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Predicting Addiction

Behavioral genetics uses twins and time to decipher the origins of addiction and learn who is most vulnerable

Lisa N. Legrand, William G. Iacono and Matt McGue

In 1994, the 45-year-old daughter of Senator and former presidential nominee George McGovern froze to death outside a bar in Madison, Wisconsin. Terry McGovern's death followed a night of heavy drinking and a lifetime of battling alcohol addiction. The Senator's middle child had been talented and charismatic, but also rebellious. She started drinking at 13, became pregnant at 15 and experimented with marijuana and LSD in high school. She was sober during much of her 30s but eventually relapsed. By the time she died, Terry had been through many treatment programs and more than 60 detoxifications.

Her story is not unique. Even with strong family support, failure to overcome an addiction is common. Success rates vary by treatment type, severity of the condition and the criteria for success. But typically, fewer than a third of alcoholics are recovered a year or two after treatment. Thus, addiction may be thought of as a chronic, relapsing illness. Like other serious psychiatric conditions, it can cause a lifetime of recurrent episodes and treatments.

Given these somber prospects, the best strategy for fighting addiction may be to prevent it in the first place. But warning young people about the dangers of addiction carries little force when many adults drink openly without apparent consequences. Would specific warnings for individuals with a strong genetic vulnerability to alcoholism be more effective? Senator McGovern became convinced that his daughter possessed such a vulnerability, as other family members also struggled with dependency. Perhaps Terry would have taken a different approach to alcohol, or avoided it altogether, if she had known that something about her biology made drinking particularly dangerous for her.

How can we identify people—at a young enough age to intervene—who have a high, inherent risk of becoming addicted? Does unusual susceptibility arise from differences at the biochemical level? And what social or environmental factors might tip the scales for kids at greatest risk? That is, what kind of parenting, or peer group, or neighborhood conditions might encourage—or inhibit—the expression of "addiction" genes? These questions are the focus of our research.

Lisa N. Legrand received her Ph.D. in behavioral genetics and clinical psychology from the University of Minnesota in 2003 and is currently a research associate at the Minnesota Center for Twin and Family Research (MCTFR). William G. Iacono is a Distinguished McKnight University Professor at the University of Minnesota and a past president of the Society for Psychophysiological Research. Matt McGue is a professor of psychology at the University of Minnesota and a past president of the Behavior Genetics Association. He and William Iacono have co-directed the MCTFR for the last dozen years. Address for Legrand: MCTFR, 75 East River Road, Minneapolis, MN 55455-0344. Internet: legra002@umn.edu

Minnesota Twins

We have been able to answer some of these questions by examining the life histories of almost 1,400 pairs of twins. Our study of addictive behavior is part of a larger project, the Minnesota Center for Twin Family Research (MCTFR), which has studied the health and development of twins from their pre-teen years through adolescence and into adulthood. Beginning at age 11 (or 17 for a second group), the participants and their parents cooperated with a barrage of questionnaires, interviews, brainwave analyses and blood tests every three years. The twin cohorts are now 23 and 29, respectively, so we have been able to observe them as children before exposure to addictive substances, as teenagers who were often experimenting and as young adults who had passed through the stage of greatest risk for addiction.

Studies of twins are particularly useful for analyzing the origins of a behavior like addiction. Our twin pairs have grown up in the same family environment but have different degrees of genetic similarity. Monozygotic or identical twins have identical genes, but dizygotic or fraternal twins share on average only half of their segregating genes. If the two types of twins are equally similar for a trait, we know that genes are unimportant for that trait. But when monozygotic twins are more similar than dizygotic twins, we conclude that genes have an effect.

This article reviews some of what we know about the development of addiction, including some recent findings from the MCTFR about early substance abuse. Several established markers can predict later addiction and, together with recent research, suggest a provocative conclusion: that addiction may be only one of many related behaviors that stem from the same genetic root. In other words, much of the heritable risk may be nonspecific. Instead, what is passed from parent to child is a tendency toward a group of behaviors, of which addiction is only one of several possible outcomes.

Markers of Risk

Personality. Psychologists can distinguish at-risk youth by their personality, family history, brainwave patterns and behavior. For example, certain personality traits do not distribute equally among addicts and nonaddicts: The addiction-vulnerable tend to be more impulsive,

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Figure 1. Steve, Debbie and Terry were characters in the coming-of-age film *American Graffiti*. Although popular culture often depicts adolescent drinking as a normal rite of passage, research shows that individuals who start to drink early in adolescence are at heightened risk for a wide range of adult substance-use and mental health problems.

unruly and easily bored. They're generally outgoing, sociable, expressive and rebellious, and they enjoy taking risks. They are more likely to question authority and challenge tradition.

Some addicts defy these categories, and having a certain personality type doesn't doom one to addiction. But such traits do place individuals at elevated risk. For reasons not completely understood, they accompany addiction much more frequently than the traits of being shy, cautious and conventional.

Although these characteristics do not directly cause addiction, neither are they simply the consequences of addiction. In fact, teachers' impressions of their 11-year-old students predicted alcohol problems 16 years later, according to a Swedish study led by C. Robert Cloninger (now at Washington University in St. Louis). Boys low in "harm avoidance" (ones who lacked fear and inhibition) and high in "novelty seeking" (in other words, impulsive, disorderly, easily bored and distracted) were almost 20 times more likely to have future alcohol problems than boys without these traits. Other studies of children in separate countries at different ages confirm that personality is predictive.

Family Background. Having a parent with a substance-abuse disorder is another established predictor of a child's future addiction. One recent and intriguing discovery from the MCTFR is that assessing this risk can be surprisingly straightforward, particularly for alcoholism. The father's answer to "What is the largest amount of alcohol you ever consumed in a 24-hour period?" is highly informative: The greater the amount, the greater his children's risk. More than 24 drinks in 24 hours places his children in an especially risky category.

How can one simple question be so predictive? Its answer is laden with information, including tolerance—the ability, typically developed over many drinking episodes, to consume larger quantities of alcohol before becoming intoxicated—and the loss of control that

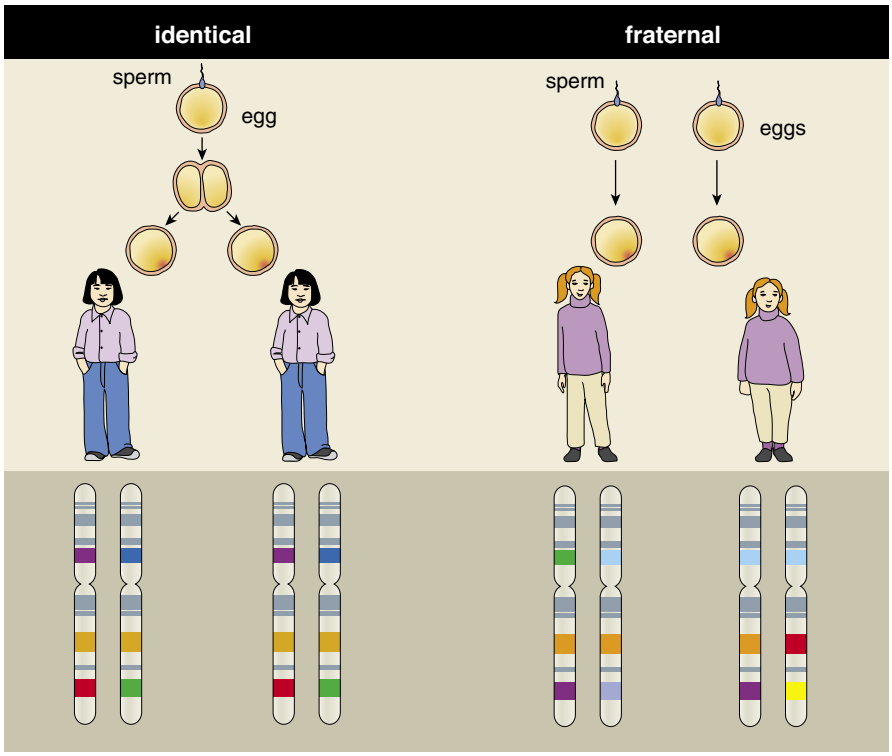

Figure 2. Monozygotic or "identical" twins occur when one fertilized egg (or zygote) divides early in development. The resulting two individuals have identical DNA (shown in cartoon form as colored bands on chromosomes, *bottom*). Dizygotic or "fraternal" twins occur when the mother's ovaries release two eggs during the same cycle and they are fertilized by two separate sperm. Genetically they are no more similar than ordinary siblings. Dizygotic twinning can result in opposite-sex twins, but the MCTFR only studies same-sex dizygotic twins, as they are the appropriate control for same-sex monozygotic twins.

mark problematic drinking. It is also possible that a father who equivocates on other questions that can formally diagnose alcoholism—such as whether he has been unsuccessful at cutting down on his drinking or whether his drinking has affected family and work—may give a frank answer to this question. In our society, episodes of binge drinking, of being able to "hold your liquor," are sometimes a source of male pride.

Brainwaves. A third predictor comes directly from the brain itself. By using scalp electrodes to detect the electrical signals of groups of neurons, we can record characteristic patterns of brain activity generated by specific visual stimuli. In the complex squiggle of evoked brainwaves, the relative size of one peak, called P300, indicates addiction risk. Having a smaller P300 at age 17 predicts the development of an alcohol or drug problem by age 20. Prior differences in consumption don't explain this observation, as the reduced-amplitude P300 (P3-AR) is not a consequence of alcohol or drug ingestion. Rather, genes strongly influence this trait: P3-AR is often detectable in the children of fathers with substance-use disorders even before these problems emerge in the offspring. The physiological nature of P300 makes it an especially interesting marker, as it may originate from "addiction" genes more directly than any behavior.

Precocious Experimentation. Lastly, at-risk youth are distinguished by the young age at which they first try alcohol without parental permission. Although the vast majority of people try alcohol at some point during their life, it's relatively unusual to try alcohol *before* the age of 15. In the MCTFR sample of over 2,600 parents who had tried alcohol, only 12 percent of the mothers and 22 percent of the fathers did so before the age of 15. In this subset, 52 percent of the men and 25 percent of the women were alcoholics. For parents who first tried alcohol after age 19, the comparable rates were 13 percent and 2 percent, respectively. So, what distinguishes alcoholism risk is not *whether* a person tries alcohol during their teen years, but *when* they try it.

In light of these data, we cannot regard very early experimentation with alcohol as simply a normal rite of passage. Moreover, drinking at a young age often co-occurs with sex, the use of tobacco and illicit drugs, and rule-breaking behaviors. This precocious experimentation could indicate that the individual has inherited the type of freewheeling, impulsive personality that elevates the risk of addiction. But early experimentation may be a problem all by itself. It, and the behaviors that tend to co-occur with it, decrease the likelihood of sobriety-encouraging experiences and increase the chances of mixing with troubled peers and clashing with authority figures.

A General, Inherited Risk

Some of these hallmarks of risk are unsurprising. Most people know that addiction runs in families, and they may intuit that certain brain functions could differ in addiction-prone individuals. But how can people's gregariousness or their loathing of dull tasks or the age at which they first had sex show a vulnerability to addiction? The answer seems to be that although addiction risk is strongly heritable, the inheritance is fairly nonspecific. The inherited risk corresponds to a certain temperament or disposition that goes along with so-called *externalizing* tendencies. Addiction is only one of several ways this disposition may be expressed.

Externalizing behaviors include substance abuse, but also "acting out" and other indicators of behavioral undercontrol or disinhibition. In childhood, externalizing traits include hyperactivity, "oppositionality" (negative and defiant behavior) and antisocial behavior, which breaks institutional and social rules. An antisocial child may lie, get in fights, steal, vandalize or skip school. In adulthood, externalizing tendencies may lead to a personality marked by low constraint, drug or alcohol abuse, and antisocial behaviors, including irresponsibility, dishonesty, impulsivity, lawlessness and aggression. Antisociality, like most traits, falls on a continuum. A moderately antisocial person may never intentionally hurt someone, but he might make impulsive decisions, take physical and financial risks or shirk responsibility.

It's worth reiterating that an externalizing disposition simply increases the risk of demonstrating problematic behavior. An individual with such tendencies could express them in ways that are not harmful to themselves and actually help society: Fire fighters, rescue

workers, test pilots, surgeons and entrepreneurs are often gregarious, relatively uninhibited sensation-seekers—that is, moderate externalizers.

So a genetic inclination for externalizing can lead to addiction, hyperactivity, acting-out behavior, criminality, a sensation-seeking personality or *all* of these things. Although the contents of this list may seem haphazard, psychologists combine them into a single group because they all stem from the same *latent factor*. Latent factors are hypothesized constructs that help explain the observed correlations between various traits or behaviors.

For example, grades in school generally correlate with one another. People who do well in English tend to get good marks in art history, algebra and geology. Why? Because academic ability affects grades, regardless of the subject matter. In statistical lingo, academic ability is the "general, latent factor" and the course grades are the "observed indicators" of that factor. Academic ability is latent because it is not directly measured; rather, the statistician concludes that it exists and causes the grades to vary systematically between people.

Statistical analyses consistently show that externalizing is a general, latent factor—a common denominator—for a suite of behaviors that includes addiction. Furthermore, the various markers of risk support this conclusion: Childhood characteristics that indicate later problems with alcohol also point to the full spectrum of externalizing behaviors and traits. Thus, drinking alcohol before 15 doesn't just predict future alcohol and drug problems, but also future antisocial behavior. A parent with a history of excessive binge drinking is apt to have children not only with substance-use problems, but with behavioral problems as well. And a reduced-amplitude P300 not only appears in children with a familial risk for alcoholism, but in kids with a familial risk for hyperactivity, antisocial behavior or illicit drug disorders.

The associations between externalizing behaviors aren't surprising to clinicians. Comorbidity—the increased chance of having other disorders if you have one of them—is the norm, not the exception, for individuals and families. A father with a cocaine habit is more likely to find that his daughter is getting into trouble for stealing or breaking school rules. At first glance, the child's behavioral problems look like products of the stress, conflict and dysfunction that go with having an addict in the family. These are certainly aggravating factors. However, the familial and genetically informative MCTFR data have allowed us to piece together a more precise explanation.

Environment has a strong influence on a child's behavior—living with an addict is rife with challenges—but genes also play a substantial role. Estimates of the genetic effect on externalizing behaviors vary by indicator and age, but among older adolescents and adults, well over half of the differences between people's externalizing tendencies result from inheriting different genes.

Our analysis of the MCTFR data indicates that children inherit the general, latent factor of externalizing rather than specific behavioral factors. Thus, an

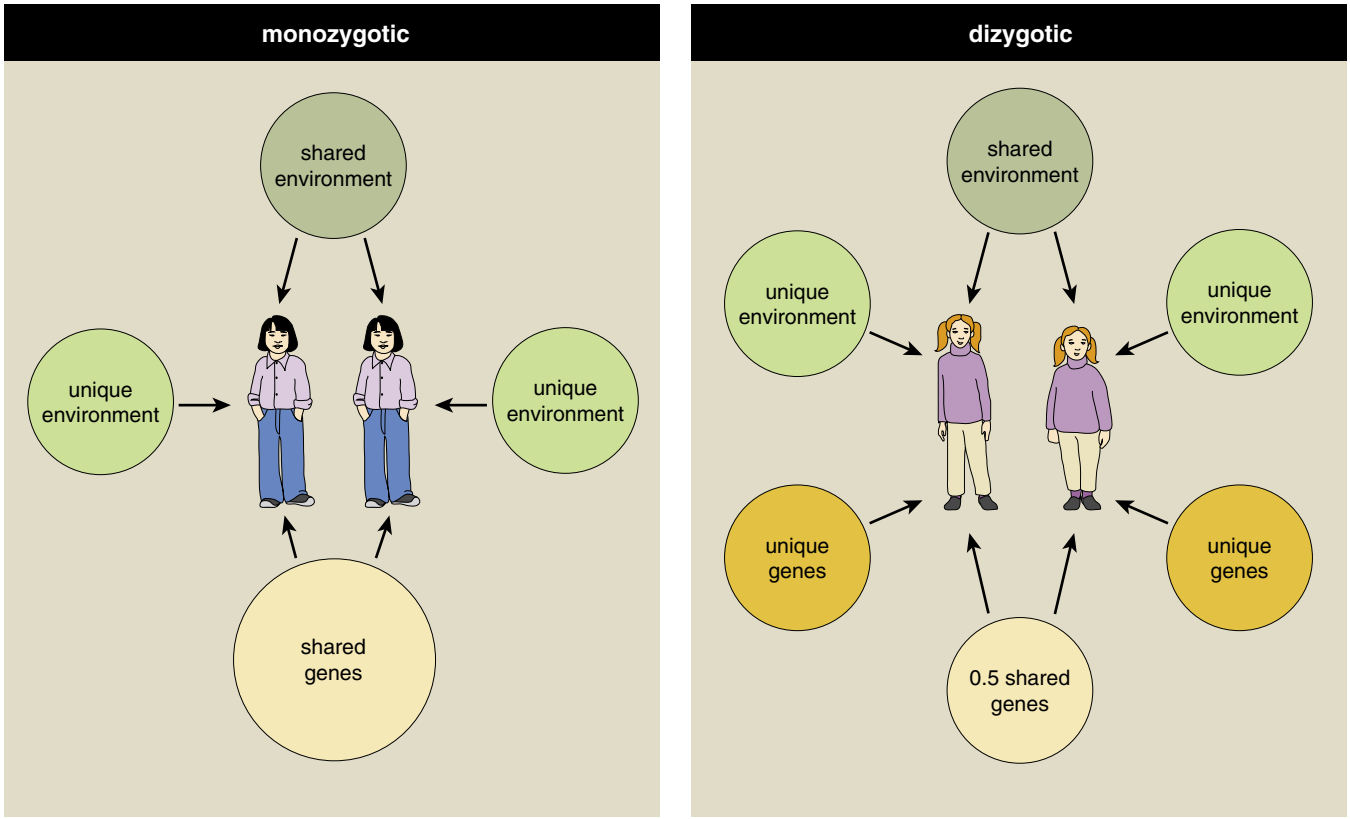

Figure 3. Behavioral geneticists view behavior as the result of three main influences: the *shared environment*, the *nonshared (or unique) environment* and *genes*. Shared environmental influences have a uniform effect on siblings; they create similarities between children reared in the same family. Parenting practices, neighborhood or school conditions, and social class are examples of shared environments. Unique environments—a friend or activity not shared by the co-twin—lead to differences between siblings. The basic assumption of a twin study is that monozygotic and dizygotic twins share environmental factors to an equal degree. Consequently, greater behavioral similarity among MZ than DZ twins is evidence for the existence of genetic factors.

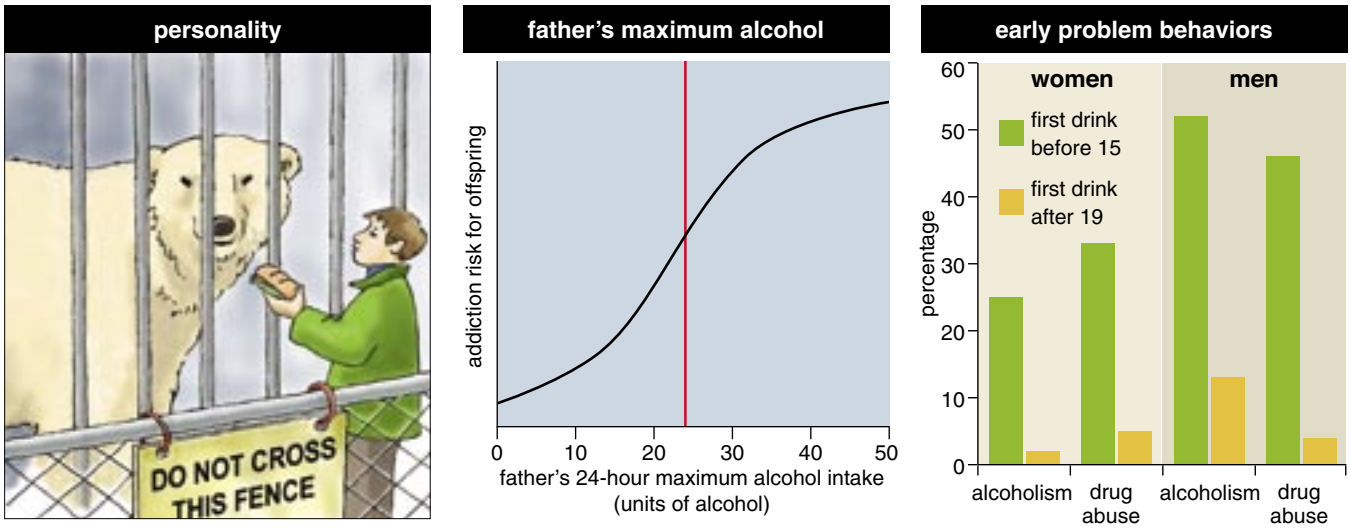

Figure 4. An elevated risk of later addiction can be predicted in childhood through several established markers, including personality, family history and early behaviors. Even early in life, kids who later become addicts are more often impulsive, "sensation-seeking" and disinhibited *(left)* than cautious and traditional. Having a father who has drunk heavily—consumed, at any time, more than 24 drinks in 24 hours—is also associated with greater risk *(center)*. Furthermore, the rate of later drug or alcohol abuse is much higher among those children who began experimenting with alcohol before the age of 15 *(right)*.

antisocial mother does not pass on genes that code simply for antisocial behavior, but they do confer vulnerability to a range of adolescent disorders and behaviors. Instead of encounters with the law, her adolescent son may have problems with alcohol or drugs. The outcomes are different, but the same genes—expressed differently under different environmental conditions—predispose them both.

The Role of the Environment

Even traits with a strong genetic component may be influenced by environmental factors. Monozygotic twins exemplify this principle. Despite their matching DNA, their height, need for glasses, disease susceptibility or personality (just to name a few) may differ.

When one member of a monozygotic pair is alcoholic, the likelihood of alcoholism in the other is only about 50 percent. The high heritability of externalizing behaviors suggests that the second twin, if not alcoholic, may be antisocial or dependent on another substance. But sometimes the second twin is problem free. DNA is never destiny.

Behavioral geneticists have worked to quantify the role of the environment in addiction, but as a group we have done much less to specify it. Although we know that 50 percent of the variance in alcohol dependence comes from the environment, we are still in the early stages of determining what those environmental factors are. This ignorance may seem surprising, as scientists have spent decades identifying the environmental precursors to addiction and antisocial behavior. But only a small percentage of that research incorporated genetic controls.

Instead, many studies simply related environmental variation to chil-

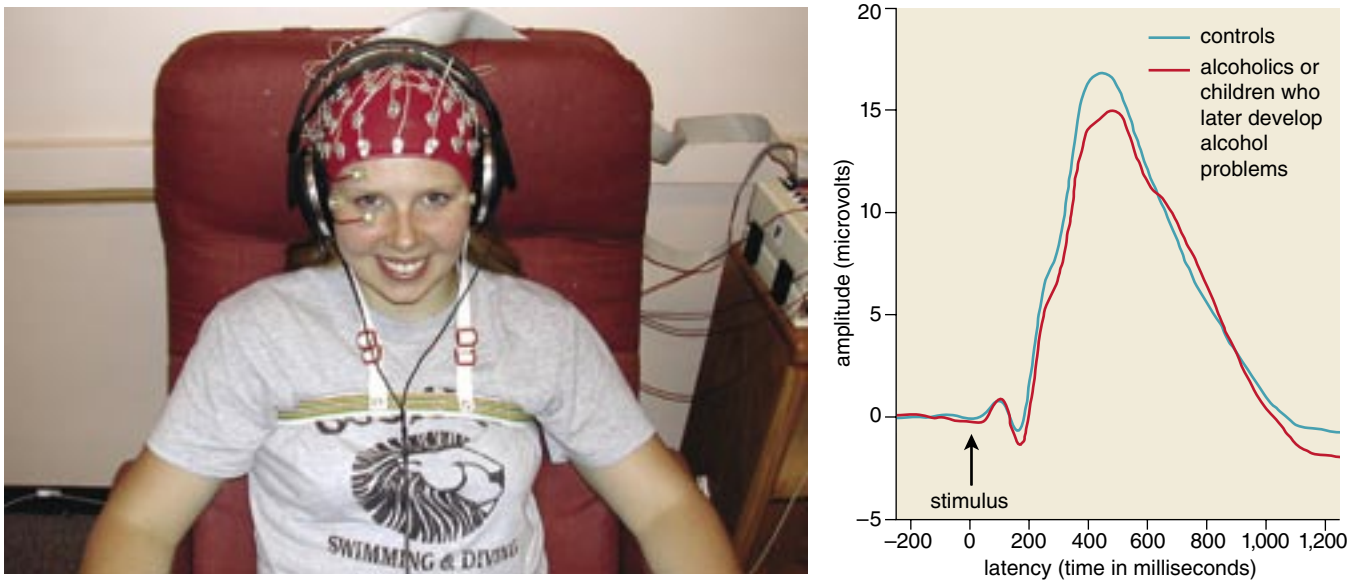

Figure 5. This photograph illustrates the electrode cap that the authors use to record brainwaves, including the P300 signal. Plotted to the right is the amplitude of the average P300 brainwave response for two groups of subjects. The blue line represents adults who have never exhibited externalizing behavior. The red line represents alcoholics and children who go on to develop alcohol problems as adults.

dren's eventual problems or accomplishments. A classic example of this failure to consider genetic influence is the repeated observation that children who grow up with lots of books in their home tend to do better in school. But concluding that books create an academic child assumes (falsely) that children are born randomly into families—that parent-child resemblance is purely social. Of course, parents actually contribute to their children's environment *and* their genes. Moreover, parents tend to provide environments that complement their children's genotypes: Smart parents often deliver both "smart" genes and an enriched environment. Athletic parents usually provide "athletic" genes and many opportunities to express them. And, unfortunately, parents with addiction problems tend to provide a genetic vulnerability coupled with a home in which alcohol or drugs are available and abusing them is normal.

To understand the true experiential origins of a behavior, one must first disentangle the influence of genes. By using genetically informative samples, we can subtract genetic influences and conclude with greater confidence that a particular environmental factor affects behavior. Using this approach, our data suggest that deviant peers and poor parent-child relationships exert true environmental influences that promote substance use and externalizing behaviors during early adolescence.

When considering the effect of environment on behavior, or any complex trait, it's helpful to imagine a continuum of liability. Inherited vulnerability determines where a person begins on the continuum (high versus low risk). From that point, psychosocial or environmental stressors such as peer pressure or excessive conflict with parents can push an individual along the continuum and over a disease threshold.

However, sometimes the environment actually modifies gene expression. In other words, the relative influence of genes on a behavior can vary by setting. We see this context-dependent gene expression in recent, unpublished work comparing study participants from rural areas (population less than 10,000) with those from more urban settings. Within cities of 10,000 or more, genes substantially influence which adolescents use illicit substances or show other aspects of the externalizing continuum—just as earlier research indicated. But in very rural areas, environmental (rather than genetic) factors overwhelmingly account for differences in externalizing behavior.

One way to interpret this finding is that urban environments, with their wider variety of social niches, allow for a more complete expression of genetically influenced traits. Whether a person's genes nudge her to substance use and rule-breaking, or abstinence and obedience, the city may offer more opportunities to follow those urges. At the same time, finite social prospects in the country may allow more rural parents to monitor and control their adolescents' activities and peer-group selection, thereby minimizing the impact of genes. This rural-urban difference is especially interesting because it represents a gene-by-environment interaction. The genes that are important determinants of behavior in one group of people are just not as important in another.

The Future of Addiction Research

This complex interplay of genes and environments makes progress slow. But investigators have the data and statistical tools to answer many important addiction-related questions. Moreover, the tempo of discovery will increase with advances in molecular genetics.

In the last fifteen years, geneticists have identified a handful of specific genes related to alcohol metabolism and synapse function that occur more often in alcoholics. But the task of accumulating the entire list of contributing genes is daunting. Many genes influence behavior, and the relative importance of a single gene may differ across ethnic or racial populations. As a result, alcoholism-associated genes in one population may not exert a measurable influence in a different group, even in well-controlled studies. There are also different pathways to addiction, and some people's alcoholism may be more environmental than genetic in origin. Consequently, not only is any one gene apt to have small effects on behavior, but that gene may be absent in a substantial number of addicts.

Nonetheless, some day scientists should be able to estimate risk by reading the sequence of a person's DNA.

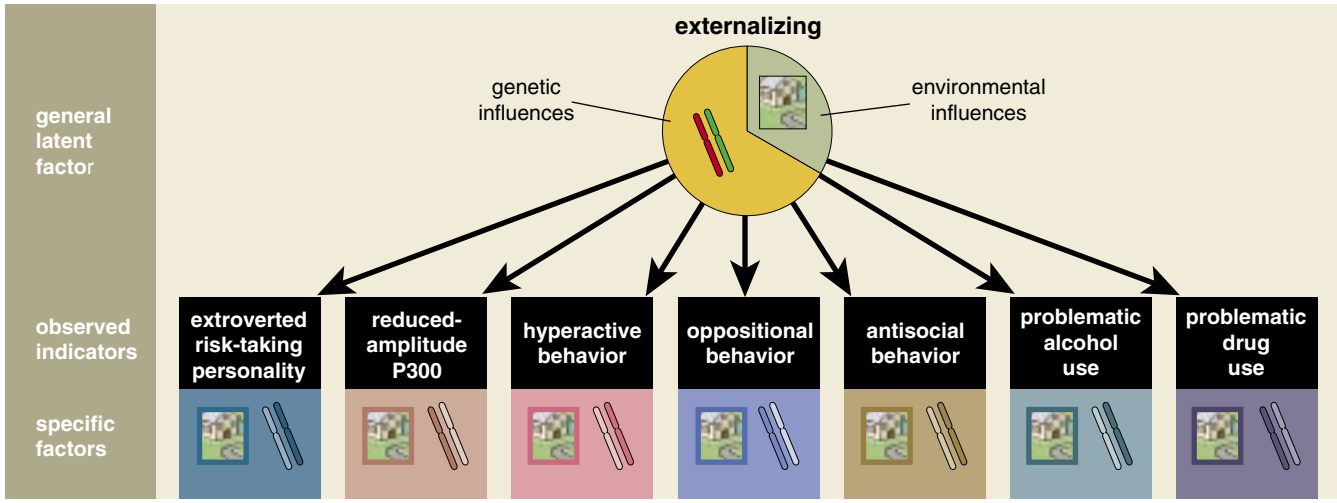

Figure 6. The general trait of externalizing, which is influenced by genetic and, to a lesser extent, environmental factors, has a variety of possible manifestations. The externalizing factor is the primary determinant of a spectrum of distinct outcomes, such as early, problematic alcohol use; all are similarly probable. Specific genetic and environmental factors then determine which specific outcome occurs (for example, antisocial behavior or an extroverted, risk-taking personality).

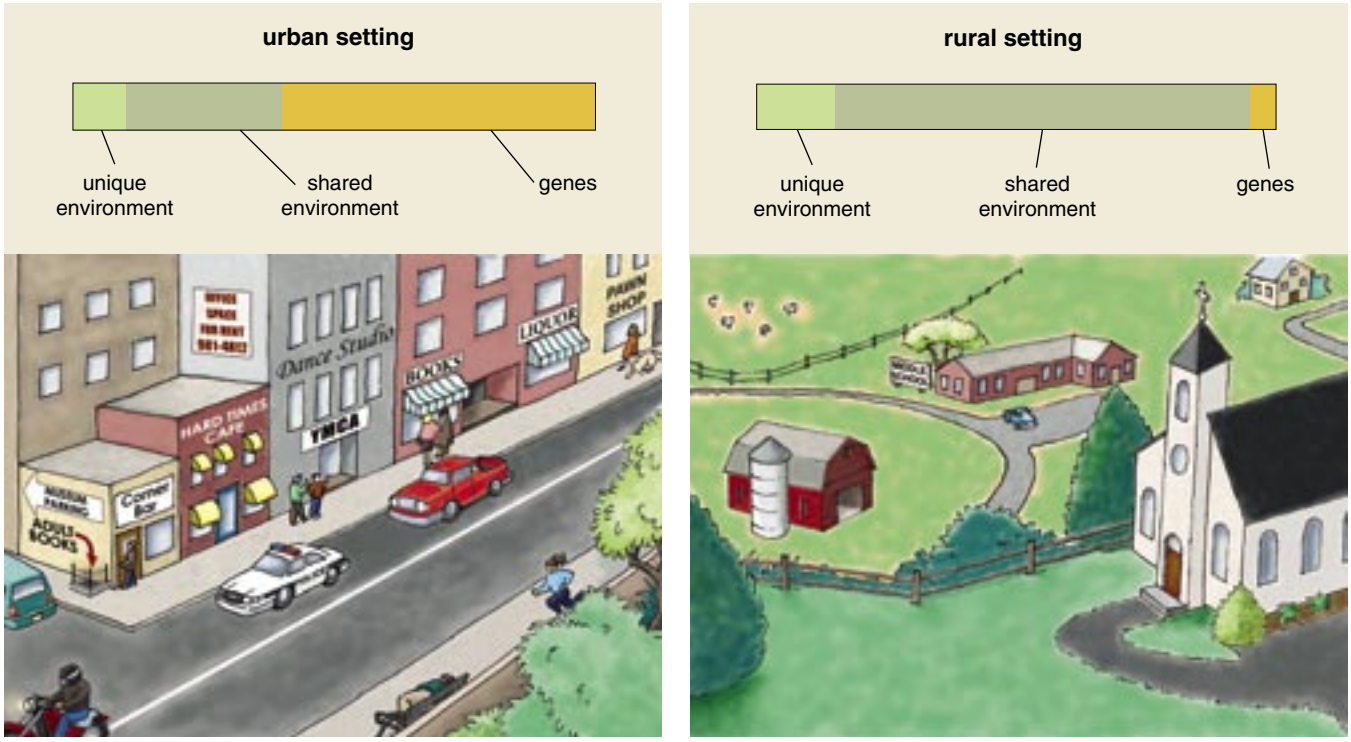

Figure 7. Authors' data suggest a gene-by-environment interaction can take place in the development of externalizing behavior. Small towns and isolated rural areas (all with populations of less than 10,000) have a constraining effect on genetic expression. In rural communities, the general latent factor of externalizing is strongly influenced by shared environmental factors, but genetic factors exert the greatest influence in urban settings. Because there is no reason to assume that the distribution of predisposing genes would vary by urban or rural residency, the authors conclude that the same genes that contribute to substance use and rule-breaking behavior among city dwellers are largely irrelevant to the development of these behaviors in the country.

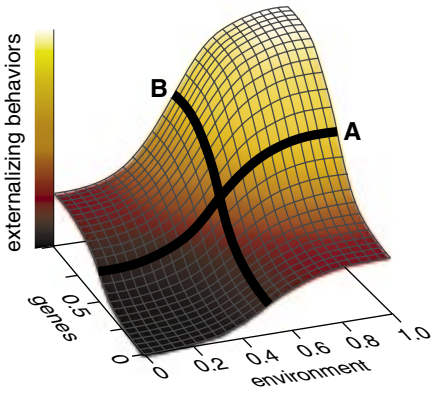

Figure 8. This hypothetical curve illustrates the way in which simultaneous contributions of genetic and environmental factors can contribute to behavioral variation. Line A shows a group of individuals with similar, moderate genetic risk for externalizing as if they were raised in a wide variety of possible environments, from protective to exacerbating. Line B corresponds to a group of individuals at moderate environmental risk, who differ over a broad spectrum of genetic vulnerability. The surface of the plot, which is referred to as a *reaction surface*, rises as genetic and environmental variables increase, and it maximizes at the point where highest genetic risk is paired with highest environmental risk. (Adapted from Turkheimer, Goldsmith and Gottesman.)

Setting aside the possibility of a futuristic dystopia, this advance will usher in a new type of psychology. Investigators will be able to observe those individuals with especially high (or low) genetic risks for externalizing as they respond, over a lifetime, to different types of environmental stressors.

This type of research is already beginning. Avshalom Caspi, now at the University of Wisconsin, and his colleagues divided a large group of males from New Zealand based on the expression level of a gene that encodes a neurotransmitter-metabolizing enzyme, monoamine oxidase A or MAOA. In combination with the life histories of these men, the investigators demonstrated that the consequences of an abusive home varied by genotype. The gene associated with high levels of MAOA was protective—those men were less likely to show antisocial behaviors after childhood maltreatment than the low-MAOA group.

Further advances in molecular genetics will bring opportunities for more studies of this type. When investigators can accurately rank experimental participants by their genetic liability to externalizing, they will gain insight into the complexities of gene-environment interplay and answer several intriguing questions: What type of family environments are most at-risk children born into? When children with different genetic risks grow up in the same family, do they create unique environments by seeking distinct friends and experiences? Do they elicit different parenting styles from the same parents? Could a low-risk sibling keep a high-risk child from trouble if they share a close friendship? Is one type of psychosocial stressor more apt to lead to substance use while another leads to antisocial behavior?

Molecular genetics will eventually deepen our understanding of the biochemistry and biosocial genesis of addiction. In the interim, quantitative geneticists such as ourselves continue to characterize the development of behavior in ways that will assist molecular geneticists in their work. For example, if there is genetic overlap between alcoholism, drug dependence and antisocial behavior—as the MCTFR data suggest—then it may help to examine extreme externalizers, rather than simply alcoholics, when searching for the genes that produce alcoholism vulnerability.

Much Left to Learn

Although the MCTFR data have resolved some addiction-related questions, many others remain, and our team has just begun to scratch the surface of possible research. Our work with teenagers indicates that externalizing is a key factor in early-onset substance-use problems, but the path to later-life addiction may be distinct. Some evidence suggests that genes play a lesser role in later-onset addiction. Moreover, the markers of risk may vary. Being prone to worry, becoming upset easily and tending toward negative moods may, with age, become more important indicators. We don't yet know. However, the MCTFR continues to gather information about its participants as they approach their 30s, and we hope to keep following this group into their 40s and beyond.

Meanwhile, the evidence suggests that for early-onset addiction, most relevant genes are not specific to alcoholism or drug dependence. Instead, the same genes predispose an overlapping set of disorders within the externalizing spectrum. This conclusion has significant implications for prevention: Some impulsive risk-takers, frequent rule-breakers and oppositional children may be just as much at risk as early users.

At the same time, many kids with a genetic risk for externalizing don't seem to require any sort of special intervention; as it is, they turn out just fine. DNA may nudge someone in a certain direction, but it doesn't force them to go there.

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