolutionary explanations rarely focus on why one individual gets sick and another does not, but they have a great deal to say about why all members of a species are vulnerable to some disorders but not others. Darwinian medicine is the field that attempts to understand why natural selection leaves us vulnerable to various diseases [21].

The global evolutionary explanations for vulnerability to disease can be organized into just a few categories [22]:

1. Defenses that appear to be pathology but usually are not, such as the capacities for pain, fever, vomiting, fatigue, anxiety, stress responses, and low mood.
2. Design features that increase reproduction at a cost to health or longevity, such as the tendency for males to die young, as described above.
3. Genes that foster their own transmission at a cost to the individual, such as the T-locus in mice, and other examples of meiotic drive.
4. Competition with other organisms. The obvious source of disease in this category is pathogens. However, competition with predators has been a major issue until just recently, and competition with other humans is a

major source of ill health, whether from physical attack or from social conflicts. The co-evolution of strategies and counter-strategies, and defenses and ways to get around those defenses, is an arms race that shapes mechanisms just as prone to excess and danger as those in a military arms race [23]. Our immune system is a good example. With its chronic damage to tissues and occasional autoimmune responses, it is a source of much disease, but because of the need to defend against constantly changing potentially fatal invaders, its excesses are products of natural selection that give a net benefit.

5. The mismatch between novel aspects of our current environment and our bodies, which were designed for a very different environment, is the cause of perhaps the majority of modern disease. Atherosclerosis and hypertension are rare in people living in the ancestral environment, while they now eventually affect most of us [24]. The vast amounts of disease caused by cigarettes, alcohol and drugs are results of our novel environment. Obesity and associated diabetes and other problems also are rare outside of technological cultures. Whether the high rates of depression and anxiety disorders we now see are an epidemic caused by novelties in our social or physical environments remains uncertain [25].
6. Constraints, such as path dependence and engineering trade-offs make us vulnerable to many diseases. While engineering trade-offs are intrinsic in any design for any machine, the body is particularly prone to constraints that arise because the body is the result of a continuous lineage from one-celled organisms with no fresh starts. With anticipation, much could have been done better. While the design of the human back is a particularly egregious maldesign, the routes of the recurrent laryngeal nerve and vas deferens is equally nonsensical, and equally unalterable. It seems inevitable that our cognitive and emotional capacities suffer under similar constraints, but it is hard to see what they might be.
7. Random factors also prevent perfection. At the species level, the vagaries of natural selection are evident in examples of deleterious genes that are perpetuated by drift and, undoubtedly, in genes and traits that would be useful but got lost in the stochastic shuffle [12]. A cornea that filters out ultraviolet wavelengths would be a boon, as would the capacity to manufacture vitamin C. At the individual level, mutations have their effects, as do random events and genes that cause disease only in particular combinations. These random factors are potent, but they are intentionally last on the list in order to counter the common misconception that the body is suboptimal mainly because natural selection is a random process and therefore cannot be expected to be all that effective. In fact, there are at least six other reasons why the body is not better, and they account for far more design defects than the randomness of natural selection.

This article emphasizes the defense functions of aversive emotions, but each of the other six areas can contribute to understanding psychopathology.

1.4. Explaining pathological dysregulation of defenses vs. direct pathology

Imagine, for a moment, if medical science approached the study of pain the way it approaches the study of anxiety and depression. Pain would be said to be caused by abnormal activity in the thalamus, and enormous efforts would go into finding out why some people are more vulnerable to pain than others. People with a tendency to experience pain readily would be examined to see if this tendency was genetic or acquired. Much would be made of the extraordinary proportion of the population who had experienced a pain disorder, as defined by a period of 2 weeks or more in which pain disrupted normal work or activities. Subtypes of pain disorder would be defined by the results of factor analytic studies of symptoms and course. Brain scans would reveal the site of abnormal brain function and the efficacy of anti-inflammatory drugs and opiates would incriminate the cytokine and the opiate systems as potential causes.

All of this is ludicrous of course, but only because we know that pain is useful. While there are variations in susceptibility to pain, we know that most of these represent different points on the normal distribution of a useful response that evolved to protect us from tissue damage. We certainly recognize syndromes of pathological pain, but we usually seek the defect in dysregulation of the response, not the mechanisms of the response itself. When we see someone with a congenital absence of pain, we realize this is abnormal and are not surprised to learn that most of such people die by early adulthood [26]. A phylogenetic perspective on pain confirms its utility, the conservation of mechanisms across phyla, and subtle associations among developmental factors and pain mechanisms [27].

The big difference between physical pain and the mental pains of anxiety and depression is that the source of physical pain is so much more readily identified. We can often see the cause of physical pain, so it is easy to see that it is a defense. With fear, the correlation is not quite so clear, but we all experience its quick arousal by something that has previously hurt us, and this makes it easy to see how fear could prevent future harm. Some anxiety, however, arises in the absence of any obvious external cue and thus is more likely to be labeled abnormal. Indeed, many approaches to anxiety tacitly assume that it is abnormal, and that it can be completely explained by the brain mechanisms that mediate it. In the proximate sense, it can, of course, but this approach confounds an explanation of the operation of the normal mechanism with the factors that cause disorders of anxiety regulation in some people and with the normal functions of those mechanisms. A proximate explanation cannot explain why the organism has the capacity for anxiety at all, why it

is regulated the way it is, and why we are so susceptible to anxiety disorders.

Low mood and depression are still more problematic. The situations that give rise to them are often internal and related to idiosyncratic individual goals. The stimulus is often a loss that has already occurred, so it is hard to see how a reaction now can be useful and the very phenomena that constitute depression seem patently pathological. How could it possibly be useful to not want to do anything, to feel fatigue, to not eat or sleep, to not want sex? Then there are low self-esteem, social withdrawal, and thoughts of suicide—phenomena that seem utterly without value. For all of these reasons, it is easy to interpret depression as akin to seizures or stroke—pathological experiences unrelated to any useful function. This is, however, a mistake. Depressed mood is not a condition that is always pathological, that occurs only to a small subset of people, and that is unregulated by life situation. It is far more like pain or cough than seizures or stroke.

The same difficulty is prevalent in the rest of medicine. While the utility of cough is widely recognized, the utility of fever, fatigue, vomiting and diarrhea are not so clear in the minds of many physicians, and the low iron levels associated with chronic infection are recognized by few [28]. Therefore, these protective defenses are often seen as the problem, and drugs are given to block them with little thought to possible negative consequences. Several factors conspire to conceal the utility of defenses. Firstly, the body has redundant defense mechanisms, so eliminating one may have few ill effects. Secondly, many defenses are regulated in a way that seems overly responsive. When defenses that are inexpensive, such as pain and anxiety, protect against potentially severe dangers, such as further injury or being killed, selection will tend to shape a regulation mechanism that expresses the defense at the least hint of the presence of the dangerous situation. This “smoke detector principle” explains why so many expressions of defenses are unnecessary but nonetheless perfectly normal [22]. Third, if an agent does cause harm, it is in the context of an illness to which the problem is readily attributed. For instance, it seems possible that some cases of septic shock are caused by cytokine dysregulation induced by antipyretic drugs [29]. However, this is hard to recognize clinically—such agents are widely used, so there is no easy way to associate the complication with the drug.

Finally, there is the subjective aversiveness associated with the expression of defenses. The capacity for suffering itself seems to be a part of the motivational system to get us to escape from situations that involve loss or danger, and to avoid them in the future [30]. As already noted, people who lack the capacity for pain die young [26]. What about people who lack the capacity for anxiety? Few such studies have been done. In one, rate of injury in falls was examined for men who had or had not had a severe injury from a fall in childhood. Contrary to expectations, the fall in childhood did not cause increased fear. Instead, those men who (were

so incautious to) fall in childhood were much *less* likely to have fears in adult life [31]! Overall, however, the syndrome of hypophobia remains unstudied, probably because few patients come to anxiety disorder clinics complaining of insufficient anxiety [32].

2. Fear and anxiety

At the most basic level, movement offers animals two advantages over most plants—going towards food or mates, and away from danger. Arousal in face of danger increases the chances of escape, and thus gives an obvious selective advantage. Once a state of defensive arousal has been shaped by natural selection, its regulation will be slowly modified so the state tends to be expressed when it is useful and not at other times. Variations in neuronal connections that elicit the response in the presence of cues when it is likely to be useful will be selected for, as well connections that prepare an association pathway for ready and enduring learning [33]. Selection also can be expected to steadily differentiate the state into subtypes to cope with different kinds of threats [32]. Thus, attack by a predator will arouse the physiological changes and behavioral tendencies of a panic attack, while a threat of falling arouses paralysis and avoidance, and the dangers of display in a social group elicit the inhibitions of social phobia. Two kinds of defensive arousal, fear and panic, seem to have fairly sharply distinct neural mediating mechanisms, suggesting that they either arose in response to different kinds of threats, or that the differentiation was early and has been substantial [34]. The importance of this principle is that it helps us to stop thinking of each subtype of anxiety as either separate or the same. It is more likely that they all are partially differentiated from a common precursor state.

It also may help guide us towards principles that can help distinguish normal from pathological anxiety. At present, we attempt to make the distinction based on severity of symptoms and how much they interfere with the normal function. What is missing is a consideration of how much anxiety would be optimal for this person, given his or her experiences and environment. As noted above, there is a strong tendency to ignore the smoke detector principle and to label all unwanted anxiety as pathological. However, the optimal regulation system will often express anxiety that is excessive or even completely unnecessary for a given situation, so that much useless anxiety is nonetheless completely normal. We are so early in the process of exploring the utility of anxiety that it is difficult to say much more. What becomes of people who have too little social anxiety? What advantages accrue to people with mild social apprehensions? We do not yet know.

We do know, however, that the regulation of anxiety can be influenced by many different neurochemicals. Benzodiazepines, of course, and antidepressants also, but in addition we are now learning about the roles of each subtype of

serotonin receptor, and the effects of myriad other neurotransmitters. They allow a pharmaceutical dissection of the anxiety system. This offers a fine opportunity to determine the extent to which pharmacologically defined subtypes match those defined by the situation they defend against [35].

3. Stress

The modern concept of stress began with Selye's observation that diverse kinds of noxious experiences all resulted in the same syndrome including gastric ulcers and adrenal hypertrophy [36]. He recognized that this was a "general adaptation syndrome" which caused pathology only when aroused for an extended period. Cannon recognized that the uniformity of the "fight flight" response could be explained by the benefits an endangered organism received from increased heart and respiratory rates, sweating, muscular tone, and blood clotting [37]. Since then, however, the concept of stress has come more and more to be associated with its abnormal consequences, so that the popular culture now labels every untoward experience stressful, and seeks to minimize stress to preserve health. A glimmer of recognition of the utility of stress survives in the phrase "good stress", but the prevailing view is that stress is abnormal and bad for the organism.

Like other special states, however, stress has been shaped because it gives a net selective advantage. Exactly what those advantages are remains somewhat an issue, but the outlines are clear [38]. Arousal of the HPA system increases gluconeogenesis, and the entry of glucose into cells changes that are useful in situations where energy is being used. In essence, arousal of the stress system adjusts metabolism for rapid expenditure [39].

Like every other bodily trait, it has trade-offs. In the case of the stress response, these tend to cause tissue damage [40]. A proximate explanation for stress is well developed [41,42], but a simple evolutionary principle about the stress response has not been widely appreciated. Many components of the stress response are likely held in reserve, instead of being expressed continuously, specifically because they cause tissue damage. They are expressed only in those situations when the benefits are likely to outweigh the costs. From this perspective, the pathology caused by chronic exposure to stress is no mystery, but an expected outcome of natural selection.

Many effects of hypothalamic pituitary axis (HPA) arousal are surprising, however. Why, for instance, would decreased immune and inflammatory response be useful in situations where injury is likely? Munck [39] has suggested that many effects of the HPA system are not designed to protect the organism from outside harm, but to protect it from damage that would be caused by other aspects of stress arousal. The fatal effects of exposure to stress in the absence of adrenal hormones support this plausible argument and

suggest possible benefits to increasing the focus of research on the factors that shaped the peculiarities of the HPA system.

Studies of immune suppression caused by stress have also been conducted mostly in the proximate domain. However, a look at the phylogeny of the HPA system reveals ACTH like molecules in mollusks that are located in macrophages [43]. This hints that the very origin of the HPA system may have involved the stresses of infection and the body's responses to infection.

Most stress research now is conducted on psychological, not physical stress, but has turned out not to be so easy to find psychological cues that stimulate the HPA system. For humans, even some extreme situations are not associated with any cortisol response [44]. The current best method for arousing stress responses requires asking subjects to participate in a sequence of embarrassing and socially awkward scenarios [45]. For rats, it has likewise been found that social stress is especially effective in arousing the HPA system and causing disease, although the arousal of the HPA system is erratic [46]. A variety of noxious situations is better than any constant stimulus to arouse stress in rats. In the chronic mild stress procedure, the animal is exposed to a predator, food deprivation, cage tilt, 24 h illumination, and loud noises [47]. The attempt is, of course, to simulate the situations that cause chronic stress in humans, situations like chronic conflict with a spouse or employer, or the experience of discrimination. That it is so difficult to find a way to reliably arouse the HPA axis over the long term in both rats and humans is an important fact in and of it. Whether the experiences of modern humans arouse the HPA system to a pathological extent or duration remains an open question. It seems possible that many of the documented negative effects of exposure to stress are the adverse trade-offs of a normal system, not any evidence for pathology per se. Such trade-offs have been well documented in *Drosophila* for heat stress [48].

A particularly effective procedure to create stress has been social defeat, especially if the loser is forced to live next to the victor [49]. The procedure seems especially effective if the submissive rat is exposed to repeated attack by the victor. In ethological terms, whether this situation is natural or not depends on whether the rat perceives it as an attack by another rat in the group who is higher in the hierarchy, or if it is perceived as repeated attack by a strange rat, a situation that would be rare in nature since the loser would yield the territory. Overall, an ethological perspective will increase the utility of existing animal models of anxiety and suggest new ones [50].

4. Depression

Much of the interest in stress models comes, of course, from the association between stress and depression [51]. Here the prevailing model seems to be that stress causes

damage that eventually results in dysregulation of neurochemical systems yielding the syndrome of depression. The evidence ranges from the HPA abnormalities that characterize about half of patients with severe depression [52], to the effects of exogenous and excessive endogenous steroids on mood [53], to the extensive evidence that losses and other negative life events precede many episodes of depression [54].

This model is based mostly on pathology, with little concern for the possible functions of normal low mood and the mechanisms that regulate it. As noted above, there are several reasons why it is easy to neglect consideration of the possible adaptive significance for low mood, starting with its general aversiveness and its apparent uselessness. The aversiveness of a state is a clue that it is an adaptation for some situation that is best avoided. As for the apparent uselessness of depression, compare it to pain, which similarly inhibits normal function but is obviously useful. The bigger difficulty, however, is that the situation to which depression most often relates to is a loss in the past. If the loss has already occurred, how can low mood be useful now? The answer is that it can only be useful if it influences future behavior in a way that avoids additional losses.

Is loss of a reproductive resource the main situation that has shaped the characteristics of low mood? Put another way, in what situations might the characteristics of depression be useful? There may not be one specific situation. Just as there are subtypes of anxiety, there well may be subtypes of low mood to cope with different situations, from being discouraged, to loss of a loved one, to being trapped in an impossible life situation. What they all have in common is a general decrease in activity and motivation, often associated with low self-esteem and pessimism. The global situation in which an organism is best off withdrawing and decreasing its effort is one in which that effort would be wasted or make a situation worse [55]. A confrontation with a dominant, for instance, is wasted effort that is likely to result in injury. A great deal of work to study yielding behaviors has been done by Price et al. [56,57]. Animal models based on arrested flight offer particular promise [58]. Other more global situations are similar, for instance, foraging at a time of day or year when the calories spent are greater than the calories gained. Whether reactions to such situations are regulated by the same mechanisms that regulate submissive behavior and arrested flight offers an example of how proximate data can help to test evolutionary hypotheses.

Some other animal models are along similar lines. In the learned helplessness paradigm, for instance, animals quit trying to escape from a setting where they have initially found escape to be impossible [59]. This is generally interpreted as pathological behavior, and treatment is conceptualized as demonstrating to the animal that it has more control over its environment than it apparently thinks it does [60]. However, is there any natural setting similar to the shuttle box? It would have to be some location that was associated

with pain and could not be escaped from at one time, but which later could be escaped.

The forced swim test is widely used to assess drugs that may be useful for depression [61,62]. A rat is dropped from a specified height into a cylinder of water from which it cannot escape. It swims frantically trying to escape for a time, and then floats quietly with just its nose out of the water. The swimming is usually interpreted as an adaptive escape response and the floating as a pathological depressed response. Imagine, however, a rat that falls into a natural pond or river. Its survival depends on how accurately it judges what strategy will work best, active struggle or passive waiting. A rat that struggles to no purpose is doomed. Drugs that relieve depression reliably increase the time a rat struggles in the water [62,63]. This suggests that antidepressants might increase the tendency to active coping in other species in other situations, and might even increase it beyond what would be optimal in the natural habitat. It seems likely that selection has had plenty of opportunity to optimize this parameter since breeding for decreased activity in swim tests over 18 generations of rats yielded individuals who were passive in general, and whose swim times could be increased by chronic, but not acute, treatment with antidepressants [64].

This kind of thinking suggests quite specific experiments. For instance, it would be interesting to train rats in a slowly increasing reinforcement ratio in order to determine if, as one would expect, the break point is near the point where calories spent exceed those gained. Then, the effect of antidepressants could be assessed. If mood is, as suggested by many, an adaptation for motivating disengagement from a task that is no longer paying off [65,66], then antidepressants should not only increase persistence on the increasing ratio task, they should increase it beyond the optimum.

Finally, an evolutionary approach suggests possible connections between anxiety, stress and depression. The epidemiological association of anxiety disorders and depression is strong, and the order effect is consistent—about half of the patients with panic disorder will have major depression 5 years later, but very few patients with depression will have a pure anxiety disorder 5 years later [67]. Proximate explanations have been proposed for this finding, many based on a presumed defect that results in a regular sequence of abnormalities. If the functional significance of anxiety is considered, however, it seems likely that a threat that creates anxiety may lead to an actual loss that precipitates depression. Alternatively, the very experience of panic symptoms inhibits normal life so completely for many patients that their world constricts and their sources of satisfaction dry up.

5. Individual differences

The goal of much research in biology and behavior is to understand what makes individuals different, especially in

their susceptibility to mental disorders. As noted above, proximate approaches are usually more germane for such questions, but an evolutionary approach can also be helpful. In particular, variation in the dangerousness of the environment, over either generations or locations, will create different selective pressures that should maintain variability in genes that influence this trait [68]. When successive generations of rodents show an increasingly population density selection seems to decrease attack latency. Whether the environment is crowded or not, a male mouse without a territory has two options: either try to take over a territory, or try to find an unoccupied territory. As density increases, the fitness pay-off for looking for an unoccupied territory must decrease, so it is not surprising that selection favors a shorter attack latency. Since variation in population is such a characteristic and important factor in the mouse environment, however, a facultative mechanism that adjusts strategy as a function of changes in population density would give great advantages, especially if sudden changes in population density sometimes occur. In this case, an evolutionary perspective cannot make a firm prediction that the system exists, but it can suggest a search for such a system based on its probable utility.

The focus of this article has been the adaptive significance of anxiety, low mood and stress, so to prevent misunderstanding, it is important to clearly state that much anxiety and depression results from diseases such as major depression and panic disorder. Furthermore, much physical, and probably mental, illness results from the complications of the stress response. The search for the etiology of these disorders is a high priority. The argument here does not undermine the hard-won recognition that these disorders really are diseases. It does, however, suggest that, like chronic pain and febrile seizures, they probably often involve dysregulation of a normal defense. If that is correct, it implies the need to use special research strategies that begin by elucidating the normal mechanisms that mediate the defense, and then proceed to study the mechanisms that regulate the defense, and finally try to understand the etiological factors that disrupt the normal regulation mechanisms. Understanding the proximate mechanisms that normally regulate these defenses, from molecules to neurons to the transduction of social cues, will provide a solid foundation for understanding why and how they become dysregulated. Evolutionary approaches that focus attention on their normal functions, how they were shaped by natural selection, and how they are regulated, will be essential in this enterprise.

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