

How Genetic and Sociocultural Factors Interact with Mental Health Disorders and Epigenetics to Predispose and Reinforce Substance Use Disorder

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ABSTRACT

The recent drug epidemics occurring nationally and globally have called for questions of “nature vs. nurture” with regard to what predisposes for addiction. What has a more significant impact on drug risk? Biological or environmental factors? The understanding of different impacts can fundamentally change how people treat substance use disorder (SUD). However, SUD is a lot more complex and requires the interaction of many risk factors. While nature may predispose addiction, your environment must aid the predisposition to facilitate and reinforce SUD. This project will show how genetic, social, and mental health risk factors interact to cause addiction as well as how SUD is reinforced through social pressures and epigenetics. Here we review literature on the different risk factors that contribute to addiction and how they interact. Specifically, we investigate the impact of genetic factors, sociocultural influences, mental health disorders, and epigenetics on SUD. Knowing what can assist a predisposal to SUD would not only further our understanding of addiction but could also help people who struggle with SUD by reinforcing social policies and health infrastructures that help with treatment and recovery from SUD. It could also help parents protect their kids from growing up in environments that may influence them and push them to develop SUD in the future. The understanding of risk factors can lower the number of people with SUD in the future and help people currently trying to recover from SUD by interrupting addiction cycles.

Introduction to SUD

Substance use disorder (SUD) is a complex illness that typically requires multiple factors to manifest and reinforce it. Biological factors, such as genetics, can directly contribute to one’s predisposition to SUD. In addition to a biological predisposition to SUD, there are external factors that work to reinforce SUD and encourage relapse following remission. When genetic factors interact with sociocultural influences such as exposure to certain social pressures and trauma, this interaction may increase the likelihood of developing SUD. Mental health disorders are also found to possibly play a role in the predisposition to SUD through self-medication and genetic linkage between the mental health disorder and SUD. Along with predisposition, reinforcement, and relapse of SUD contributes to someone’s overall addiction. Relapse is influenced by social groups, mental health disorders, and long-term changes made in the brain after prolonged use of drugs even after quitting. After prolonged drug use, the nicotine and dopamine receptors in your reward pathway may be altered, as well as circuits in your frontal cortex, which can make quitting substance use harder. Understanding the factors that contribute to SUD or prevent relapse and support recovery would help determine medical and social policies for people currently struggling with addiction and those genetically or environmentally predisposed to SUD. For example, surrounding those who struggle with SUD with a supportive community can assist in recovery, while dangerous environments could lead to relapse. In this literature review, I piece together how the interactions of different factors contribute to the development of substance use disorder.

The Genetic Influence on SUD

Different genes have been linked to the increased or decreased abuse risk of various substances, including alcohol, tobacco, nicotine, and others. It is important to note that genes are probabilistic factors, not deterministic factors (Heilig et al., 2021); they can increase the chance that an individual develops SUD, but multiple influences like personal choice, social groups, home life, etc. have to coincide to lead to an increased likelihood of SUD. Genetics alone cannot determine SUD because there is no single gene that gives a yes or no answer to whether one will develop SUD. The interaction of many risk factors influences the development of SUD. Genes linked to increasing the risk of substance abuse are said to be about 50% of the determining factor when it comes to alcohol, but in other substances like opioids, addiction may be much more heritable (Heilig et al., 2021).

Protective genes are genes that reduce the risk of developing SUD. These genes have certain allele forms that decrease your risk. Some alleles could give you unpleasant side effects from consuming substances, or neutralize the substance so that the reinforcing effects are reduced. Different variations of the gene could cause different effects. ALDH1 deficiency is an example of a protective allele form of the protein-coding gene ALDH1. ADH and ALDH are the primary enzymes that break down alcohol. Depending on the form of the genes coding for the protein, the enzymes will vary. Specifically, ADH1B, ADH1C, and ALDH2 genes have been linked to altering the metabolization of alcohol (Edenberg., 2007). The altering of the enzymes ADH and ALDH can cause a deficiency in the ability to metabolize alcohol. This deficiency causes facial flushing, headache, nausea, and a rapid heartbeat. The facial flushing and other unpleasant symptoms caused by the ALDH1 enzyme deficiency are protective factors against alcohol dependency. Those who get negative side effects from alcohol are likely less inclined to continue to drink, lessening the likelihood of addiction. The ALDH1 enzyme deficiency causing negative symptoms which potentially decrease chances of alcohol dependence illustrates an example of genetic protective factors.

There are also genes that have been discovered to increase the risk of substance addiction. The DRD2 gene is said to be responsible for dopamine D2 receptor binding in the post-synaptic cell, the deficiency of which dysregulates the uptake of dopamine, which can cause a higher risk of SUD. D2 receptors transmit dopamine by uptaking a dopamine signal from the pre-synaptic neuron to the post-synaptic neuron. The improper binding of D2 receptors to the post-synaptic neuron has been linked to impulsivity, but Trifilieff's study in 2014 primarily focuses on the linkage of impulsivity to addiction. In the paper *Imaging addiction: D2 receptors and dopamine signaling in the striatum as biomarkers for impulsivity*, addiction are demonstrably linked to four types of impulsivity, choice impulsivity, impulsive action, reflection impulsivity, and attention impulsivity which are traced back to risk factors of addiction. Impulsivity and lack of sufficient D2 receptors in the post-synaptic neuron could be a major risk factor (Trifilieff, Martinez, 2014), as poor decision-making justified by the craving for a higher release of dopamine can influence the predisposition of SUD.

The A1 form of the DRD2 gene is responsible for decreasing D2 receptor expression. When taking substances such as cocaine and opioids, the dopamine transporters in the transmitting neuron are blocked, so the post-synaptic receptors receive more dopamine than usual. People with fewer D2 receptors have impaired dopamine signaling, thus resorting to substance use for the craving for a higher release of dopamine. There are other DRD2 polymorphisms that regulate the synthesis and release of dopamine, although the A1 form is most commonly noted. The allele forms that produce insufficient D2 receptors are more likely to predispose an individual to addiction because people with those allele forms of the DRD2 gene crave a higher release of dopamine (Noble, E. P., 2020). This is why dopamine receptor imbalances are commonly found in people who have struggled with addiction. The impulsivity found to be from the lack of enough and/or sufficient D2 receptors may also directly affect addiction, as impulsive people can give into societal pressure and experience drug cravings easier (Noble, E. P., 2020). While DRD2 is the most commonly believed gene to be linked to substance abuse disorder, as it carries a genetic marker showing its relation to addiction, there have been studies that show that genes neighboring DRD2 may also have a hand in altering D2 receptors.

Recently researchers have found that the DRD2 gene may not be the primary determinant of the expression of dopamine receptors. The genetic marker that pointed to the polymorphisms linked to addiction in the DRD2 gene

has actually been found in the ANKK1 gene, which neighbors the DRD2 gene on chromosome 11, meaning it may also be linked to addiction. The research done in the study *Alcoholism: Clinical & Experimental Research* suggests that genetic markers in people with addiction are not only associated with DRD2 but also with neighboring genes like ANKK1. This suggests that ANKK1 may be the gene that truly affects D2 receptor expression and the lack thereof, but it just has not been noted (Dick et al., 2007). ANKK1 and DRD2 are not possible to tell apart yet as an advanced enough genetic marker has not been found, so it is unclear which is the true risk factor for SUD.

Other genes linked to addiction, specifically alcohol dependence, are the Per 1 and Per 2 genes, which are in charge of the circadian rhythm. The circadian rhythm controls an organism's daily rotation through homeotic functions such as metabolism and body temperature. Disruption of a person's circadian clock can result in physical, mental, and emotional disorders. Mutations to any of the three-period genes that control circadian rhythm have been connected to increased alcohol use, although mutations in Per1 and Per2 are most recognized. People who struggle with alcohol abuse have been found to show signs of a dysfunctional circadian rhythm, which matches up perfectly with studies that tested mice Per1 and Per2 mutations and their reaction to ethanol (alcohol). In Gatsby's 2013 study, researchers found that mice with Per2 mutations drink more ethanol than wild-type mice with the same unlimited access to ethanol. It was also found that mice with Per1 mutations also drink more ethanol, but only when put under stress (Gamsby et al., 2013). This study suggests that an organism's preference for ethanol is influenced by its circadian phenotype, meaning ethanol dependency is associated with circadian rhythm processes. Genes Per1 and Per2 are not only genes that control circadian rhythm but mutations in the genes seem to be involved in ethanol dependency.

The CHRNA5–CHRNA3–CHRN4 gene cluster has recently been linked with nicotine dependency. Certain forms of this gene cluster have been connected to not only smoking but also smoking-related illnesses like lung cancer. The gene cluster codes for three of eleven neuronal nicotinic acetylcholine receptors (nAChRs) subunits. NACHRs are ligand-gated ion channels that open in response to the binding of acetylcholine and nicotine. Lassi's paper from 2016 connects the dysfunction of nAChRs to behavioral changes that could affect smoking habits. Mutations in the gene cluster can cause nicotine dependency because the deficiency nAChRs can decrease the effect of nicotine release in the medial habenula which mainly projects to the interpeduncular nucleus (MHb-IPN). The MHb-IPN takes an important role in the reward pathway and requires sufficient nicotine regulation. A missense mutation in CHRNA5 at the 398th amino acid creates an insufficient $\alpha 5$ subunit, changing its response to nicotine (Lassi, G., et al., 2016). The mutation causes a complex in the $\alpha 5$ subunit that leads to the inability to regulate the intake of nicotine when the MHb-IPN tract is stimulated. MHb-IPN circuit has the highest density of nAChRs in the human brain, and that is where most nicotine stimulation occurs. When the $\alpha 5$ subunit cannot limit nicotine intake, the brain is much more stimulated by nicotine, increasing the chance of one's addiction. The CHRNA5–CHRNA3–CHRN4 gene cluster is seen as a risk genetic factor because its mutation can allow for nicotine dependency to come much easier.

In these sections, there are many genes that act as risk or protective factors for SUD. ALDH1 is one of the most commonly recognized protective factors of SUD, while DRD2, Per 1 and Per 2, and CHRNA5–CHRNA3–CHRN4 are risk factors for SUD. Having certain allele forms of any of these genes can raise or lower your risk of SUD in comparison to your peers, giving you a biological and genetic predisposition.

Sociocultural Influences of SUD

The sociocultural environment can impact the risk of SUD as much as genetic factors. Sociocultural factors include experiences during development/childhood, such as chronic SUD exposure at one's household or frequented area or childhood trauma and adverse childhood experiences. These can affect how easily one might start to use drugs and develop SUD.

Childhood trauma has been heavily connected to SUD as a risk factor. Adverse childhood experiences (ACEs) were found to predispose one to SUD and behavioral addiction in adolescence and adulthood. During research, when dividing people into four groups of high exposure to adverse experiences, low exposure to adverse experiences,

child abuse, and parental substance use, those who were either raised in high adversity, child abuse, or parental substance use showed drastically higher rates of SUD (Kim et al., 2021). Childhood exposure to SUD in frequented areas like school or home can have a higher risk of predisposition because the normalization of substance use can affect how people view the use of drugs and alcohol, making it more likely for them to use in the future. Despite the correlation between ACEs and SUD, the role of mental health in this connection is often overlooked. Studies note that ACEs are associated with a higher risk of developing mental health disorders which can lead to addiction or SUD (Leza, L., et al., 2021). ACEs, when severe, can change cognitive functions, as well as psychologically change susceptibility to peer pressure and decision-making skills, all of which increase the risk of SUD. Childhood stressors like household dysfunction and violence or substance use in the household are all examples of trauma-related changes that can predispose SUD. In most circumstances, the connection between ACEs and SUD can also be linked to mental disorders that have developed through ACEs and trauma. Some may use substances to self-medicate the mental disorders and emotional pain their trauma has caused.

Comorbidity of Mental Health Disorders and SUD

Although mentioned previously in this review manuscript, there is a distinction between genetic and environmental factors, there is a gray area. Some influences that predispose addiction result from a mixture of genetics and social environment. For example, many mental health disorders comorbid with SUD can be influenced by both a biological predisposition and an environmental stressor. Mental health disorders cause stress and can lead someone to use substance abuse as a form of self-medication. In some instances, the same genetic predisposition to SUD has been implicated in causing mental/psychiatric disorders. Schizophrenia and Post Traumatic Stress Disorder (PTSD) are the conditions most commonly linked to SUD.

Schizophrenia is a severe mental disorder that is known to alter one's perception of reality through delusions and hallucinations (auditory or visual), resulting in struggles with daily tasks; those diagnosed with schizophrenia require lifelong treatment. Patients with schizophrenia have been found to be three times more likely to encounter dysfunctional substance use than the general population (Khokhar et al., 2018). There are a few possibilities for what may explain the high comorbidity of SUD and schizophrenia, but most have insufficient evidence so it is unknown which is the true cause. In Khokhar's 2018 paper, it is pointed out that some researchers predict that patients with schizophrenia use substances to lessen the symptoms or side effects of their antipsychotic medication. Other research claims that patients with schizophrenia have a history of cannabis and alcohol use in adolescence. However, as their schizophrenia progresses they may be more inclined to use more severe drugs. The question is which causes a predisposition? Does substance abuse act as an environmental stressor to schizophrenia? Or can schizophrenia predispose to substance abuse?

It has also been found that schizophrenia and SUD may have overlapping causes like certain dysfunctioning brain circuits or allele forms of certain genes. Genetic susceptibility to schizophrenia has been associated with brain circuits responsible for reward and motivation as well as other neural systems that, when dysfunctioning, can be connected to SUD. A few genes have also been found to connect to schizophrenia as well as SUD, specifically brain-derived neurotrophic factor (BDNF), catechol-O-methyltransferase, catecholamine metabolism, and protein kinase B (Khokhar et al., 2018). One of the most commonly recognized genes linked to schizophrenia is BDNF. BDNF is a gene known for its effects on synaptic plasticity and development. Polymorphisms in the BDNF gene have not been linked directly to SUD but have been strongly connected to schizophrenia and co-occurring alcohol dependency. This suggests that the predisposition of schizophrenia through a relation to BDNF could also predispose to SUD. SUD and schizophrenia share specific alleles making the question of their causation much more complex.

There are studies that state many struggling with SUD also show symptoms of post-traumatic stress disorder (PTSD). The research demonstrates that those with SUD are 6.5 times more likely to have PTSD (Wei et al., 2018). However, the roots of this high comorbidity have been very minimally explored. It should be noted that many ACEs like abuse or even extreme poverty could cause PTSD. As this paper covered before, ACEs have been strongly linked

to a predisposition to SUD, so this could explain some of the comorbidity rates between PTSD and SUD. As with schizophrenia, it is also possible that people suffering from PTSD would use substances as self-medication.

The interaction between biological and social factors that link SUD and mental health disorders is far too complex to fully understand right now. We don't have enough research to fully understand the correlations but exploring SUD's connection to mental disorders can vastly increase our understanding of the predisposition of SUD.

Factors that Reinforce SUD Recovery and Relapse

SUD is a very complicated disorder that is reinforced with chronic relapsing use of substances. People who struggle with addiction will often be treated in a social setting that can complicate their recovery. In addition, there are also biological factors that can reinforce substance use. Understanding how biological and environmental factors such as demographics, social groups, and epigenetics affect recovery would help establish treatments and policies that would be more helpful or could be applied to a wider range of people.

For example, one's social environment can affect their recovery from SUD. The way someone is seen by their environment plays a huge part in whether they receive proper treatment, or even decide to pursue it. A commonly overlooked factor is how someone sees themselves in society and what social groups they belong to. This contributes to their social identity, which is a prime factor of social behavior. Individuals associate themselves with a social group and start to perceive the world through the group's perspectives (Dingle et al., 2015).

Social identity can heavily impact how well someone responds to treatment. Dysfunctional substance use often leads to isolation, which further progresses one's addiction. The 2015 study by Dingle et al. explains that social factors are involved in the development and recovery of SUD. Social isolation has been linked to dysfunctional substance use because when a user's social identity conflicts with their addict identity they will often isolate themselves to avoid social issues. However, associating yourself with a supportive group has been found to aid in recovery and decrease the chance of predisposition (Dingle et al., 2015). This is because, in social groups, individuals often share opinions, even about health. Using social factors and social identity dynamics to support recovery is a main pillar of recovery groups that link people who struggle with addiction to support systems like AA (alcoholics anonymous) and NA (narcotics anonymous). The individual will often relate to the group's opinions, even about health. If their social group is often engaging in drug use, an addict might be drawn to such a group and never recover, but groups who refuse that lifestyle would encourage a person with SUD to stay sober. Utilizing social identities as a form of treatment can be useful because many people who struggle with SUD may be using substances because of isolation.

Certain demographics can affect the efficiency of recovery. Acevedo's study in 2012 uncovered the difference between the treatment of people of color and white people during substance abuse recovery. The study revealed that Hispanics and Black/African Americans have reported being dissatisfied more frequently by treatment, although when given the same treatment as their white peers they recover similarly. African Americans are also found less likely to seek treatment when confronted with their disorder (Acevedo et al., 2012). This study concluded that the medical system doesn't aid people of color identically to white people, so they are less likely to seek treatment, especially if they themselves have had unfortunate experiences with medical facilities. It is important to notice that when given the same level of treatment and care different races and ethnicities respond and recover similarly, so the issue is not biological or cultural, it is about how the medical system treats patients of different races differently. Understanding the difference between treatments can aid in enforcing policies and encouraging people of color to feel safe asking for help.

Another factor that impacts SUD recovery and relapse is the epigenetic changes that follow prolonged substance use. Epigenetics can be identified as the environment changing a phenotype that was previously expressed differently by a certain genotype. The Oxford Dictionary defines the term as "the study of changes in organisms caused by modification of gene expression rather than alteration of the genetic code itself." Drug and alcohol use has been linked to epigenetic changes in receptor expression and brain function (Hamilton & Nestler, 2019; Daviet et al., 2022). Even if someone isn't biologically predisposed to substance use disorder, prolonged drug use can alter epigenetics

and lead to the biological reinforcement of SUD. This could make recovery harder because the substance would affect the reward system and other crucial areas affecting impulsivity.

Prolonged substance use can alter the expression of receptors at an epigenetic level. Chronic drug use can affect your reward circuitry by altering the sufficiency of certain receptors. Natural rewards as well as drugs increase dopaminergic neurotransmission which is commonly associated with the reward system (Hamilton & Nestler, 2019). The long-term use of a substance is what contributes to the pathogenesis of addiction by making certain reward pathways less sensitive to naturally-released dopamine, leaving a higher craving for dopamine in the brain. This higher craving will encourage relapse and harsher recovery. Opioids specifically have been linked to promoting higher levels of histone acetylation, which alters chromatin architecture and changes gene expression (Browne et al., 2020). This is known to change non-coding RNA patterns through brain circuitry. The brain circuitry, after repeated exposure to opioids, integrates internal and external cues that encourage drug-taking even after sobriety. Drug use can epigenetically alter brain circuitry to encourage continuous use.

Alcohol use has been linked to harmful effects on cognitive brain function. A study done with adults from the UK Biobank showed that chronic alcohol use decreased gray matter in the brain (Daviet et al., 2022). When the frontal cortex loses gray matter in circuits involved in impulsivity, it could increase impulsivity and spontaneous thinking which could lead to relapse as it harms people's self-control. This is an example of how previous substance use can impact future substance use through the changing of brain matter.

Relapse and recovery are equally as complex as predisposition to SUD. Although this paper only covered a few, there are many factors that are known to affect recovery. Studying these risk and protective factors will help inform healthcare programming and social policies that make recovery more effective.

The question of SUD being predisposed by nature or nurture is too simplistic: the interaction of many biological and environmental factors is involved in predisposing and reinforcing SUD. The more society understands and accepts these factors, the closer we will be to set medical and social policies to support people recovering from SUD, as well as useful treatments that would aid in prevention or recovery.

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