

EVOLUTION, SUBSTANCE USE, AND ADDICTION

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Abstract

The emerging field of evolutionary medicine has the potential to open up new avenues of investigation into a variety of clinical conditions that have often otherwise proved intractable. The extent to which evolutionary medicine is successful hinges on the abilities of researchers to frame new questions about the etiology as well as the evolution of disease. In this paper we outline the basic assumptions of Darwinian theory as it applies to evolved traits, namely that there exists (1) an inherited basis, (2) individual variation, and (3) a functional effect for any specific trait. We then analyze how these three areas apply to substance abuse by examining the genetic basis to substance abuse, outlining different sources of variation such as reactions to drugs and differing personality traits, and providing an adaptive analysis of the compulsive wanting and withdrawal seen in substance abuse. Finally, we outline some therapeutic strategies suggested by evolutionary theory.

Introduction

Evolutionary medicine is an important attempt to refocus thinking about various diseases and widely recognized clinical conditions using Darwinian evolutionary theory. Still developing as a field of study, evolutionary medicine has already permitted researchers and clinicians to rethink a number of clinical conditions, for example, infectious disease, pregnancy sickness, asthma, allergies, congestive heart failure, and certain cancers (1-5). For substance abuse, evolutionary medicine provides five different perspectives that differ from the traditional biomedical approach (6).

First, evolutionary medicine on its own does not provide specific explanations for particular diseases or conditions—it examines the underlying vulnerabilities to diseases and conditions. Its emphasis, then, is not on the details of how to ameliorate current adverse conditions *per se*, but on deeper explanations for the presence of these conditions. This analysis of underlying vulnerability is especially relevant for substance abuse, given the evolutionary novelty of large quantities of highly concentrated psychoactive drugs in the environment.

Second, within evolutionary theory, the focus is on adaptation which is a radically different notion than the concept of a disease. An adaptation is an evolved trait that solves some particular life problem for an individual organism in a way that improves its ability to grow, survive, reproduce, and ultimately ensure the reproduction and growth of offspring. A disease carries the opposite

connotation—that is, the idea that a characteristic or trait is malfunctioning. Often, by better understanding how and why an organism functions, we can better understand its malfunctions—for example, we can begin to understand how addiction might have emerged from evolved capacities involved in other functions such as learning and foraging behavior.

Third, the evolutionary approach does not emphasize perfection in adaptation or functioning. For example, natural selection has not weeded out all those individuals with many chronic or debilitating diseases and conditions. In particular, diseases that appear after cessation of reproduction or diseases that have only a minor detrimental effect are not likely to be selected against. Rare conditions and diseases due solely to environmental exposure are also resistant to the evolutionary process. Furthermore, the evolutionary process is not a design process that starts with a blank slate. Rather, functional attributes are built over time, and often “cobbled together” from available variation in expressed characteristics. These functions are not expected to be engineered exactly, but simply to be better than any of the available competition.

Fourth, the point of evolution is individual fitness, increasing one’s genetic representation in future generations. Thus, the evolutionary process does not focus solely on “health”—if sacrificing health nonetheless results in a higher reproductive and survivorship rate for offspring, this type of individual will out-reproduce healthier but less reproductively successful competitors. Together, the lack of perfection in design and the emphasis on fitness, rather than health,

help to explain why addiction is a difficult behavior for individuals to change and health professionals to treat.

Finally, evolutionary medicine points to the discordance between the modern environment and the ancestral environment. For example, individuals who suffer today from arteriosclerosis have the physiology of humans 50,000 years ago when diets were considerably different than today (7). We evolved eating modest amounts of protein and fat, and our body is not well equipped to handle the higher levels found in today's diet. However, given the importance of protein, fat and salt in the ancestral diet, we have an evolved taste for these types of foods. Hence high fat, low fiber, high calorie foods are the currency of exchange in modern cuisine. But from an evolutionary perspective we are not adapted to eat such foods over long periods of time nor in great quantities. This discordance between our evolved physiology and behavior can be clearly seen in addictive behavior, where the abuse of substances today builds off adaptations evolved for solving fitness problems in yesterday's ancestral environment. Indeed, we might say that just like we have a taste for salt, we also have a "taste" for drugs given their psychoactive effects and impact on our evolved neurophysiology.

Evolutionary Characteristics and Addiction

Addiction is a heterogeneous disorder, and refers at a minimum to the over-use of psychoactive substances. This disorder is generally defined (and

diagnosed) in behavioral terms. In particular, the loss-of-control over drug taking and compulsive drug seeking despite high individual costs are today considered two central behavioral markers of substance abuse (note that in this paper, substance abuse is used interchangeably with addiction). Withdrawal, once considered a main component of addiction, is still recognized as applying to many types of addictive behavior, in particular the psychological discomfort at the loss of the substance as well as the emergence of “cravings” as a central factor in relapse.

This definition of addiction points to a central problem for an evolutionary analysis of substance abuse. It is a central tenet of Darwinian evolutionary theory that a trait could not evolve if it reduced the reproductive success of its carrier. Given that substance abuse imposes significant costs on an individual, how could it have evolved? This question can be answered in three ways: a) Substance abuse appears to represent an evolutionarily novel behavior in terms of its consistency and effects. Thus, the negative fitness consequences of addiction have not had time to significantly alter the genetic basis of human populations. b) Some aspects of substance abuse can be taken as an extreme variant of substance use in general. Evolved mechanisms (e.g., memory, learning) that orchestrate the acquisition and ingestion of psychoactive substances also apply to the extreme case of drug abuse. c) For other aspects of substance abuse (in particular, compulsive wanting), the pharmacological impact of psychoactive substances on specific parts of the brain alters the

functioning of evolved neural systems, thus compromising their effectiveness as evolved mechanisms regulating substance-use behaviors.

Overall, the argument presented here is that substance abuse does not represent an evolved trait in itself—rather, it is like a disease, representing malfunctioning in specific individuals living in today's environment. Nevertheless, given both the general learning mechanisms and specific functional systems involved in substance use and abuse, we can apply an evolutionary analysis to the vulnerabilities and underlying causes. The first step in application of the Darwinian evolutionary paradigm is to demonstrate that these underlying causes of substance abuse behavior meet three basic conditions for a trait to be considered in Darwinian terms: 1) some heritable genetic component of the trait; 2) variation in the phenotypic expression of the trait; and 3) the trait must have some effect on the evolutionary fitness of the bearer.

Genetic Basis

The first assumption of the evolutionary perspective is that any potential Darwinian character be heritable. Heritability here does not necessarily mean rigid genetic control, but simply that a behavior is partially determined by underlying genetics and can pass from generation to generation.

Many researchers have concluded that substance abuse has at least a partial underlying genetic basis (8-12). Compelling data to support this position come from twin studies focusing on alcoholism (13, 14). Monozygotic or

genetically identical twins show much higher rates of alcoholism than dizygotic twins (sharing 50% of genetic material), indicating a significant genetic basis for alcoholism. For example, in one of the earliest studies, Kaij (15) found that monozygotic twins had roughly double the rate of alcoholism as dizygotic twins. Adoption studies have also demonstrated the heritable basis of alcoholism, showing that offspring raised apart from an alcoholic biological parent have a significantly higher probability of developing alcoholism than those adopted children with nonalcoholic biological parents (16-18). Finally, family studies, looking at parent-child and sibling-sibling concurrence of alcoholism (19), also support the conclusion that substance abuse is inherited along lines of descent.

A recent review estimates that the heritability (the genetic component of variance in interindividual variability) of alcohol abuse is approximately 0.38 (20). Some studies point to heritabilities as high as 0.73 in males (21) and 0.61 in females (13). For drug abuse, a recent large twin study (22) indicates that the heritability of any drug abuse is about 0.34, with earlier research demonstrating drug abuse heritability of 0.46 (23). These general levels of heritability seen with substance abuse (0.40-0.50) are similar to those seen for many personality traits (24-26), including novelty-seeking (a risk factor for substance abuse) which was recently shown to have a heritability of approximately 0.50 (27). Overall, this level of heritability appears due to both a general genetic vulnerability for substance abuse as well as specific vulnerabilities to certain drugs. For example, alcoholism and smoking as well as alcoholism and drug dependence are highly

genetically comorbid (28-30). Nevertheless, each of these disorders also has distinct, independent genetic influences (31).

However, some caveats are due before hasty conclusions are reached like “there’s a gene for alcoholism” or “substance abuse is due to the genes.” First, addiction is a complex behavior, and to date, genetic research on complex behavior points to the heritable basis of these behaviors as due to the small additive effects of many different genes in coordination (32). Thus, there is no single “gene” for substance abuse. Second, the same studies that generally support a genetic basis for substance abuse also support the role of the environment in the development of substance abuse. Thus, in no sense is addiction “all genetic”—rather, as a complex behavior, it reflects the impact of genes, environment and their interaction. Indeed, research has supported that some types of substance abuse appear to be more genetically mediated (early-onset alcoholism among sons of male alcoholics) while other types have quite weak genetic influences (late-onset alcoholism among women, for example), being more determined more by particular environmental and developmental factors (33, 34).

Variation

The second assumption a trait must meet in order to be considered for Darwinian analysis is that there is phenotypic variation in the trait or behavior. Without variation, there is no way for the process of natural selection to take

place, because there is no field of competitors from which selection can choose. It should be obvious that individuals vary in their levels of substance use and abuse. What is crucial, then, is to examine the genetically influenced component of phenotypic variation as it relates to drug use and abuse. This heritable variation involves at least three different factors: 1) physiological reactions to drugs; 2) general neuropsychological systems that vary in relevant ways in response to substance use; and 3) specific functional systems that are disrupted by drug use.

Physiological Reactions

It has been demonstrated that physiological reactions to drugs have a significant impact on the development of substance abuse. For example, between 30 and 50% of the Asian population lacks aldehyde dehydrogenase (ALDH), the major enzyme that degrades the first metabolite of ethanol, acetaldehyde, in the liver. After consuming alcohol, affected individuals develop heightened blood acetaldehyde levels associated with facial flushing, tachycardia and a burning sensation in the stomach. Not surprisingly, Asians missing this enzyme are generally less likely to drink heavily and have lower rates of alcoholism (35, 36). As more recent studies have shown, the allele ALDH2*2 is associated with this lack of ALDH in Asian populations, so that individuals homozygous (carrying two alleles) for this trait have never been found in large samples of alcoholic subjects in Japan (37, 38).

Besides traits (or variation) that discourage the development of abuse, research has shown that humans vary in their neurological responsiveness to drugs. The research by De Wit et al. (39) and O'Brien et al. (40) firmly established that humans have individual differences in their drug reactivity. A recent family study of alcoholism focusing on genetically vulnerable individuals found that initial responsiveness to alcohol—likely reflecting genetic influences—accounted for most of the vulnerability in susceptibility to alcoholism in this population (41).

Studies on animal models specifically illustrate how there can be genetic vulnerability to abuse of a specific drug. Selective breeding of rats and mice have produced lines that favor alcohol, cocaine, heroin and other drugs and other lines that do not (32). This research suggests that specific genetically-mediated responses like experiencing less severe withdrawal or having a high self-administration response to a specific drug both favor higher substance use. Piazza et al. (42) establish that this responsiveness in rats is due to a specific heightened sensitivity in these animals to the substance. These vulnerable (or sensitive) animals have greater maximal response to a drug than other animals and tend to self-administer more of the drug at any dose-level. However, while the difference in response was most likely due to genetic differences between individual animals in this case, these authors nonetheless note that this same sort of heightened maximal response can also be induced by repeated environmental exposure to stress and/or drugs of abuse.

Finally, one specific neurological system is affected by most drugs of abuse, the mesolimbic dopamine system (43-45). Significant individual variation has been demonstrated in dopamine receptors and genes, and this neurochemical individuality can have a significant functional effect on individual behavior (46). Specifically, the DRD2 dopamine gene appears to contribute to liability for substance abuse (47-49), and significant associations have been found between genetics variants coding for a specific dopamine receptor (D4DR) and novelty-seeking, which is associated with substance abuse (50-52).

Neuropsychological Systems

Two general neuropsychological traits relate to substance abuse—self-regulation involving executive cognitive function, and personality factors. Risk factor research has repeatedly demonstrated that a lack of impulse control, emotional regulation, and execution of goal-directed behavior is associated with greater substance use and abuse (53, 54). Recently, it has been proposed that disruption in “executive cognitive function” (mediated by the prefrontal cortex) is a core component in the development of substance abuse (55, 56). In turn, a lack of self-control, particularly behavioral inhibition, has been demonstrated to have a significant genetic component that is specifically involved in substance abuse (57).

Besides behavioral inhibition, two aspects of personality have been consistently linked to substance use and abuse. These are novelty/sensation

seeking and anxiety-proneness (33, 58). Novelty-seeking is a heritable behavioral trait that refers to a tendency for exploratory activity and the exhilaration that is activated by novel or appetitive stimuli. Animals who are “high responders” (high locomotor response to novel environments) are preferentially vulnerable to drug use over low responding animals (32, 42). Epidemiological research with humans was established that sensation seeking is one of the major predictors of drug use, in particular among adolescents (53). Research has also shown that children who measure higher in individual novelty-seeking in kindergarten initiate substance use at an earlier age (and early initiation is a major indicator of later problems with substance use) (58). Finally, a significant subset of individuals with a family history of alcoholism demonstrates much greater behavioral activation (an index of reaction to novelty) due to alcohol (59). Thus, novelty and sensation seeking is a clear personality trait linked to substance use and abuse, especially among younger individuals.

Anxiety, linked to harm avoidance, refers to intense reactions to aversive stimuli, thus raising anxiety and stress as well as facilitating inhibitive or withdrawal behaviors. Individuals measured as more anxious self-administer more alcohol in comparison to controls in response to stressful situations (59), while a sample of alcoholics who measured high for anxiety-sensitivity preferentially used alcohol as a coping mechanism to deal with their anxiety in comparison to less anxious alcoholics (60). Finally, the research on self-

medication has pointed to anxiety, stress and fear management as one of the major motives for using alcohol and other drugs among certain individuals, especially women and those with later onset substance abuse problems (33).

However, not everyone who is sensation seeking or anxious develops substance abuse. Indeed, relatively few individuals end up abusing alcohol and other drugs, even among vulnerable populations. For individual differences, what appears to make the difference is the combination of personality or behavioral traits with specific reactions to substance use (such as higher responsiveness). For example, anxious individuals who display a negative physiological reaction to alcohol (such as caused by a lack of ALDH) will find little sedative or calming effect in alcohol. However, if substance use does lower anxiety, then the combination of physiological and neuropsychological traits is more likely to result in the development of substance abuse. As Conrod et al. (59) write, "What is highlighted in the present study is that individuals presumed at risk for alcoholism demonstrate autonomic reactivity patterns that are particularly susceptible to the effects of alcohol (p. 594)."

Functional Effects

Besides heritability and variation, a trait or behavior needs to have effects on the overall reproductive success of the bearer to be considered from a Darwinian evolutionary perspective. In other words, without establishing that the process of selection has shaped a trait (or its underlying components), it is

impossible to use a crucial part of evolutionary theory, adaptation—those functional traits or behaviors that promote the successful development, maintenance and reproduction of the individual. One striking thing about two of the most crucial determinants of evolutionary success—foraging for food and reproduction—is that they consist of similar behavioral patterns. With foraging, one must seek out the food and then consume it; with reproduction, one must find a mate and then engage in sexual behavior. Addiction, like foraging and reproduction, involves both seeking and consummatory behaviors, the first related to positive incentives for approach (wanting) and the second to pleasure, liking, and reward.

Indeed, White (61) has proposed that three separate brain systems mediate different functions involved in substance use and abuse: 1) approach behavior, 2) reward and pleasure, and (3) contextual cues relating approach and reward with drug stimuli in the environment. Similarly, Robinson and Berridge (62, 63) have suggested that drugs affect incentive salience or “wanting” (which underlies approach behavior), reward or “liking”, as well as associative learning. Individuals vary in their responsiveness to environmental cues (what is liked), the magnitude of reward or pleasure drugs produce (how much it is liked), and the degree to which a seeking signal is generated (how much something is sought out). Beyond these three functional systems, some individuals who abuse drugs also display withdrawal reactions which play a central role in

continuing addictive behavior. As outlined below, substance abuse involves alterations in the adaptive functioning of all four of these areas.

Drugs and Association

One crucial thing to recognize about drugs is that due to their impact on brain functioning, they can alter patterns of associative learning. As Panksepp et al. (64) write, “We suspect that drugs of abuse ‘trick’ animals by causing them to associate changes in these fitness-tracking systems with arbitrary drug-related stimuli rather than species-specific fitness relevant stimuli (463).” The *arbitrary* nature of this association with drug-related stimuli can move individuals away from more species-normal associations (those involved in foraging, reproduction, and close social relationships) to environmental associations foregrounding substance use. Moreover, given their potency, drugs produce an evolutionary novel impact on the brain, so drugs *themselves* help to create even stronger associations with their related stimuli.

Overall, this impact of drugs helps to (a) make drug-using individuals relate differently to their environment (they will both perceive and process information about the environment in ways that highlight drug-related stimuli) and thus (b) get these individuals involved in specific environments (e.g., sociocultural environments where substances are more often present and use is the norm) that subsequently reinforce drug-using behavior. On its own, then, associative learning plays a central role in the development of substance use and

abuse, providing the contextual framework in which drugs affect the *adaptive* functioning of the individual.

Why Use Drugs? Evolutionary Considerations

Within evolutionary approaches to human behavior, one finds two general theoretical orientations—the first emphasizes how behavior can be analyzed in terms of its *present* fitness consequences, the second examines how natural selection will have shaped behavior (in particular, the adaptations underlying behaviors) in *past* environments (65). At times these two approaches are seen as producing alternative and conflicting understandings. However, in the case of substance abuse, it is necessary to understand both the present behavior of the individual *and* the way selection has shaped the basic adaptive mechanisms of humans in the past. This section will analyze how present benefits (both real and perceived benefits) play a role in substance use behavior.

Within evolutionary approaches to substance abuse, four basic benefits have been proposed, the first specific to behavioral ecology and the other three largely complementary to specific orientations in the substance abuse field. They are (1) substances should be considered an environmental resource, in ways similar to food; (2) substances play a role in redressing balances in neurotransmitter function in the brain; (3) substances are used to manage stress and anxiety internally; and (4) drugs provide an actual and/or perceived fitness benefit in relation to the environment.

As an environmental resource, a recent article by Dudley (66) argues that humans, as primates, have a long evolutionary history with ethanol through foraging for fruit. Free ranging primates will consume fallen, fermenting fruit, and present subsequent changes in locomotory behavior and overall physical coordination (6), while functionally, ethanol can signal the presence of other food, be an appetitive stimulant, and provide calories, thus indicating that humans might have adaptations that favor current ingestion of ethanol (66). Similarly, Sullivan & Hagen (67) point out that among tribal peoples today, most psychoactive substances are derived from plants and are seen more like “food” given how substances like betel nut and coca leaves can provide energy and sustenance (including access to vitamins and micronutrients). However, both papers recognize that though these functions can play a role in substance use, they do not per se explain abuse from an evolutionary perspective.

Sullivan & Hagen (67) also propose another function for substance ingestion by pointing out that the neurotransmitters most implicated in substance abuse—the monoamines and acetylcholine—are nutritionally constrained in the environment. To maintain adequate brain function, individuals will ingest substances from the environment that correct these deficiencies. Indeed, simple ingestion is a more cost-effective way of changing neurotransmitter levels than producing new neurotransmitters physiologically. This proposal is similar to the idea that there are certain “deficiencies” in normal brain functioning among

individuals who abuse, thus they raise neurotransmitter levels back to what is considered normal through their substance use (68).

Sullivan & Hagen (67) also note that the stress reaction within the individual can deplete these same neurotransmitters, so the use of these substances can help individuals to manage neurotransmitter depletion resulting from stressful situations. By ingesting these chemicals, individuals aim to avoid the long-term negative consequences of the stress response and be able to “tolerate prolonged stress states in aversive conditions.” This idea is consistent with the research linking stress and drug use, as well as the observation that greater amounts of trauma are associated with greater substance use. In particular, through substance use, individuals are able to manage both the negative physiological consequences from the stress reaction due to anxiety and to replenish their neurotransmitter deficit due to a consistent anxious appraisal of the world.

Finally, several evolutionary thinkers on substance abuse have proposed that drugs provide direct fitness benefits or perceived fitness benefits through the creation of “false” signals in the brain by drugs (6). For example, among drug abusers, the use of substances is often associated with more sexual behavior. Moreover, especially among many men, the use of substances is related to a real or perceived ability to fight better, resist more pain, and/or perform better in competitions. Others note how drugs help them be more sociable, again a potent benefit in such a social species as ours. Thus, it is

important to consider that for drug abusers, the use of these drugs relates to *actual benefits* from an evolutionary point of view, especially among the initial stages of substance use.

Other theorists have placed more emphasis on the signal that drugs create within the brain, surmising that this is a “false” fitness signal (69, 70). In particular, drugs’ ability to bring a high, produce pleasure, and/or dull pain are crucial to these sorts of arguments, because these internal signals acted in the past to indicate fitness benefits. Through these sorts of experiences today, individuals *think* that drugs are bringing them benefits—but they are actually not, for it is just the effect of the drug. It is this “false” fitness signal, produced internally by potent drugs, that then prompts the individual to repeat the behavior of using substances.

Overall, these four arguments—psychoactive substances used like food, to balance neurotransmitter levels, to counteract the effects of stress, and to provide actual and perceived benefits—comprise a variety of reasons for why individuals will engage in substance use. Two types of present benefits relate directly to the personality dimensions considered above: the reduction of anxiety and stress (managing negative internal feelings) through substance use, and the seeking out and enjoyment of benefits linked to drug use (sensation seeking). Moreover, the combination of present benefits and associative context provides an understanding of how individuals initially become involved with substance use through the association of specific positive outcomes with the behavior of

obtaining and using drugs. However, benefits on their own leave unexplained the self-destructive and loss-of-control aspects of addictive behavior. The next sections, by addressing past selection (rather than present benefits), will illustrate how evolution helps us to understand the adaptive mechanisms in the mind that underlie compulsive wanting and withdrawal.

Why Abuse? Wanting and the Dopamine System

Engagement in behavior—in particular approach and appetitive behavior—is mediated in part by the dopamine system. Specifically, dopamine seems to be involved in the trade-off between staying involved in a present behavior or switching to an alternative behavior (71). Another way of putting this is that the dopamine system mediates the “wanting” involved in seeking behavior (62, 63), affecting the decision to continue with a behavior or not (72).

This adaptive function of the dopamine system can be altered in two ways by drugs of abuse. First, through the immediate pharmacological impact of the drug (especially among sensitive individuals), a signal of wanting and engagement is produced. This has two effects: first, simply engaging in appetitive behavior will generally be reinforcing for organisms; second, “drugs” as environmental stimuli will become imbued with wanting/seeking salience, thus acting as potent triggers for behavior. The second adaptive change happens over time as continued exposure to the substance drives neuroadaptations in the dopamine circuit, often resulting in a system that is sensitized to produce larger-

than-normal signals of “wanting” (43). These immediate and long-term changes then lead to two outcomes: (1) drugs are “wanted” excessively—sensitized signals in the dopamine system can drive craving and the obsessive pursuit of drugs; (2) there is preferential engagement in the behavior of seeking out drugs versus other behaviors.

Robinson and Berridge (43, 62, 63) argue that this sensitization in wanting and focus on drugs occurs even as the costs of using substances have risen and the reported pleasure or liking of consumption has been severely reduced. Dopamine only mediates one aspect of addictive behavior, the appetitive side, with consumption and its associated satiation mediated by other systems. Under the influence of drugs and a particular environmental context, the normally tight coupling between wanting, consumption, and satiation is disrupted (43, 62-64). Drugs of abuse continue to produce signals in the dopamine system even as tolerance to the subjective effects of consumption has risen. Moreover, drugs of abuse do not provide a satiation signal like food can—they simply don’t produce these sorts of signals in the brain or body.

Moreover, today’s environment—where highly potent drugs are regularly available and drug-associated stimuli often abound—is different from the environment in which the dopamine system’s function evolved. In the past, environmental limitation regularly occurred. Both foraging and reproduction involved resources and sexual partners that were generally available in limited quantities at limited times (73). Thus, in ancient environments there was little

need for instinctive regulation of dopamine signaling because of limitation present in the environment. Therefore, instinctive moderating mechanisms never evolved within the dopamine system itself. This is precisely what can make the dopamine system so vulnerable to excessive signaling in today's super-rich environment. These conditions place a premium on higher-level regulation (executive cognitive function and behavioral inhibition) which is often limited or compromised in individuals who abuse drugs.

Thus, the compulsive behavior, craving and excessive pursuit of substances seen in addictive behavior can be seen as due to a suite of three factors: (1) the dopamine system, due to the impact of drugs on its functioning, produces a sensitized signal of wanting and engagement around drug use; (2) as drug use continues, wanting and satiation are de-coupled, and drugs provide no further satiating signal, thus promoting continued engagement in the behavior; (3) there is no instinctive (or built-in) regulation of the dopamine system, placing a premium on environmental regulation (through limitation and through relationships) and on executive cognitive function, both of which are generally compromised for substance abusers.

Why Abuse? Withdrawal

Most understandings of withdrawal are based on the idea of physical dependence, where the sudden removal of the drug produces a loss of homeostasis followed by the initiation of opponent-process regulatory

mechanisms (74). The activation of these mechanisms then drives the organism to engage in behaviors to re-establish the lost physiologic balance (even when this balance has been artificially altered under the impact of drugs). However, it is also possible to develop an adaptive understanding of withdrawal which can help us to understand why, even when drugs do not produce physical dependence, individuals can experience withdrawal-like symptoms to the loss of the drug and/or cessation of drug-taking. In other words, an evolutionary approach focuses on the question of *why* have a withdrawal reaction.

To answer this question, it is important to establish first that withdrawal can be considered an evolved trait. Thus, this section begins by pointing to (a) a common set of symptoms across different types of withdrawal, (b) an underlying brain system that can mediate the high-arousal and irritability associated with withdrawal, and (c) two possible evolutionary precursors that can provide a phylogenetic (or inherited) base for the dependence and withdrawal behaviors associated with addiction. Based on these three areas, the last part of this section presents an evolutionary analysis of withdrawal, focusing on *why* withdrawal would have been adaptive in the past, though with substances today it can turn out to maintain a maladaptive behavioral pattern.

A study of common withdrawal symptoms across a number of addictive substance and loss categories (specifically alcohol, nicotine, caffeine, food and relationship loss) showed that individuals differ consistently in their withdrawal responses (i.e., there is individual variation) (75). More importantly, this study

demonstrated that there is a high degree of similarity in the withdrawal pattern across the different behaviors. For example, for all types of loss or withdrawal, eight symptoms were consistently mentioned: irritability, restlessness, impatience, anxiety, concentration problems, anger, and depression. This pattern is similar to that found in high frequency gamblers (75).

These symptoms appear to be mediated in part by the opioid system, which plays an important role in the development of social dependencies and attachments (64). Specifically, the opioid system evokes “calm and positive feelings of security... both by the presence of a loved one or an abundance of natural resources (462).” However, with withdrawal or loss this system provokes “highly arousing negative states (e.g., anxiety, irritability) which are the opposite feelings of calmness and security that opioids produce (463).”

Gerald & Higley (76) analyze the attachment relationship between mother and infant as one evolutionary precursor to this sort of anxious reactions (see also Panksepp et al. (77)). They write, “anxiety and arousal are proximate influences that motivate the young infant to stay close to its mother... By contrast, an excess of anxiety can elicit chronic physical contact between mother and infant, which can prevent infants from pursuing [other] social relationships (416).”

Besides attachment, the evolution of dominance, submissive, and dependence behaviors represents another evolutionary behavioral precursor to substance dependence and its accompanying withdrawal. As reviewed in Lende

& Smith (73), social dependence—marked by maintaining close contact with dominant allies—provides more gains (through reduced aggression and greater access to resources) than merely being submissive to a dominant individual. The dependent individuals achieves this benefit through close reciprocal interaction, social manipulation and deception, types of behavior often seen in addicts.

Based on a common set of symptoms and an underlying brain system, with possible evolutionary precursors, we can now look at the process of forming an attachment to drugs (as well as social attachments more generally).

Panksepp et al.(64) present three steps: (1) the formation of an initial “liking” response (attraction), (2) the gradual diminution of active liking accompanied by formation of a social bond (the building of “tolerance”), (3) the possibility of an “affectively compelling withdrawal response” when the person (or drug) is withdrawn. By understanding each of these steps, we will be in a better position to understand not only the loss of subjective response accompanying greater dependence, but the occurrence of a withdrawal response as one possible reaction to loss of the person or object.

Without an initial attraction, an individual will never establish a relationship with another person, thus losing out on any possible benefits from this relationship. Attraction is evolution’s way of getting two individuals together—without this adaptation, most affiliative social relationships would not form between individuals. However, once a relationship is formed, continued “liking” does not always lead to the most successful relationship—being “blinded

by love” is not necessarily the best way to figure out who washes the dishes. Through social manipulation and reciprocity, individuals in relationships are able to actively negotiate the costs and benefits of on-going interactions. However, this is at the loss of subjective “liking.”

This reduction in “liking” (or the build-up of “tolerance”) raises a dilemma. At any point, since active liking is not so strong, one might find it immediately in one’s benefit to abandon the relationship. Withdrawal now emerges with a function—to keep the individual involved in close relationships that over time have produced consistent benefits. For example, the child in the middle of the temper tantrum over not getting candy might say he hates his mommy and wants to leave—however, running away at this point is not in his long-term interest. A withdrawal reaction thus ensures that the child stays with his mother or that a socially dependent individual stays close to a dominant one. This closeness ensures continued access to benefits such as provisioning of resources for the child and reduced aggression and greater access to food for the socially dependent individual.

In sum, withdrawal can be seen as an evolved behavior related to social relationships and with underlying adaptive mechanisms in the brain. However, as noted above, the impact of associative learning can move individuals from normal social relationships to involvement with substances. Without the long-term benefits of most social relationships and the reciprocal give-and-take involved in relationships, a withdrawal response with substance use can quickly

become maladaptive, prompting continued involvement in a behavior whose long-term benefits do not outweigh the costs.

The development of withdrawal responses with psychoactive substances is facilitated in humans who have evolved symbolic and linguistic capabilities (78, 79). Involvement with drugs often takes on social, moral, and meaning dimensions that are mediated through ritual, symbols, and language (80-82). As analyzed in Lende & Smith (73), these symbolic elements help mediate the transference of evolved patterns like withdrawal onto behaviors involved with consuming substances, promoting the development of withdrawal symptoms with evolutionary arbitrary but culturally relevant behaviors like gambling or cocaine use.

Wanting, Withdrawal, and Short-term Strategies

As individuals become more involved with drugs, the combination of heightened wanting and the development of withdrawal can drive substance use into high levels of abuse. First, withdrawal promotes continued involvement with drugs (as it has done in the past with social relationships), a pattern reinforced by the dopamine system which signals continued behavioral engagement with drugs. Second, given the heightened irritability and arousal linked to withdrawal, individuals will tend to seek out the possible benefits that drugs provide so as to ameliorate this aversive situation. Thus, the alterations in two formerly adaptive

patterns—approach behavior and withdrawal—together help form a powerful addictive cycle that keeps individuals involved in abusing substances.

What makes the cycle of involvement worse is that many individuals who use and abuse substances are already in high-risk situations where short-term strategies can be seen as a way to gain an evolutionary advantage. Individuals raised in sub-optimal conditions such as poverty and marginalization, individuals who have suffered trauma during development (e.g., physical and sexual abuse), and individuals who are chronically stressed or recently gone through a major negative life change (loss of employment, loss of a family member) are all expected to pursue short-term benefits despite long-term costs (73, 83). Moreover, drugs not only provide these sorts of immediate benefits, but, through their pharmacological impact on the dopamine system, signal the imminent arrival of benefits. This combination of the adaptive nature of short-term benefits and the internal signaling of short-term behavioral engagement is a crucial problem for addiction, as it reinforces the addictive cycle and undermines the individual's consideration of the long-term costs and benefits of continued substance use.

Implications for Treatment

The evolutionary approach we have outlined provides both general and specific suggestions for therapeutic work with individuals abusing psychoactive substances. As a general framework, evolutionary theory suggests that decision-

making individuals live and respond to their local social environments. Darwinian evolutionary theory describes these individuals as having psychological adaptations that respond functionally to problems they encounter, rather than having a generalized intelligence that begins as a blank slate. Moreover, these individuals are not simply rational decision makers interested only in maximizing personal benefit. Rather, individuals display emotions that play a major role in decisions, and these decisions often can be understood better when seen from the light of fitness (overall reproduction success) rather than simple economic gain. Given this tendency for people to attempt to further their own individual reproductive interests, social relationships are expected to be fraught with conflict unless the calculus of costs and benefits to the individual favors cooperation.

These general points lead to three major emphases regarding substance abuse. First, individuals can engage in drug use for any number of immediate and evolutionary relevant reasons—for pleasure, to reduce pain or stress, to gain energy, to change to a more positive emotional state, for sexual opportunities, and so forth. Thus, when attempting to change substance abuse behavior, it is crucial that an individual take care of basic needs first. As Alcoholics Anonymous puts it, “Don’t get too hungry, angry, lonely, or tired (HALT),” because these states will heighten the immediate perceived benefits of drug use. In similar fashion, given our immediate responsiveness to the environment and our general reliance on short-term calculus, abusers should take it “one day at a time”,

another injunction of Alcoholics Anonymous. In this fashion, recovering abusers can build on short-term successes and deal with immediate problems during a difficult and transitional time.

Second, given that humans are highly social animals, we are extremely sensitive both to group pressure and to the demands of social relationships. Thus, it is important for substance abusers to change their peer group from one of abusers to a group where substance use is discouraged, otherwise both the opportunities and the positive social pressure will be extremely difficult to ignore. Conflict in important relationships is also likely to create an environment that does not favor change, while encouragement from precisely the same individuals (in particular family members, close friends, and important dominant individuals) will likely facilitate change.

Third, given that therapists are often placed in a dominant position relative to a substance abuser, it is important to be aware of how social individuals respond to dominance. Today, it is understood the individuals will engage in manipulative and deceptive behaviors to try to subvert the costs (such as major life change) that dominant individuals often impose on a relationship (84-86), especially if this relationship is marked by confrontation to "break through the denial." While confrontation has its place in therapy, we believe that a supportive relationship that relies on both guidance and on the use of subtle manipulative techniques will be more conducive to change. Motivational Interviewing (87) does this, employing a non-confrontational, supportive

approach that uses the client's own words and behaviors to motivate the individual to change, often by having the person engage in a explicit consideration of the costs and benefits of various decisions they might make.

A number of specific treatment recommendations can also be made. First, individuals with poor "executive cognitive function" (marked by poor self-regulation and self-direction in affective, cognitive, and/or behavioral domains) will have a difficult time regulating their intake of drugs, unless their ability to manage themselves improves. Second, cognitive-behavioral therapies can explicitly address the perceived positive characteristics of particular drugs as well as the intensity of these positive attributes—by pointing out the costs, the initial assumption that the substance provides some sort of benefit can be overturned, and training programs can aim to reduce how much the substance is "liked." Third, the wanting and seeking behaviors involved in substance abuse need to be addressed. Relapse prevention work that focuses on how cues can trigger craving is one good therapy (see Robinson & Berridge (62) for further recommendations). In general, individuals must become aware of the often unconscious and automatic activation of goal-directed behavior in order to successfully engage in a more considered decision not to continue substance use. If individuals are also cognizant of the costs involved and have been motivated to change, they are more likely to act on their decision to stop using substances.

In conclusion, within psychiatry, the overall success of a therapeutic intervention relies on an understanding of the psychobiology as well as the evolutionary basis of a behavior or disorder. For substance abuse, understanding both the pharmacological and functional effects of drugs on evolved neurological systems will aid in the development of better therapies, provided that the place of the individual as a decision maker acting within a local social and symbolic environment is taken into account.

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1. Ewald, P. W., *Evolution of Infectious Disease*, Oxford University Press, Oxford, 1994.
2. Profet, M., The evolution of pregnancy sickness as protection to the embryo against Pleistocene teratogens. *Evolutionary Theory* 8:177-190 (1988).
3. Nesse, R. M., and Williams, G. C., *Why We Get Sick: The New Science of Darwinian Medicine*, Times Books, New York, 1995.
4. Eaton, S. B., Pike, M. C., Short, R. V., Lee, N. C., Trussell, J., Hatcher, R. A., Wood, J. W., Worthman, C. M., Blurton Jones, N. G., and Konner, M. J., Women's reproductive cancers in evolutionary context. *Quarterly Review of Biology* 69:(3)353-367 (1994).
5. Trevathan, W., Smith, E. O., and McKenna, J. J. (Eds.), *Evolutionary Medicine*, Oxford University Press, New York, 1999.
6. Smith, E. O., Evolution, substance abuse, and addiction, in *Evolutionary Medicine* (W. R. Trevathan, Smith, E.O., McKenna, J.J., Ed.), Oxford University Press, New York, 1999, pp. 375-405.
7. Eaton, S.B., Konner, M., and Shostak, M., Stone agers in the fast lane: Chronic degenerative diseases in evolutionary perspective. *The American Journal of Medicine* 84:739-749 (1988).
8. Goodwin, D. W., Alcoholism and genetics: The sins of the fathers. *Archives of General Psychiatry* 42:171-174 (1985).
9. Harford, T. C., Family history of alcoholism in the United States: Prevalence and demographic characteristics. *British Journal of Addiction* 87:931-935 (1992).
10. Karp, R. W., Genetic studies in alcohol research. *American Journal of Medical Genetics (Neuropsychiatric Genetics)* 54:304-308 (1994).
11. Li, T. K., Lumeng, L., McBride, W. J., and Murphy, J. M., Genetic and neurobiological basis of alcohol-seeking behavior. *Alcohol & Alcoholism* 29:(6) 697-700 (1994).
12. Svikis, D. S., Velez, M. L., and Pickens, R. W., Genetic aspects of alcohol use and alcoholism in women. *Alcohol Health & Research World* 18:192-196 (1994).
13. Anthenelli, R. M., and Schuckit, M. A., Genetic influences in addiction, in *Principles of Addiction Medicine*, 2nd Edition (A.W. Graham and T.K. Schultz, Eds.), American Society of Addiction Medicine, Chevy Chase, MD, 1998, pp. 17-35.
14. Kendler, K. S., Heath, A. C., Neale, M. C., Kessler, R. C., and Eaves, L. J., A population-based twin study of alcoholism in women. *J.A.M.A. - Journal of the American Medical Association* 268:1877-1882 (1992).
15. Kaij, L., *Studies on the Etiology and Sequels of Abuse of Alcohol*, University of Lund Press, Lund, Sweden, 1960.

16. Bohman, M., Sigvardsson, S., and Cloninger, C. R., Maternal inheritance of alcohol abuse: Cross-fostering analysis of adopted women. *Archives of General Psychiatry* 38:965-969 (1981).
17. Cadoret, R. J., Yates, W. R., Troughton, E., Woodworth, G., and Stewart, M. A., Adoption study demonstrating two genetic pathways to drug abuse. *Archives of General Psychiatry* 52:42-52 (1995).
18. Goodwin, D. W., Schulsinger, F., Hermansen, L., Guze, S. B., and Winokur, G., Alcohol problems in adoptees raised apart from alcoholic biologic parents. *Archives of General Psychiatry* 28:238-243 (1973).
19. Cotton, N., The familial incidence of alcoholism. *Journal of Studies on Alcohol* 40:89-116 (1987).
20. Heath, A. C., and Martin, N. G., Genetic influences on alcohol consumption patterns and problem drinking: results from the Australian NH&MRC twin panel follow-up survey. *Annals of the New York Academy of Sciences* 708:72-85 (1994).
21. McGue, M., Pickens, R. W., and Svikis, D. S., Sex and age effects on the inheritance of alcohol problems: a twin study. *Journal of Abnormal Psychology* 101:(1)3-17 (1992).
22. Tsuang, M. T., Lyons, M. J., Eisen, S. A., Goldberg, J., True, W., Lin, N., Meyer, J. M., Toomey, R., Faraone, S. V., and Eaves, L., Genetic influences on DSM-III-R drug abuse and dependence: A study of 3,372 twin pairs. *American Journal of Medical Genetics (Neuropsychiatric Genetics)* 67:(5)473-477 (1996).
23. Grove, W. M., Eckert, E. D., Heston, L., Bouchard, T. J., Jr., Segal, N., and Lykken, D. T., Heritability of substance abuse and antisocial behavior: a study of monozygotic twins reared apart. *Biological Psychiatry* 27:(12)1293-304 (1990).
24. Bouchard, T. J., Jr., Lykken, D. T., McGue, M., Segal, N. L., and Tellegen, A., Sources of human psychological differences: the Minnesota Study of Twins Reared Apart. *Science* 250:(4978)223-228 (1990).
25. Pedersen, N. L., Plomin, R., McClearn, G. E., and Friberg, L., Neuroticism, extraversion, and related traits in adult twins reared apart and reared together. *Journal of Personality & Social Psychology* 55:(6)950-957 (1988).
26. Eaves, L. J., Eysenck, H. J., and Martin, N. G. (Eds.), *Genes, Culture, and Personality: An Empirical Approach*, Academic Press, San Diego, 1989.
27. Stallings, M. C., Hewitt, J. K., Cloninger, C. R., Heath, A. C., and Eaves, L. J., Genetic and environmental structure of the Tridimensional Personality Questionnaire: three or four temperament dimensions? *Journal of Personality & Social Psychology* 70:(1)127-140 (1996).
28. Rose, R.J., Genes and human behavior. *American Review of Psychology* 46:625-654 (1995). Rose, R.J. (1995).

29. Stallings, M.C., Hewitt, J.K., Beresford, T., Heath, A.C., and Eaves, L.J., A twin study of drinking and smoking onset and latencies from first use to regular use. *Behavior Genetics* 29:409-421 (1999).
30. Pickens, R.W., Svikis, D.S., McGue M., and LaBuda M.C., Common genetic mechanisms in alcohol, drug, and mental disorder comorbidity. *Drug and Alcohol Dependence* 39:129-138 (1995).
31. Enoch, M.A. and Goldman, D., The genetics of alcoholism and alcohol abuse. *Current Psychiatry* 3:144-151 (2001).
32. Crabbe, J.C., Genetic contributions to addiction. *Annual Reviews of Psychology* 53:435-462 (2002).
33. Cloninger, C.R., Neurogenetic adaptive mechanisms in alcoholism. *Science* 236: 410-416 (1987).
34. Cloninger, C.R., Sigvardsson, S. and Bohman, M., Childhood personality predicts alcohol abuse in young adults. *Alcoholism: Clinical and Experimental Research* 12:494-505 (1988).
35. Ewing, J. A., Rouse, B. A., and Pelizzari, E. D., Alcohol sensitivity and ethnic background. *American Journal of Psychiatry* 131:206-210 (1974).
36. Wall, T. L., and Ehlers, C. L., Acute effects of alcohol on P300 in Asians with different ALDH2 genotypes. *Alcoholism: Clinical & Experimental Research* 19:(3)617-22 (1995).
37. Higuchi, S., Matsushita, S., Imazeki, H., Kinoshita, T., Takagi, S., and Kono, H., Aldehyde dehydrogenase genotypes in Japanese alcoholics. *Lancet* 343:(8899)741-742 (1994).
38. Nakamura, K., Iwahashi, K., Matsuo, Y., Miyatake, R., Ichikawa, Y., and Suwaki, H., Characteristics of Japanese alcoholics with the atypical aldehyde dehydrogenase 2*2. I. A comparison of the genotypes of ALDH2, ADH2, ADH3, and cytochrome P-4502E1 between alcoholics and nonalcoholics. *Alcoholism: Clinical & Experimental Research* 20:(1)52-55 (1996).
39. De Wit, H., Uhlenhuth, E.H. and Johanson, C.E., Individual differences in the reinforcing and subjective effects of amphetamine and diazepam. *Drug and Alcohol Dependence* 16: 341-360 (1986).
40. O'Brien, C.P., Ehrman, R.N. and Terns, J.N., Classical conditioning in human opioid dependence, in *Behavioral Analysis of Drug Dependence*, (Goldeberg, S.R., Stolerman, I.P., Ed.), Academic Press, New York, 1986, pp. 329-335.
41. Schuckit, M.A. and Smith, T.L., An 8-year follow-up of 450 sons of alcohol and control subjects. *Archives of General Psychiatry* 53: 202-210 (1996).
42. Piazza, P.V., Deroche-Gamonet, V., Rouge-Pont, F. and Le Moal, M., Vertical shifts in self-administration dose-response functions predict a

- drug-vulnerable phenotype predisposed to addiction. *The Journal of Neuroscience* 20(11):4226-4232 (2000).
43. Robinson, T. E., and Berridge, K. C., The neural basis of drug craving: an incentive-sensitization theory of addiction. *Brain Research - Brain Research Reviews* 18:(3)247-291 (1993).
 44. Di Chiara, G., The role of dopamine in drug abuse viewed from the perspective of its role in motivation. *Drug & Alcohol Dependence* 38:(2)95-137 (1995).
 45. Self, D. W., Neural substrates of drug craving and relapse in drug addiction. *Annals of Medicine* 30:(4)379-389 (1998).
 46. Cravchik, A., and Goldman, D., Neurochemical individuality: genetic diversity among human dopamine and serotonin receptors and transporters. *Archives of General Psychiatry* 57:(12)1105-14 (2000).
 47. Comings, D. E., Rosenthal, R. J., Lesieur, H. R., Rugle, L. J., Muhleman, D., Chiu, C., Dietz, G., and Gade, R., A study of the dopamine D2 receptor gene in pathological gambling. *Pharmacogenetics* 6:(3)223-234 (1996).
 48. Comings, D. E., Ferry, L., Bradshaw-Robinson, S., Burchette, R., Chiu, C., and Muhleman, D., The dopamine D2 receptor (DRD2) gene: a genetic risk factor in smoking. *Pharmacogenetics* 6:(1)73-79 (1996).
 49. Vanyukov, M. M., and Tarter, R. E., Genetic studies of substance abuse. *Drug & Alcohol Dependence* 59:(2)101-123 (2000).
 50. Benjamin, J., Li, L., Patterson, C., Greenberg, B. D., Murphy, D. L., and Hamer, D. H., Population and familial association between the D4 dopamine receptor gene and measures of Novelty Seeking. *Nature Genetics* 12:(1)81-84 (1996).
 51. Ebstein, R. P., Novick, O., Umansky, R., Priel, B., Osher, Y., Blaine, D., Bennett, E. R., Nemanov, L., Katz, M., and Belmaker, R. H., Dopamine D4 receptor (D4DR) exon III polymorphism associated with the human personality trait of Novelty Seeking. *Nature Genetics* 12:(1)78-80 (1996).
 52. Cloninger, C. R., The genetics and psychobiology of the seven-factor model of personality, in *Biology of Personality Disorders*. Review of psychiatry series (K. R. Silk, Ed.), American Psychiatric Press, Inc, Washington, DC, 1998, pp. 63-92.
 53. Glantz, M. D., and Pickens, R. W. (Eds.), *Vulnerability to Drug Abuse*, American Psychological Association, Washington, DC, 1992.
 54. Martin, C. S., Earleywine, M., Blackson, T. C., Vanyukov, M. M., Moss, H. B., and Tarter, R. E., Aggressivity, inattention, hyperactivity, and impulsivity in boys at high and low risk for substance abuse. *Journal of Abnormal Child Psychology* 22:(2)177-203 (1994).
 55. Giancola, P. R., and Tarter, R. E., Executive cognitive functioning and risk for substance abuse. *Psychological Science* 10:(3)203-205 (1999).

56. Giancola, P. R., and Moss, H. B., Executive cognitive functioning in alcohol use disorders, in *Recent Developments In Alcoholism: The Consequences Of Alcoholism: Medical Neuropsychiatric Economic Cross-Cultural. Recent Developments In Alcoholism*, Vol. 14 (M. Galanter, Ed.), Plenum Press, New York, 1998, pp. 227-251.
57. Iacono, W. G., Carlson, S. R., Taylor, J., Elkins, I. J., and McGue, M., Behavioral disinhibition and the development of substance-use disorders: findings from the Minnesota Twin Family Study. *Development & Psychopathology* 11:(4)869-900 (1999).
58. Masse, L.C. and Tremblay, R.E., Behavior of boys in kindergarten and the onset of substance use during adolescence. *Archives of General Psychiatry* 54(1):62-68 (1997).
59. Conrod, P.J., Pihl, R.O., and Vaassileva, J. *Alcoholism: Clinical and Experimental Research* 22(3):585-597 (1998).
60. Kushner, M.G, Thuras, P., Abrams, K., Brekke, M. and Stritar, L., Anxiety mediates the association between anxiety sensitivity and coping-related drinking motives in alcoholism treatment patients. *Addictive Behaviors* 26(6):869-885 (2001).
61. White, N. M., Addictive drugs as reinforcers: Multiple partial actions on memory systems. *Addiction* 91:(7)921-949 (1996).
62. Robinson, T. E., and Berridge, K. C., The psychology and neurobiology of addiction: An incentive-sensitization view. *Addiction* 95:(Suppl2)S91-S117 (2000).
63. Robinson, T. E., and Berridge, K. C., Incentive-sensitization and addiction. *Addiction* 96:(1)103-114 (2001).
64. Panksepp, J., Knutson, B. and Burgdorf, J., The role of brain emotional systems in addictions: A neuro-evolutionary perspective and new 'self-report' animal model. *Addiction* 97(4):459-469 (2002).
65. Smith, E.A., Three styles in the evolutionary analysis of human behavior, in *Adaptation and Human Behavior: An Anthropological Perspective* (Cronk, L., Chagnon, N., Irons, W., Ed.), Aldine de Gruyter, New York, 2000, pp. 27-46.
66. Dudley, R., Fermenting fruit and the historical ecology of ethanol ingestion: Is alcoholism in modern humans an evolutionary hangover? *Addiction* 97(4):381-388 (2002).
67. Sullivan, R.J. & Hagen, E.H., Psychotropic substance-seeking: Evolutionary pathology or adaptation? *Addiction* 97(4):389-400 (2002).
68. Blum, K., Cull, J.G., Braverman, E.R. & Comings, D.E., Reward deficiency syndrome. *American Scientist* 84: 132-145 (1996).
69. Nesse, R.M. & Berridge, K.C., Psychoactive drug use in evolutionary perspective. *Science* 278:63-66 (1997).

70. Newlin, D.B., The self-perceived survival ability and reproductive fitness (SPFit) theory of substance use disorders. *Addiction* 97(4):427-445 (2002).
71. Jaber, M., Robinson, S.W., Missale, C. and Caron, M.G., Dopamine receptors and brain function. *Neuropharmacology* 35: 1503-1520 (1996).
72. Ikemoto, S. and Panksepp, J., The role of nucleus accumbens dopamine in motivated behavior: A unifying interpretation with special reference to reward-seeking. *Brain Research Reviews* 31: 6-41 (1999).
73. Lende, D. H., and Smith, E. O., Evolution meets biopsychosociality: An analysis of addictive behavior. *Addiction* 97:(4)447-458 (2002).
74. Koob, G.F, Caine, S.B., Parsons, L., Markou, A. and Weiss, F., Opponent process model and psychostimulant addiction. *Pharmacology, Biochemistry & Behavior* 57(3):513-521 (1997).
75. Wray, I. and Dickerson, M.G., Cessation of high frequency gambling and "withdrawal" symptoms. *British Journal of Addiction* 76: 401-405 (1981).
76. Gerald, M.S. and Higley, J.D., Evolutionary underpinnings of excessive alcohol consumption. *Addiction* 97(4):415-425 (2002).
77. Panksepp, J., Herman, B.H., Vilberg, T., Bishop, P. and Deeskinazi, F.G., Endogenous opioids and social behavior. *Neuroscience and Biobehavioral Reviews* 4: 473-487 (1980).
78. Deacon, T. W., *The Symbolic Species : The Co-evolution of Language and the Brain*, W.W. Norton, New York, 1997.
79. Pinker, S., *The Language Instinct*, W. Morrow and Co., New York, 1994.
80. Alasuutari, P., *Desire And Craving: A Cultural Theory Of Alcoholism*, State University of New York Press, Albany, 1992.
81. Stephens, R. C., *The Street Addict Role: A Theory Of Heroin Addiction*, State University of New York Press, Albany, NY, 1991.
82. Peele, S., *The Meaning Of Addiction: Compulsive Experience And Its Interpretation*, Lexington Books, Lexington, Mass., 1985.
83. Hill, E.M. and Chow, K., Life-history theory and risky drinking. *Addiction* 97(4): 401-413 (2002).
84. Byrne, R. W., and Whiten, A., Cognitive evolution in primates: Evidence from tactical deception. *Man* 27:609-627 (1992).
85. Whiten, A., and Byrne, R., Tactical deception in primates. *Behavioral and Brain Sciences* 11:233-273 (1988).
86. Smith, E. O., Deception and evolutionary biology. *Cultural Anthropology* 2:50-64 (1987).
87. Miller, W. R., and Rollnick, S., *Motivational Interviewing: Preparing People to Change Addictive Behavior*, Guilford Press, New York, 1991.