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Psychoactive Drug Use in Evolutionary Perspective

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Pure psychoactive drugs and direct routes of administration are evolutionarily novel features of our environment. They are inherently pathogenic because they bypass adaptive information processing systems and act directly on ancient brain mechanisms that control emotion and behavior. Drugs that induce positive emotions give a false signal of a fitness benefit. This signal hijacks incentive mechanisms of "liking" and "wanting," and can result in continued use of drugs that no longer bring pleasure. Drugs that block negative emotions can impair useful defenses, although there are several reasons why their use is often safe nonetheless. A deeper understanding of the evolutionary origins and functions of the emotions and their neural mechanisms is needed as a basis for decisions about the use of psychoactive drugs.

The neural mechanisms that regulate emotion and behavior were shaped by natural selection to maximize Darwinian fitness, so psychoactive drugs that disrupt those mechanisms should impair adaptation. As the toll of substance abuse tragically demonstrates, they can. But psychoactive drugs can also improve adaptation in some circumstances (what would many scientists do without caffeine?), relieve the symptoms of mental disorders, and induce pleasures that can sometimes be safe. Here, we consider substance use and abuse from the perspective of Darwinian medicine, the enterprise of seeking evolutionary explanations for design characteristics that make organisms vulnerable to disorders (*1*–*3*). This perspective suggests that explanations of substance abuse based on brain mechanisms or on individual and social differences can be augmented by evolutionary explanations for

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the universal human vulnerability to the maladaptive effects of psychoactive drugs, and for the functions of emotions they influence.

Emotions are coordinated states, shaped by natural selection, that adjust physiological and behavioral responses to take advantage of opportunities and to cope with threats that have recurred over the course of evolution (*4, 5*). Thus, the characteristics and regulation of basic emotions match the requirements of specific situations that have often influenced fitness. Emotions influence motivation, learning, and decisions and, therefore, influence behavior and, ultimately, fitness (*6–10*). Subjective feelings offer a window (often distorted) into motivation, but they are not the essence of emotion (*9, 11, 12*) and are not even always a necessary component (*13, 14*). For example, in a recent study of a forced-choice task, normal people start to avoid the poor choice and to show emotion-associated skin conductance changes even before they become aware of any preference (*15*). Nonetheless, subjective positive or negative valence is a prominent aspect of basic emotions, with distinct kinds of negative states outnumbering positive ones. These observations are consistent with the origins of emotions as specialized states shaped to cope with situations that involve opportunities or gains and a greater number of different kinds of situations that involve threats or losses. This offers a potential evolutionary explanation for the nonintuitive, but well-documented, relative independence of positive and negative affect (*16*), and suggests that the effects of psychoactive drugs on positive and negative emotions should be considered separately.

Drugs that Stimulate Positive Emotions

Substance abuse is explained, according to folk psychology, by human tendencies to repeat behaviors that bring pleasure or relieve suffering. This global explanation is correct but incomplete. Most drugs of abuse act on ancient and remarkably conserved neural mechanisms, associated with positive emotions, that evolved to mediate incentive behavior. Heroin, cocaine, alcohol, marijuana, amphetamine, and their synthetic analogs activate mesolimbic dopamine-containing neurons and associated opioid receptors in mammalian brains, a system that may be a "common neural currency" for reward and a substrate for regulating motivations (*17–21*). Some of the transmitter molecules used by these systems evolved as much as 1000 million years ago (*22*), and mammalian dopamine, serotonin, and norepinephrine neurotransmitters are also used by invertebrate phyla, such as mollusks and arthropods, that diverged from prevertebrate lines roughly 600 million years ago. Most vertebrate brains have μ opioid receptor-like DNA sequences (*23*), and even nonmammalian vertebrate brains have mesolimbic systems comprising dopamine-containing neurons that ascend from the midbrain to a dorsal and ventral striatal complex (*24*). Although these neurotransmitter systems may not all serve the same functions, some neurotransmitters play similar roles in very different organisms: Dopamine mediates feeding in organisms ranging from slugs to primates (*25*), and a similar molecule, octopamine, mediates the effects of sucrose rewards in bees (*26*). This conservation of function for reward-signaling chemicals contrasts with a diversity of receptors (*27, 28*), probably because a mutation that changes a transmitter is likely to disrupt a whole system, whereas gene duplication allows differentiation of receptors that can gradually take on new functions (*29*).

Drugs of abuse create a signal in the brain that indicates, falsely, the arrival of a huge fitness benefit. This changes behavioral propensities so that drug-seeking increases in frequency and displaces adaptive behaviors. Other novel aspects of the modern environment have similar effects. For instance, playing video games also displaces more adaptive behaviors but via psychological instead of direct neurochemical means. Snacks high in fat, salt, and sugar tend to displace more nutritious foods in the diet. We are vulnerable to such fitness-decreasing incentives because our brains are not designed to cope with ready access to pure drugs, video games, and snack foods (*30*). Hundreds of generations of exposure would likely shape resistance to their allure and their deleterious effects. Far less time might be sufficient, if the genetic deficit in alcohol dehydrogenase in many Asian populations is indeed a product of selection by a few thousand years of exposure to alcohol (*31*). In the meanwhile, the mismatch between our bodies and our modern environments is a major cause of behavioral and medical problems.

This simple perspective leaves many aspects of substance abuse unexplained. For instance, as addiction develops, drug-induced pleasure declines or remains constant, even as cravings increase and maladaptive consequences accumulate, thus making it clear that the pursuit of pleasure is an insufficient explanation. One likely reason is the separation of mammalian brain reward systems into components that correspond roughly to "liking" (hedonic pleasure on receiving a reward) and to "wanting" (incentive motivation and behavioral pursuit of a reward). Although the nature of these components is just beginning to be understood, they appear to have different neural substrates. "Liking" of sweet foods, for example, is mediated by certain opioid forebrain systems and by brain-stem systems, whereas "wanting" seems to be mediated by ascending mesolimbic dopamine neurons (*12, 32*). The separate neural mediation of "wanting" may have evolved so that disparate "likes" for food, sex, and other incommensurate incentives could be compared in a common currency of utility (*33*). The "liking" system is activated by receiving the reward, while the "wanting" system anticipates reward and motivates instrumental behaviors. When these two systems are exposed to drugs, the "wanting" system motivates persistent pursuit of drugs that no longer give pleasure, thus offering an explanation for a core paradox of addiction.

Another aspect of physiology that makes us susceptible to substance abuse is neural sensitization–hyperresponsivity in ascending dopamine projections induced by addictive drugs, through a mechanism gated by genetic and experiential factors (*34, 35*). Such sensitization of brain substrates that mediate "wanting" can result in compulsive seeking of a drug that causes neither pleasure nor withdrawal (*32, 34*). Any organism with a chemically mediated incentive system and technological capabilities is intrinsically vulnerable to addiction, but these special design features of vertebrate reward systems magnify the risks and may explain the otherwise bizarre phenomenon of addicts who sacrifice everything else in life to get drugs that do not reliably bring pleasure, and who return to drug use even after extended periods of abstinence.

Important implications follow from the origin of our vulnerability to drug abuse in the mismatch between ancient mechanisms and modern environments. From this evolutionary perspective, individual variations that increase susceptibility to drug abuse are better described as quirks than defects, because they probably had no deleterious effects in the ancestral environment. Genetic differences set parameters of basic neurobehavioral systems that are shared by all members of a species. Nongenetic differences in emotional experience can also influence susceptibility to drug use, as demonstrated by the substantial comorbidity of substance abuse and posttraumatic stress disorder. The strong association between emotional symptoms and susceptibility to addiction has been studied carefully for smoking, and the ability of nicotine to relieve these feelings has been interpreted in a sophis-

ticated evolutionary perspective (*36*). Instead of only seeking explanations for substance abuse in individual differences in genes, temperament, early experiences, social conditions, cultural setting, or exposure to drug use, an evolutionary perspective suggests that we also consider how these factors interact with the emotional and behavioral mechanisms that make all humans vulnerable to substance abuse. This view encourages therapeutic attention to the diversity of factors that influence people's emotions, such as relationships, social support, social inequity, the experience of discrimination, and opportunities or blocked opportunities. There are reasons why people who are not succeeding in the social competition are likely to experience positive emotions less often and negative emotions more often, take drugs more often, and be less responsive to treatment. This view also suggests that the mismatch between novel pharmacological hyperincentives and ancient brain mechanisms is likely to worsen with the discovery of new drugs and new routes of administration. Finally, it suggests that we cannot reasonably expect to win the war on drug abuse, but we can use our knowledge to develop sensible strategies for prevention, treatment, and public policy to manage a problem that is likely to persist because it is rooted in the fundamental design of the human nervous system.

Drugs that Block Negative Emotions

An evolutionary perspective also has implications for drugs that block anxiety, low mood, and other negative emotions. Psychiatrists may soon have drugs that control emotional suffering just as well as other drugs can control pain, cough, fever, diarrhea, and vomiting. Our understanding of when and how emotional reactions are useful remains superficial, but understanding the utility of many physical defenses has also proved elusive. While most physicians know that blocking a cough can lead to death in a patient with pneumonia, and many know that blocking *Shigella*-induced diarrhea leads to slower recovery and more complications (*37*), some do not appreciate the utility of defenses such as fever and low blood iron levels in infection (*38, 39*), and some do not readily differentiate between manifestations of disease that are aspects of defenses and those that arise from defects in the body's machinery (*3*). Such difficulties are magnified in psychiatry. The utility of anxiety is known but often ignored (*40–42*), the utility of jealousy remains controversial (*43*), and the utility of low mood and depression is just being considered (*44–47*). Quantitative studies that explicitly address the evolutionary functions of emotions have just begun. For example, new data support the function of embarrassment and guilt in regulating the individual's hierarchical role in a group (*48, 49*). Our understanding of the functional significance of negative emotions grows slowly, while new psychotropic drug development races far ahead at a furious pace. We lack the scientific knowledge about emotions that would support detailed advice on when these agents should or should not be used.

We do, however, have several reasons to think that psychotropic drugs can often be safe and useful, even if the capacities for negative emotions are adaptations. First, there are disease states, in which drugs can normalize or compensate for pathology, for example, lithium's ability to prevent mania. Second, many normal painful emotional responses may be no more useful in the modern environment than the pain caused by surgery. A panic attack may save the life of a hunter fleeing from a lion, but cost the life of a driver on an expressway. Third, the body has redundant defenses, so blocking one negative emotion may have few deleterious consequences, just as blocking fever does not necessarily slow the recovery from infection. Fourth, the biological systems that regulate defense expression must (according to signal detection principles) have been shaped to express the defensive response whenever, on average, it is worth it. Because many defenses are inexpensive but protect against potentially fatal threats whose presence is signaled by unreliable cues, even an optimal system will produce many false alarms (*4*). Like vomiting, which can eliminate a possibly fatal toxin at the cost of losing a few hundred calories, fear and low mood may decrease the tendency for behaviors that are dangerous or useless. Finally, the brain was not designed to benefit individuals, but their genes. As Wilson puts it, "Love joins hate, aggression, fear, expansiveness, withdrawal, and so on, in blends designed not to promote the happiness of the individual, but to favor the maximum transmission of the controlling genes." (*50*)

Such considerations make it possible to envision, or even to predict, a future in which drugs will eliminate much normal as well as pathological emotional suffering, just as they now relieve physical suffering. On the other hand, the same factors also undermine the simplistic view, advocated by some psychiatrists and pharmaceutical companies, that intense aversive emotions almost always result from a brain abnormality. Some anxiety and low mood has a primary cause in brain defects, but much also arises from normal brains and is caused by an imbalance of brain chemicals only in the same superficial sense that cough is caused by excessive neural activity in the brain locus that controls cough. Furthermore, just because a drug relieves a negative emotion does not mean that the emotion is abnormal, nor does it imply that the drug works by reversing a brain defect. Aspirin, after all, reduces body temperature only in people with fever, but fever is a defense against disease, not a disease itself.

Conclusion

Emotional capacities evolved to improve the Darwinian fitness of individuals as they seek resources and avoid dangers. The pursuit of emotion-associated goals tends to move organisms up a hedonic and adaptive gradient, but neurobehavioral systems are designed to maximize Darwinian fitness, not happiness, so our pleasures are often fleeting, and we experience much unnecessary suffering. The neurochemical mechanisms that mediate these states confer intrinsic vulnerability to substance abuse in environments where drugs are available. A better understanding of the mechanisms, origins, and functions of the emotions will enhance our ability to cope with substance abuse and our wisdom in making decisions about the therapeutic use of psychoactive drugs.

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A Range of Research-Based Pharmacotherapies for Addiction

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Modern approaches to the treatment of addiction have been influenced by several important factors. These include advances in our understanding of the nature of addiction based on longitudinal studies, and progress in elucidating the biological underpinnings of addictive behavior. In addition, changes in the system for delivery of services have begun to shape the way that addiction is treated.

Addiction used to be defined as tolerance to and physical dependence on a drug of abuse. Tolerance represents an adaptation to repeated exposure to a drug such that the pharmacological response is diminished (*1*). Physical dependence is a state manifested by withdrawal symptoms when drug-taking is terminated or significantly reduced. Withdrawal symptoms tend to be a quasi "rebound" opposite in direction to the initial drug effects, which begin as the drug disappears from the body through metabolism and excretion (*2*). If tolerance and withdrawal symptoms were the only problems of addicts, "treatment" would consist of detoxification, a process that allows the body to cleanse itself while the individual receives medication to block withdrawal symptoms (*2*). If drug-taking does not resume, homeostatic mechanisms will gradually readapt to the absence of the drug (*3*). We now know that detoxification is, at best, a first step in beginning treatment and that achieving the drug-free state is not a particularly significant accomplishment. The more difficult aspect is prevention of relapse to drug-taking behavior.

It is important to note that tolerance and withdrawal symptoms occur commonly among nonaddicts who are treated with any of the common medications to which the body adapts. These include medications for high blood pressure, for anxiety, and for pain. Indeed, the fear of producing "addiction" leads to the undertreatment of pain (*4*) even in terminal cancer patients and may indirectly fuel the debate in the United States over physician-assisted suicide. Many patients are allowed to suffer needlessly when effective pain relief is available, because of the fear of addiction; thus, suicide may appear to be the only alternative (*5*).

If tolerance and physical dependence are not the core of addiction, then what is the preferred definition? As the definition has evolved (*1*), addiction is a syndrome characterized by compulsive drug-seeking behavior that results in an impairment in social and psychological functions or damage to health. Whereas initial drug use is voluntary, the individual, once addicted, is beset by nearly irresistible urges to continue or to resume drug-taking. Even after detoxification and long periods of abstinence, relapse frequently occurs despite sincere efforts to refrain. People or situations previously associated with drug use produce involuntary reactions and may provoke a relapse (*6*). The biological mechanisms for these apparent reflex patterns are suggested by data from animal models at the neurochemical level [see a review by Koob and Le Moal (*7*), this issue] and the molecular level [see a review by Nestler and Aghajanian and (*8*), this issue]. At the clinical level, these behavior patterns are manifested by repeated return to drug-taking behavior that is often patently self-destructive. A key point for the clinician to realize is that the proneness to relapse is based on changes in brain function that continue for months or years after the last use of the drug. Of course, these changes in brain function interact with environmental factors such as social stress and situational triggers.

Confusion about the diagnosis and prognosis of addiction stems from the fact that by the time an addicted person presents for treatment, there are numerous complicating social and psychological problems that frequently overshadow the addiction process. The typical patient evolves from drug user, to abuser, to dependent or addicted person over a period of years. During this time it is common for social, occupational, family, medical, and legal problems to develop. The Addiction Severity Index (*9*) contains seven classes of variables that are assessed in order to obtain a severity rating. Those patients who rank at the severe level only on quantity of drugs used and not on other dimensions have a reasonably good prognosis. In contrast, those with severe psychosocial complications scoring high in the nondrug areas have a poor prognosis and are likely to relapse regardless of their level of drug use severity (*10*).

Psychiatric disorders commonly coexist with addictive disorders. These include anxiety disorders, psychotic disorders, and affective disorders such as depression. Although some of these so-called "dual diagnosis" cases

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