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FEATURE REVIEW

Genetic susceptibility to substance dependence

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Despite what is often believed, the majority of those who experiment with substances with a dependence potential do not develop dependence. However, there is a subpopulation of users that easily becomes dependent on substances, and these individuals exhibit pre-existing comorbid traits, including novelty seeking and antisocial behavior. There appears to be a genetic basis for the susceptibility to dependence and these comorbid traits. Animal studies have identified specific genes that can alter susceptibility to dependence and response to novelty. The mechanisms underlying the genetic susceptibility to dependence and response to novelty are complex, but genetic susceptibility plays a significant role in the transition from substance use to dependence and from chronic use to addiction. We discuss two models to explain how genetic variations alter dependence susceptibility. Identification of the specific genes involved in these processes would help to identify individuals that are vulnerable to dependence/addiction and to devise novel treatment strategies.
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Chronic use of several classes of substances results in physical, psychological, and behavioral changes in humans. Distinct sets of symptoms characterize dependence and addiction. Dependence, which includes both physical and behavioral dependence, is the most comprehensive definition of substance-related disorder.[1] Physical dependence refers to the tolerance and withdrawal that appear after chronic use. Withdrawal also results in psychological dependence, in which a substance user continuously or intermittently craves the substance to avoid a dysphoric state. Behavioral dependence, in contrast, refers to the pathological pattern of substance seeking. Behavioral dependence is defined as uncontrollable, persistent use despite negative physical, psychological, societal, or legal consequences. Addiction is defined as a state in which an individual loses control over the use of substances despite the adverse consequences associated with substance use.[2] Addiction is essentially equivalent to behavioral dependence. The most troubling aspect of dependence is behavioral dependence or addiction, as an individual can develop physical dependence without addiction and compulsive substance users may not exhibit physical dependence.[3] In this review, we will use the terms 'addiction' and 'behavioral dependence' interchangeably, whereas 'dependence' refers to a more global framework that includes both physical and behavioral dependence.

Recent animal studies have clearly demonstrated that there are molecular alterations associated with the chronic use of substances with dependence potential.[2,4] These animal studies assume that chronic use of a substance causes molecular and synaptic plasticity, which manifests itself as dependence. However, plasticity-based dependence models do not fully account for the fact that only a subpopulation of chronic users becomes dependent. Here, we review evidence that individuals susceptible to dependence exhibit pre-existing behavioral traits and that specific genes contribute to susceptibility to dependence and these comorbid traits. We discuss two hypothetical models to explain this aspect of dependence.

Individual susceptibility to substance dependence

How often does the use of an addictive substance lead to dependence? Estimates vary from study to study, but the consensus is that a majority of those who try substances with dependence potential do not become dependent. Among a sample of people in the US between the ages of 15 and 54 years who tried a substance at least once in their lifetimes, the probability of becoming dependent is estimated to be 32% for tobacco, 23% for heroin, 17% for cocaine, 15% for alcohol, 11% for stimulants other than cocaine, 9% for cannabis, 9% for anxiolytic, sedative and hypnotic drugs, 8% for analgesics, 5% for psychedelics, and 4% for inhalants.[5] A more recent survey including 67 500 persons aged 12 years old or older yielded similar estimates.[6] For example, among the 120

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million current drinkers in the US, 15.9 million aged 12 or older are heavy alcohol drinkers (13%). These estimates are based on individuals who 'tried a substance at least once in their lifetime'[5] or at least once in the past 30 days.[6]

A series of studies on the rate of addiction/behavioral dependence in chronic users of nicotine, alcohol, and opioids elegantly demonstrated that only a subpopulation of *chronic* substance users become dependent, as discussed below.

Nicotine

It has been established that nicotine is the critical ingredient for the development of tobacco addiction. Persistent smoking of tobacco products is not simply a habit, but represents addiction or behavioral dependence, as smokers prefer regular cigarettes to denicotinized cigarettes when given a choice.[7,8]

There is considerable individual variation in susceptibility to nicotine dependence. A third of those who try tobacco products on at least one occasion in their lifetime become regular smokers and develop dependence.[5] A small fraction of smokers find it hard to quit even after consuming 20 or fewer cigarettes.[9] Moreover, in a subpopulation of youths, the first symptoms of nicotine dependence appear within days to weeks of occasional tobacco use, prior to the onset of daily smoking.[10] Smoking also targets individuals dependent on other substances; 43% of individuals with substance use disorders are regular smokers.[11]

It is not only the transition from initial use to nicotine dependence that shows individual variation. Even after regular smoking sets in, there are those who do not meet the criteria of dependence. A subgroup (5–10%) of smokers, termed 'chippers', smoke fewer than five cigarettes per day. Chippers find it easy not to smoke, and exhibit little craving, withdrawal, or mood/sleep disturbances during abstinence. In contrast, regular smokers show both physical and behavioral dependence. These individuals smoke 20–40 cigarettes per day; they find it extremely difficult to quit and experience withdrawal symptoms upon abstinence.[12–15]

There are several possible explanations as to why chippers do not become regular smokers. One is that chippers consume far fewer cigarettes than regular smokers. They may not develop dependence because the initial load of nicotine does not reach a threshold necessary for the transition to dependence. However, before becoming fully dependent, regular smokers normally go through a phase of being 'chippers' for only 22 days; after this time, they gradually increase the amount of smoking to the point of becoming regular smokers. In contrast, chippers remain chippers and show few signs of dependence even after smoking an average of 46 000 cigarettes in 19 years.[16] The difference between chippers and regular smokers does not appear to be due to different rates of elimination of nicotine, as regular smokers and chippers inhale the same amount of cigarette smoke, absorb equal amounts of nicotine, and eliminate nicotine at equal rates.[14,17,18] The difference is also not attributable to the age at which individuals began smoking, because there was no difference in the age at which chippers and regular smokers started to smoke.[13,17] Finally, it has been hypothesized that chippers might find the initial effects of smoking highly aversive and therefore do not progress to become regular smokers. However, chippers retrospectively report that their experience of initial cigarettes was actually not as aversive as that felt by regular smokers.[13]

Alcohol

One recent survey shows that 51% of Americans aged 12 years and older reported using alcohol, but only 6.7% of this age group were found to be heavy drinkers, who consumed five or more drinks on the same occasion on at least 5 different days in the past 30 days.[6] Approximately 12–15% of alcohol users are estimated to be dependent.[5,6] What distinguishes heavy drinkers from nondependent users is their high rates of use of other illicit substances. Among heavy drinkers, 32.6% had used illicit substances at least once during the 30 days prior to the survey. The rates of illicit substance use were 16.6% among binge drinkers, who consumed five or more drinks on the same occasion at least once during 30 days prior to the survey, 5.8% among nonbinge drinkers, and 3.6% among nondrinkers.[6]

Opioids

Vietnam War Studies involving US military personnel in Southeast Asia during the Vietnam War and after their return to the US suggested that narcotic addiction develops only in a subpopulation of chronic users. In a series of studies, Robins *et al*[19,20] published a surprising group of statistics after interviewing a sample of 451 Vietnam returnees to assess the rate of narcotics use and dependence. During the period of 1970–1971, 43% of the sample had tried narcotics at least once and 20% had used narcotics more frequently than once a week for longer than 6 months. However, by 8–12 months after returning to the US, only 10% of the same population was using narcotics and 1% showed symptoms of dependence. Only 14% of those who were addicted at the time of departure were dependent after return.

Treatment for opioid addiction does not seem to account for the surprisingly low addiction rate of soldiers returning to the US.[21] Only a third of those dependent on narcotics in Vietnam received detoxification while in the service, and treatment rates were less than 2% for those who used narcotics in Vietnam and 14% for those who were positive for narcotics at the time of departure and continued to use narcotics after return. The relatively limited availability and environmental and societal constraints, combined with the lower levels of stress in the US, are likely to have contributed to the low rate

of addiction in these soldiers. However, it remains unknown why a subpopulation of individuals remained dependent on narcotics upon their return.

Chronic pain There is a controversy as to whether analgesics should be more frequently prescribed to patients with chronic pain. The underlying debate concerns whether those patients would become addicted to analgesics. Although most patients who are prescribed opioid analgesics develop physical dependence, addiction typically does not develop.[22] Studies have included patients who received opioid medication for chronic pain associated with various illnesses. Most studies show that medical use of opioids causes addiction in only 3.2–16% of patients.[23] The stress associated with the chronic pain of terminal illnesses (eg, cancer) is likely to be high, but the rate of addiction is low.

One trait that characterizes individual patients in pain clinics who are likely to become dependent on opiates is the use of multiple substances. Among users of codeine for chronic pain management, those found to become dependent on codeine also more frequently used alcohol and stimulants, compared with nondependent users.[24]

Summary
These examples consistently illustrate three points. First, not all individuals exposed to an addictive substance develop dependence or addiction; the rate of transition from use to dependence/addiction is low. Second, prolonged exposure is not a sufficient condition for dependence or addiction. Despite the long-term use of nicotine, alcohol, and narcotics, some users do not develop dependence/addiction. On the other hand, some individuals are easily addicted to substances after only a few exposures. Third, those susceptible to dependence/addiction tend to be multiple substance users.

Comorbid behavioral traits of substance users with dependence

The majority of people in the general population will not exhibit behavioral dependence in response to chronic exposure to a substance with dependence potential. This is likely to reflect many factors, including the effects of genetic variations and environmental factors (eg, stress, developmental factors, and social factors). While it remains unclear how various factors increase addiction susceptibility, certain pre-existing personality traits distinguish those who are prone to dependence/addiction from those who are not.

Novelty/sensation seeking
There is a high degree of correlation among personality traits variably labeled as 'novelty seeking' and 'impulsive sensation seeking'.[25] Cloninger[26] defined 'novelty seeking' as a heritable tendency toward intense exhilaration or excitement in response to novel stimuli or cues for potential rewards or potential relief of punishment, leading to frequent exploratory activity in pursuit of potential rewards. High novelty/sensation seeking scores are correlated with impulsiveness, exploratory excitability, extravagance, and disorderliness.[26,27] Zuckerman and Kuhlman[28] defined 'impulsive sensation seeking' as a trait by which an individual seeks varied, novel, complex, and intense sensations and experiences and is willing to take physical, social, legal, and financial risks for the sake of such experiences, combined with impulsivity, in which an individual enters into situations or rapidly responds to cues for potential reward without much planning or deliberation or without considering the potential for punishment or loss of reward. In other words, individuals with high sensation seeking-impulsivity scores tend to seek novel and risky situations and show less anxiety about these situations.

Nicotine Smokers exhibit higher levels of novelty/sensation seeking, as compared to nonsmokers, and this correlation has been confirmed in different age groups and countries, using various scales.[28] Even among nonsmokers, individuals with high sensation seeking scores tend to show a higher level of subjective responses to nicotine.[29]

Novelty seeking is an index that predicts whether one will start smoking, but not how much one eventually becomes addicted to or dependent on cigarettes.[30,31] Chippers, who do not develop nicotine dependence and do not escalate smoking after many years of smoking, do not differ from regular smokers in sensation seeking.[32] Nor does sensation seeking predict whether one is capable of quitting smoking.[33] The degree of relapse is correlated with the degree of dependence, but not with the level of novelty seeking.[30] This personality trait is not a consequence of smoking or dependence, because longitudinal studies show that this trait is present before individuals start to smoke.[33–35]

Alcohol There are at least two distinct types of alcohol dependence, termed Type I and Type II. Type I is characterized by few premorbid comorbidities, few antisocial behaviors, low impulsivity and a relatively late onset. By contrast, Type II alcohol dependence is defined by multisubstance dependence, antisocial behaviors, aggression, impulsivity, and early onset of alcoholism; Type II alcohol dependence is also thought to have a genetic component.[36–39] Novelty seeking is one of the behavioral traits that define Type II alcohol dependence.[40] Novelty seeking was found to precede the onset of alcohol dependence in longitudinal studies,[37] suggesting that the higher level of novelty seeking among alcoholics is not a consequence of alcohol dependence.

Other substances Novelty/sensation seeking has also been found to be correlated with the degree of use of marihuana and other addictive substances.[35,41–43]

Novelty/sensation seeking is more tightly correlated with the use of multiple substances than with the use of a single substance.[44]

Other comorbid behavioral traits
Conduct disorder in adolescents and antisocial personality disorder in adults are associated with progression from experimentation to regular smoking and difficulty in quitting smoking.[45–49] Conduct disorder and antisocial personality disorder are predictors of alcohol dependence.[50,51] Treatment outcome for alcohol dependence is also inversely correlated with the presence of conduct disorder.[52] Antisocial behavior precedes the onset of Type II alcohol dependence, suggesting that this personality trait is a pre-existing trait for addiction susceptibility.[53–57] The most reliable predictor of opiate addiction among Vietnam War returnees was pre-existing conduct disorders that were present before they were sent to Vietnam.[21] Antisocial personality has also been reported to be associated with multisubstance use.[58,59]

Genetics of addiction and comorbid traits

It seems clear that there is a subpopulation of substance users who become dependent or addicted more easily than others. While many environmental factors are likely to contribute to the different degrees of dependence susceptibility, this is also likely to be heavily influenced by an individual's genetic make-up.

Human studies
Twin studies have demonstrated that genetic factors play a significant role in the initiation of smoking and in nicotine dependence. Estimates indicate that the genetic contribution to smoking initiation in twins accounts for 60% of the variance; heritability can also account for 70% of the variance in persistent smoking and nicotine dependence.[60] Sibs of alcohol-dependent probands are three- to eight-fold more likely to be alcoholics, and the heritability estimates range from 50 to 60%. Heritability is estimated to be particularly high in male Type II alcohol dependence.[39] It has been estimated that heritable factors account for 22–34% of the variance in addiction to substances other than alcohol and nicotine.[61,62]

One methodological limitation of estimates of this kind is that limited availability of illicit substances is likely to reduce the influence of genes on their use and dependence. The influence of genes on behavior manifests itself fully when there is less environmental constraint. Ironically, a lack of environmental constraints on substance use maximizes the impact of genes on the initiation of use and on addiction. For example, the impact of heritability on smoking is more apparent when cigarette use is more widely accepted.[63] In the current societal and legal environment, nicotine and alcohol are by far more accessible to the general population than are illicit substances. Thus, nicotine and alcohol serve as model substances to determine the genetic component of addiction.

Human association studies have suggested that specific genes contribute to comorbid behavioral traits as well as to the susceptibility to dependence/addiction. Polymorphisms in various monoamine genes are a likely basis for comorbid behavioral traits as well as susceptibility to dependence/addiction. There are several comprehensive reviews on these candidate genes.[64–69] In general, genes related to dopamine and serotonin have been implicated in novelty seeking and antisocial behaviors, as well as dependence/addiction susceptibility. However, the impact of polymorphisms in each of the single genes on addiction susceptibility is thought to be small, and many association studies have yielded conflicting results in different population samples.

Animal studies
Animal studies are more suitable than human association studies for isolating the impact of specific genes on behavior. When various strains of rats and mice are evaluated, it becomes apparent that certain strains are prone to addiction. Outbred rats (eg, Sprague–Dawley) show considerable individual variations in their locomotor response to a novel open field and in the reinforcing and rewarding effects of substances. A subpopulation of outbred rats that show heightened responsiveness to a novel open field also exhibits a higher degree of addiction to substances, compared to those showing low locomotor responses.[70] Given that outbred rats are genetically undefined, such individual variations in behavior could reflect genetic and/or environmental factors.

A number of inbred mouse lines have been used to examine the role of genetic variation or polymorphisms in behavior. Mice within a single inbred strain are genetically identical, but those of different inbred lines are genetically distinct. Thus, group differences among separate inbred mouse lines can be attributed to genetic impacts; individual differences within each mouse line are likely to reflect nongenetic, environmental influences such as stress, developmental events, and interindividual factors. Behaviors exhibited by various inbred mouse lines can be compared to determine the degree to which a specific behavioral trait is influenced by genetic variation. If multiple genes control a behavioral trait, separate lines of recombinant inbred mice, created by crossing between two inbred mouse lines at the extreme ends of the spectrum of a behavioral trait, would be expected to show gradual differences, but not an all-or-none difference.

Locomotor activity in a novel, inescapable environment is thought to reflect an animal's responsiveness to novelty and is correlated with individual variations in responsiveness to addictive substances.[71–74] Since recombinant inbred lines generated by crossing C57BL/10 and A/Jax mice or C57BL and BALB mouse strains show gradual, bidirectional segregation of

levels of locomotor activity in a novel, inescapable open field across generations, this behavior is thought to be multigenetic in origin.[75] Moreover, this trait continues to segregate during 30 generations of crosses of BALB/cJ and C57BL/6J mice, indicating that a large number of genes contribute to the behavior exhibited in a novel, inescapable open field.[75] Since a similar strain difference exists for an animal's responsiveness to addictive substances, addictive behaviors also are likely to be influenced by multiple genes.[76]

Recent animal studies have begun to examine the correlation of addiction susceptibility and comorbid traits directly, using genetically engineered mice or constitutive knockout mice. These mice have deletions in specific genes throughout development and are suitable for modeling the impact of specific genetic factors on behavior in humans. In humans, genetic polymorphisms are present throughout development and are likely to influence neuroanatomical development as well as behavior.

Another advantage of the constitutive knockout mouse is that the complete deletion of a gene would be expected to have more impact on behavior than would a slight sequence variation induced by polymorphisms in inbred mice and humans. As the contribution of any individual gene to behavior is thought to be relatively small, this is a significant advantage.

Studies of various knockout mice have shown that a number of genes contribute to dependence/addiction,[77] but far fewer genes have been shown to contribute to a response to novelty as well as addiction. These studies suggest that genes can be categorized into three classes. First, genes could contribute to both addiction susceptibility and a behavioral response to a novel environment. Second, genes could affect a response to novelty without affecting addictive behavior. Third, some other genes could affect susceptibility to addiction but not a response to novelty.

A small number of genes have been found to affect both addiction susceptibility and a behavioral response to novelty. One of these, the transcription factor FosB/ΔFosB, is a postsynaptic molecule in the dopamine signaling cascade. This transcription factor is induced by cocaine, amphetamine, morphine, nicotine, and ethanol along the mesolimbic dopamine pathway, a neuronal substrate critical for addiction.[78,79] Once activated, FosB/ΔFosB regulates the expression of a number of downstream target genes.[80–82] *Fos*B knockout mice show heightened locomotor response in a novel, inescapable environment and heightened behavioral responses to cocaine.[79] This category of genes also includes the serotonin 5HT-1B receptor.[83,84]

FosB/ΔFosB is more strongly induced by chronic cocaine treatment in the core region of the nucleus accumbens than in the shell region; both regions are targets of the mesolimbic dopamine pathway.[79] Lesions of the core subregion of the nucleus accumbens impair an animal's ability to value large, delayed rewards over small, immediate rewards.[85] Thus, this brain region may be one locus in which FosB/ΔFosB contributes to impulsivity, one of the parameters of novelty seeking/sensation seeking in humans.

Certain genes are known to exert opposing influences on addiction susceptibility and novelty response. The presence of these genes suggests that a behavioral response to novelty is not necessarily a prerequisite for susceptibility to addiction. A locomotor response to a novel environment is increased, but behavioral responses to addictive substances are reduced in mice that lack the dopamine transporter gene[86,87] (but see Sora *et al*[88]). Similarly, deletion of the dopamine D4 receptor gene[89,90] or the norepinephrine transporter gene[91] reduces behavioral reaction to a novel environment, but increases behavioral responses to addictive substances.

There are also genes that influence either addiction susceptibility or a behavioral response to novelty, but not both. Mice lacking the monoamine oxidase-B (MAO-B) gene exhibit normal nicotine intake but are deficient in habituating to a novel, inescapable open field.[92] Genes whose deletion or attenuation enhances addiction susceptibility without affecting a behavioral response to novelty include the serotonin transporter (SERT)[88,93] and glial-derived neurotrophic factor (GDNF).[94]

Lerman and Niaura[67] suggested that genetic influences on addiction susceptibility are mediated partly by individual differences in comorbid personality traits, as well as individual differences in the reinforcing effects of substances. These animal studies suggest that, under certain circumstances, genetic variations could enhance a comorbid trait independently of addiction susceptibility, however.

Taken together, these animal studies support the notion that some pre-existing genetic variations exert complex modes of influence on susceptibility to addiction and on behavioral responses to a novel environment. A goal of future studies is to more precisely delineate the genetic basis by which genes contribute to comorbidity or addiction susceptibility, or both.

Hypothetical addiction models

How do genetic variations influence addiction susceptibility in humans? For this discussion, we divide addiction models into two broad categories (Figure 1). First, addiction could be the direct consequence of plasticity triggered by a substance. Model 1 proposes that a substance with dependence potential causes plastic alterations in the brain in response to chronic use. This plasticity, in turn, causes addiction and dependence. Specific genes might influence the rate of plasticity, thereby affecting the vulnerability to addiction. Consistent with this model, Fischer and Lewis inbred lines of rats exhibit different rates of plastic gene expression in the brain in response to addictive substances that correlate with their

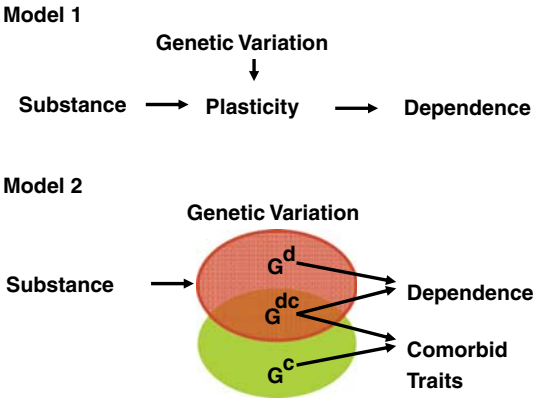

Figure 1 Hypothetical models of genetic influence on dependence. 'Dependence' is defined as physical dependence and behavioral dependence (ie, addiction). In Model 1, an individual's genetic makeup affects the degree of plastic alterations triggered by addictive substances, which alter the development of and the ultimate degree of dependence. In Model 2, the onset and development of dependence is partially determined (together with environmental factors) by genetic susceptibility. Genetic variations could affect either dependence alone (G^d, eg, SERT and GDNF) or comorbidity alone (G^c, eg, MAO-B); some of the genetic variations could manifest themselves, in the absence of exposure to addictive substances, as comorbid traits only, but are simultaneously associated with dependence susceptibility in the presence of addictive substances (G^{dc}) (eg, *fos*B and 5HT-1B). In the absence of genetic susceptibility to dependence (G^d or G^{dc}), the probability of developing dependence and addiction upon exposure to addictive substances diminishes. The impact of genes on dependence results from the combined effects of many genes, making it a probabilistic rather than all-or-none phenomenon.

behavioral response to addictive substances.[95–98] The fact that the degree of addiction is correlated with the degree of molecular alteration in the brain is consistent with the hypothesis that no addiction could occur without some neuroplastic alterations in the brain.

This model assumes that neural plasticity is the causal event for the development of dependence/addiction. However, there is a paucity of evidence that plastic alterations, such as those seen in rodents, actually occur in the brains of human substance users with dependence/addiction. Alterations in expression of the genes for various monoamine and glutamatergic receptors and related neuropeptides have been demonstrated in the brains of substance users with dependence.[99–101] However, it remains unclear from these studies whether these alterations are the pre-existing conditions of substance users, the consequence of chronic substance use, or the result of an acute overdose. Given the technical limitations in identifying plastic alterations as the causative factors for addiction in humans, this model can only be evaluated in experimental animals and so suffers from the limitations inherent in generalizing animal findings to humans. Moreover, this model does not fully account for the presence of pre-existing comorbid traits in addicts.

Another conceptual framework for understanding dependence/addiction is to identify genetic variations as the primary factor for the development of addiction (Model 2). The primary difference between these two models is that Model 1 emphasizes that plastic alterations induced by addictive substances are central for the development of addiction, whereas Model 2 assumes that the development of addiction is determined by pre-existing genetic differences. Model 2 does not assume, albeit it does not deny, that plastic alterations cause the development of addiction and dependence. It could be that G^d and G^{dc} influence the rate of plastic alterations upon exposure to addictive substances. Alternatively, G^d and G^{dc} might prewire a brain so that a few exposures to a substance are sufficient for the development of addiction and dependence without plastic alterations.

One obvious advantage of Model 2 is that it can be tested in both animals and humans. A large body of evidence clearly suggests that pre-existing genetic variations influence the behavioral responses to addictive substances in inbred mouse and rat lines.[76] Recent studies of genetically engineered mice have identified a number of specific genes that influence the degree of dependence/addiction or comorbid traits or both. In humans, pre-existing genetic variations can be identified before the onset of dependence/addiction. As such, Model 2 has a heuristic value.

Some pre-existing genetic variations could increase both the probability of exhibiting specific behavioral traits such as novelty seeking and antisocial behavior and the probability of developing dependence and addiction (see G^{dc}). In other cases, genes could influence either addiction susceptibility (see G^d) or comorbid traits (see G^c), but not both. Our finding that deletion of MAO-B alters habituation in a novel environment without affecting nicotine intake is consistent with G^c.[92] Model 2 predicts that effective treatments for addiction/dependence should also target the pre-existing genetic variations.

Model 2 assumes that dependence susceptibility is influenced by a large number of genes and that these genes affect multiple brain regions, as distinct aspects of addiction are likely to involve different brain regions.[102] This is particularly true given that dependence is a multifaceted phenomenon.

Summary and conclusions

A majority of substance users do not develop addiction to nicotine, alcohol, or opiates. Currently available plasticity-based models of addiction do not adequately account for the limited prevalence of addiction among chronic substance users and the presence of pre-existing, comorbid traits. The genetic model (Model 2) of addiction predicts that addiction is more likely to develop after initial substance use in

individuals with genetic susceptibility, which is also associated with comorbid traits in some (G^{dc}), but not all cases (G^{d}). Model 2 highlights the need for a new direction in addiction research as well as new treatment strategies.

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