Drug Addiction and Disease

Jenny Besse

Writer's Comment: Since the beginning of my college career here at UC Davis I had been eager to enroll in NPB 168: Neurobiology of Addictive Drugs. Spring quarter of my junior year finally afforded the opportunity, and I cannot be happier with my experience and all that I have learned. While my paper was initially written along with this course to fulfill a requirement for the Davis Honors Challenge, I do have a very personal and sincere interest in this topic, as drug addiction has intimately touched my life. Like many others, I previously thought of addiction as a choice, and viewed those who succumbed to it as personally or socially flawed. However, throughout this course I was introduced to a number of different models attempting to elucidate the complex concept of addiction, including the disease model, and now have a much greater understanding of this disorder. I would like to thank my professor, Dr. Liets, for working with me on this honors contract, allowing me to explore this topic of interest, and encouraging me to enter the *Prized Writing* competition. I would also like to dedicate this paper to my mom, as she is my inspiration, and her experiences, the source of my motivation and strength.

—Jenny Besse

Instructor's Comment: Every now and then a teacher runs across a student who is remarkable and has a remarkable story to tell. Jennifer Besse is one such student. Her high school and early college years were shaped in part by her personal experience with drug addiction, being the daughter of a woman embroiled in a battle with methamphetamines. Between her early undergraduate experience as a student in the College of Biological Sciences and her experience with her mother, the course I teach in the Section of Neurobiology, Physiology and Behavior on the Neurobiology of Addictive Drugs was a natural choice for her. The impetus for the paper you are about to read was Jenny's participation in the Davis Honors Challenge, a four year program at UC Davis aimed at providing a more challenging and interactive undergraduate experience. As part of Jenny's participation in this program she was charged with finding an upper division course with which to associate a Davis Honors Contract course, a one-unit student-designed program of independent study. While my course is more heavily focused on the neurobiological mechanisms of addictive drugs, Jenny wanted to do a project focusing specifically on the mechanisms of addiction. The following is a portion of Jenny's journey to understand herself, her life, her mother, and addiction.

—Lauren Liets, Neurobiology, Physiology, and Behavior

I was trying to ignore the whining whistle of the wind as it seeped through the tiny cracks in my mom's weather-beaten old Ford Taurus, when I heard the words that changed my life, but surprisingly, not for the worse. These words offered hope, an explanation, and a name to a problem, one that could be fixed. I looked ahead on the freeway and watched as the luxury vehicles, sassy sports cars, and expensive SUVs passed us by. I felt my own seat hiccup and suffered once again the embarrassment of our car, the one whose driver side door had to be lifted up and to the right in an effort to be slammed shut. But at that moment, it didn't matter.

"For the past four years, I have been addicted to speed," my mother admitted as she looked at me and then into the rearview mirror at my younger brother and sister in the back seat. She had just come back from a three-month stay in another state, and it was then that I finally understood why. I wasn't shocked, only angry with myself for not having figured it out on my own. But even more than anger, I was filled with relief. I saw only change, and improvement, in the future.

Thus reads the opening paragraphs of my personal statement, written at the age of sixteen for the purpose of college admissions, a reflection of who I am and the person I will strive to be. As the child of a recovering addict, I have certainly been affected by my mom's decisions and experiences, and thus have very strong, personal views on the matters of drug use and addiction. Now a third-year undergraduate at a large, well-respected California university, seven years after the beginning of my mom's initial recovery (she, like many others suffering from addiction, experienced a year-long relapse ending only nine months ago), I am curious about my mom's addiction, and am eager to learn more. What factors contributed to her addiction? Were her actions and behaviors a reflection of poor personal character? Is she at fault, or is it possible she is plagued with biological or genetic susceptibility? Is she suffering from a disease, just like any other? Although it is easier for me just to blame her—she did make the decision to buy and smoke the methamphetamines to which she became addicted, did she not?—I have decided to be more open-minded and set aside my bias. Understanding and

elucidating the concept of addiction is no small task, and may still be beyond me at this point, but the following is what I have learned.

Drug addiction, also known as substance dependence, is defined by Koob and Le Moal as "a chronically relapsing disorder that is characterized by (1) compulsion to seek and take the drug, (2) loss of control in limiting intake, and (3) emergence of a negative emotional state . . . when access to the drug is prevented" (Koob & Le Moal, 2006). More simply, it is defined by Meyer and Quenzer as a "chronic, relapsing behavioral disorder" (Meyer & Quenzer, 2005). The concept of addiction commonly emphasizes drug seeking behavior driven by intense craving, periods of remission followed by relapse, and persistent drug use despite harmful consequences (Meyer & Quenzer, 2005). It is estimated that 15.6% (29 million) of the U.S. adult population will engage in nonmedical or illicit drug

Table 1: Estimated Prevalence Among 15- to 54-year-olds of Nonmedical Use and Dependence Among Users (1990–1992) from The National Comorbidity Survey (from Anthony, J.C., Warner, L.A., & Kessler, R.C. (1994). Comparative epidemiology of dependence on tobacco, alcohol, controlled substances, and inhalants: Basic findings from the National Comborbidity Survey. *Exper. & Clin. Psychopharm.* 2, 224-68. Repr. Koob & Le Moal, 2006. Reprinted here with permission from Elsevier.).

	Ever Used (%)	Prevalence of dependence (%)	Dependence among users (%)
Tobacco	75.6	24.1	31.9
Alcohol	91.5	14.1	15.4
Illicit Drugs	51.0	7.5	14.7
Cannabis	46.3	4.2	9.1
Cocaine	16.2	2.7	16.7
Stimulants	15.3	1.7	11.2
Anxiolytics	12.7	1.2	9.2
Analgesics	9.7	0.7	7.5
Psychedelics	10.6	0.5	4.9
Heroin	1.5	0.4	23.1
Inhalants	6.8	0.3	3.7

use at some point in their lives, 3.1% (5.8 million) will go on to drug abuse, and 2.9% (5.4 million) will become substance dependent on illicit drugs (Koob & Le Moal, 2006). Data from the Substance Abuse and Mental Health Services Administration's National Household Survey on Drug Abuse shows that the percentage of 15- to 54-year-olds addicted to a given drug, of those who ever used, increases from alcohol to marijuana, to cocaine, and then to heroin (Table 1) (Koob & Le Moal, 2006). The path from drug use to addiction for each individual is also similar and follows a well established cycle. It regularly begins with social drug-taking and acute reinforcement, and often, but not always, escalates to compulsive use, leading then to dependence, withdrawal, and protracted abstinence, which more commonly results in relapse than in recovery (Figure 1) (Koob & Le Moal, 2006). Drug addiction also comes at a tremendous cost to society. The National Institute on Drug Abuse found the cost of

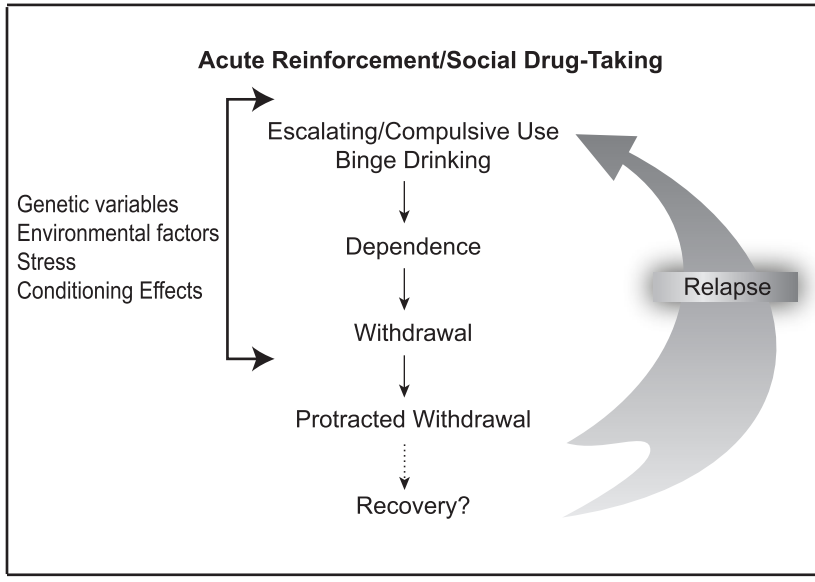

Figure 1: The pathway from drug use to addiction. Drug use often begins with social drug-taking and acute reinforcement, and often, but not always, escalates to compulsive use, leading then to dependence and withdrawal. During withdrawal and abstinence, relapse to compulsive drug use is common. Many factors including genetics, the environment, stress, and conditioning contribute to the vulnerability of entering this cycle of substance abuse and dependence (from Koob & Le Moal, 2006, with permission from Elsevier).

drug and alcohol abuse to be about $246 billion in 1992 (without considering nicotine addiction). This estimate includes health consequences and their effects on the health care system, criminal behavior, negligent driving, job loss, and the effects of impaired productivity on these individuals and their employers (Chou & Narasimham, 2005).

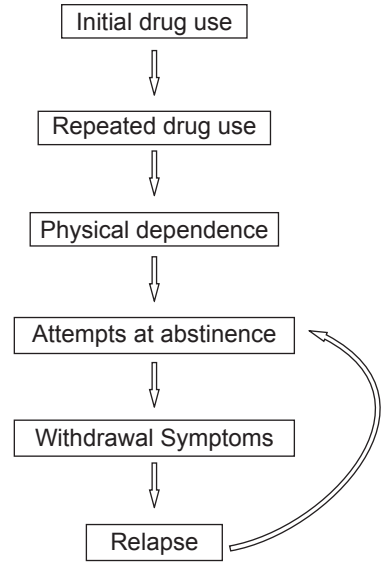

Figure 2: The physical dependence model of addiction. This model emphasizes withdrawal symptoms as the primary factor leading to relapse via negative reinforcement (from Meyer & Quenzer, 2005).

A number of models have been developed to explain the complex concept of addiction, some more successfully than others. One example is the physical dependence model, which emphasizes withdrawal symptoms as the primary factor leading to continued drug use via negative reinforcement (Figure 2) (Meyer & Quenzer, 2005). This refers to the idea that repeated drug use is reinforced by removal of an undesirable stimulus, such as withdrawal symptoms suffered as a result of substance dependence (Meyer & Quenzer, 2005). In contrast, another model of addiction is the positive reinforcement model, which is based on the rewarding and reinforcing effects of abused drugs (Figure 3) (Meyer & Quenzer, 2005). It focuses on a drug's euphoric effects as the primary means of reinforcement. While both of these models seem valid, each fails to explain the occurrence of relapse after detoxification, or continued self-administration of a drug with increased tolerance, both of which are significant characteristics of addiction. More recently described models include the incentive sensitization and opponent process models, which focus on the neurobiological effects of abused drugs (Figures 4 & 5,

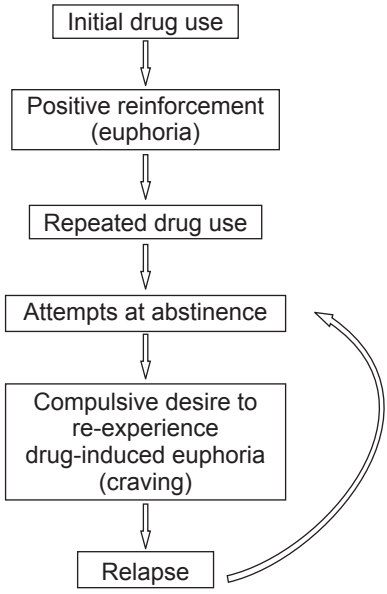

Figure 3: The positive reinforcement model of addiction. This model describes the rewarding and reinforcing effects of a drug as the primary factor contributing to relapse (from Meyer & Quenzer, 2005).

respectively). The former highlights the distinction between drug "liking" and drug "wanting," presenting the theory that repeated drug use leads to an increase in drug "wanting," or craving, due to sensitization, and a decrease in drug "liking," the rewarding or euphoric effects of a drug, as a result of tolerance (Meyer & Quenzer, 2005). The latter model proposes that the initial positive response to a drug is followed by an opposing withdrawal response as the initial positive stimulus wears off (Meyer & Quenzer, 2005). Each of these models is superior to the previous two, as both contribute significantly to contemporary thinking of the mechanisms of addiction, yet are still inadequate as they do not explain the initial stages of drug use and consider only some of the relevant psychological and neurobiological factors involved in addiction (Meyer & Quenzer, 2005).

The most recent and widely accepted model of addiction is the disease model, which treats addiction as a medical disorder, and includes both the susceptibility and exposure models (Figure 6) (Meyer & Quenzer, 2005). The susceptibility model argues that the disease of addiction stems primarily from an inherited susceptibility to uncontrolled drug use (Meyer & Quenzer, 2005). On the other hand, the exposure model maintains that chronic drug use leads to significant changes in the brain that are responsible

for both loss of control and other prominent characteristics of addiction (Meyer & Quenzer, 2005). Together, these views describe addiction as a chronic medical disorder based on both neuronal mechanisms and heritability, and due to recent technological advances and greater understanding of neurobiological mechanisms, are gaining greater credibility among the scientific community and general public. Not surprisingly, this model has had a tremendous impact on society's reaction toward drug abuse and addiction, as well as on the treatment and recovery of addicted individuals (Meyer & Quenzer, 2005). It effectively promotes greater public understanding, and provides relief from the prejudice and guilt often experienced by addicted individuals. Below is a more substantial discussion of the disease model, supported by both the imbalance of neural systems and neurological adaptations that contribute to the behavior and personality traits of addicted individuals, and evidence of genetic susceptibility, both of which suggest that addiction is, in fact, a medical disorder.

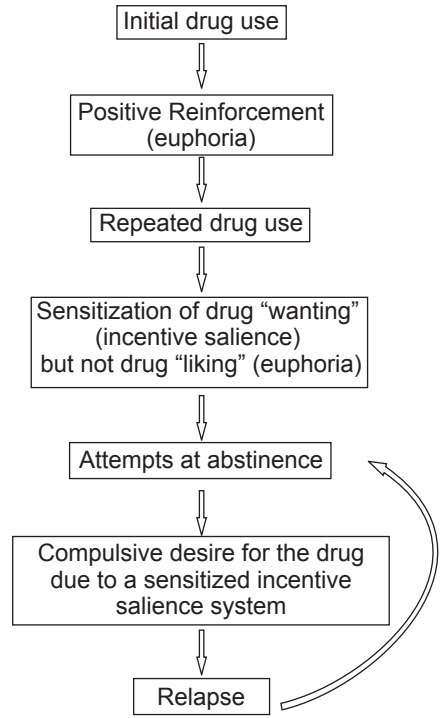

Figure 4: The incentive sensitization model. This model states that drug use is perpetuated due to sensitization of drug "wanting" and not drug "liking." While tolerance to the rewarding or euphoric effects of a drug may occur, there is a compulsive drive to seek and take the drug, commonly resulting in relapse (from Meyer & Quenzer, 2005).

Recent research suggests that "variation in personality dimensions, such as impulsivity, risk taking, and novelty seeking, may contribute to the initiation of drug use as well as the transitions

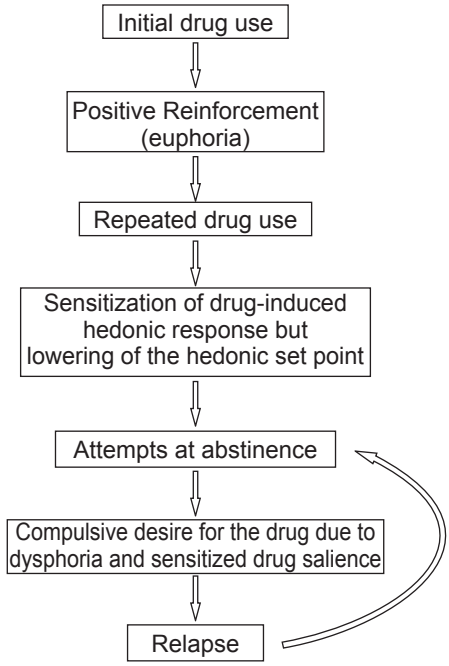

Figure 5: The opponent process model. This model proposes that the initial positive response to a drug is followed by an opposing withdrawal response as the initial positive stimulus wears off. Craving for the drug (due to dysphoria) and sensitization often lead to relapse (from Meyer & Quenzer, 2005).

from initial use to addiction" (Kreek et al., 2005). Impulsivity, a form of behavioral disinhibition, is described as acting suddenly in an unplanned manner to satisfy desire (Kreek et al., 2005). Antoine Bechara, from the Institute for the Neurological Study of Emotion and Creativity at the University of Southern California, states that impulsivity is, in fact, significant in the progression of drug abuse to addiction. He argues that addicted individuals become unable to make drug-use choices on the basis of long-term outcome due to an "imbalance between two separate, but interacting, neural systems that control decision making: an impulsive amygdala system . . . and a reflective prefrontal cortex" (Bechara, 2005). The amygdala, a telencephalic forebrain structure, is part of the limbic system, which is responsible for integrating emotional responses and regulating motivated behavior and learning (Meyer & Quenzer, 2005). Specifically, the amygdala is involved in "triggering the affective/emotional signals of immediate outcomes" (Bechara, 2005). Research shows that conditioned approach behavior, or fast, automatic, and exaggerated autonomic responses to drug cues relates to abnormal activity in the amygdala-ventral striatum system, thereby resulting in exaggerated processing of incentive values of substance-related cues (Bechara, 2005). This finding is quite significant, as cue-

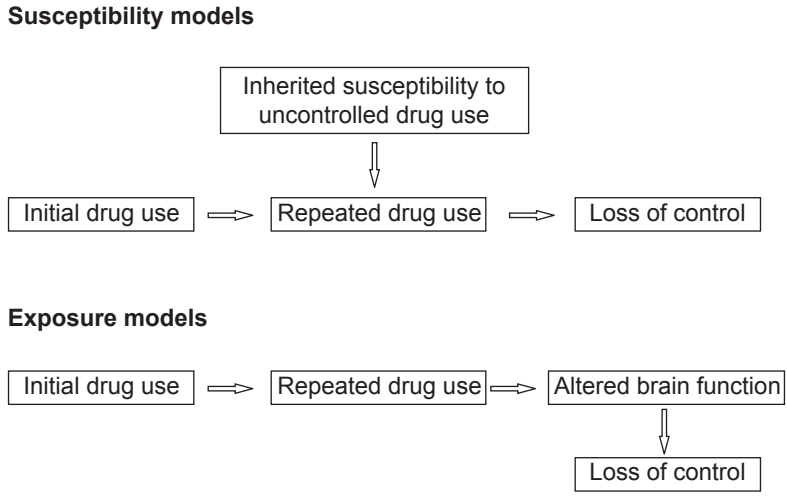

Figure 6: The disease models of addiction. The susceptibility model argues that addiction stems primarily from an inherited susceptibility to uncontrolled drug use, while the exposure model states that chronic drug use leads to prominent changes in the brain that contribute to the development of drug addiction (from Meyer & Quenzer, 2005).

induced craving is an often ominous precursor to relapse.

On the other hand, the ventral medial prefrontal cortex is a neural structure involved in "triggering the affective/emotional signals of long-term outcomes" (Bechara, 2005). It is necessary for triggering affective states from recall or from imagination. As in the amygdala, addicts also show functional abnormalities in parietal regions when performing decision-making tasks. Bechara also argues that a degree of abnormality exists prior to the addiction state and therefore facilitates the progress from experimentation to addiction (Bechara, 2005). Consequently, addicted individuals demonstrate poor decision making because the process that enables them to inhibit the actions of the impulsive system, via the reflective system, is dysfunctional (Bechara, 2005).

Worth emphasizing again, a hyperactive impulsive system increases the reward utility of a drug while decreasing the threshold for signaling subsequent affective signals related to drugs, ultimately

leading to an amygdala which is overresponsive to reward (Bechara, 2005). This is particularly significant as neuroimaging studies have demonstrated dramatic limbic responses to drug-related cues that correlate with the degree of reported craving (Dackis & O'Brien, 2005). It is well understood that the intensity of cue reactivity correlates with the likelihood of relapse (Dackis & O'Brien, 2005). Interestingly, studies also link drug-related craving with natural drive states, and support the idea that "addictive drugs hijack endogenous reward circuits that have evolved to ensure survival" (Dackis & O'Brien, 2005). Therefore, poor/weak decision-making mechanisms, coupled with intense cue-induced craving and limbic activation, increase an individual's susceptibility to addiction by contributing to the initiation and continuation of drug use. An addict's impulsivity is subsequently said to progress to compulsivity in a three-stage cycle leading to addiction (Koob & Le Moal, 2005).

As mentioned earlier, a number of addiction models highlight the reinforcing effects of illicit drugs as the primary factor contributing to the development of addiction. However, it is widely known that compulsive drug use continues even with tolerance to pleasurable drug effects and impending adverse consequences. It is, therefore, also argued that addiction is a disease of compulsion and drive that involves dysfunction of the prefrontal, and specifically, orbitofrontal cortex (Volkow & Fowler, 2000; Dackis & O'Brien, 2005). The prefrontal cortex plays a significant role in decision making, risk/reward assessment, and impulse control and perseverance (Dackis & O'Brien, 2005). Functional and structural abnormalities in this area may therefore contribute to the clinical characteristics commonly displayed by addicted individuals, including poor impulse control, lack of resolve and faulty decision making (Dackis & O'Brien, 2005). The orbitofrontal cortex, a division of the prefrontal cortex, is involved with drive and compulsive repetitive behaviors (Volkow & Fowler, 2000). Due to its functions in emotion, it is also considered a part of the limbic system. Abnormal activation of the orbitofrontal cortex may explain why drug self-administration occurs even after the euphoric effects of a drug have subsided (Volkow & Fowler, 2000). Reduced baseline metabolism in the prefrontal cortex, hypofrontality, is also associated with addiction (Dackis & O'Brien, 2005). According to Volkow and Fowler,

brain glucose metabolism serves as an indicator of brain function (Volkow & Fowler, 2000). A study with cocaine abusers showed that during early withdrawal metabolism in the orbitofrontal cortex was significantly higher than it was in controls, with the level of metabolism positively correlated with the intensity of drug craving (Volkow & Fowler, 2000). In contrast, during protracted withdrawal, cocaine abusers showed significant reductions in several frontal areas, which persisted even three to four months after their initial detoxification (Volkow & Fowler, 2000). This reversal signifies a change in brain function as a result of both substance dependence and withdrawal.

Hypofrontality in the prefrontal, and specifically orbitofrontal cortex is also significantly associated with reduced D_2 receptor availability (Dackis & O'Brien, 2005; Volkow & Fowler, 2000; Figure 7). D_2 receptors are metabotropic receptors for the catecholamine neurotransmitter dopamine. When bound to an agonist, the D_2 autoreceptor decreases calcium influx into the presynaptic nerve terminal in order to decrease the release of neurotransmitter into the synaptic cleft. Dopamine is both a neurotransmitter and a neurohormone, which plays an important role in various brain functions including movement, cognition, pleasure, and motivation

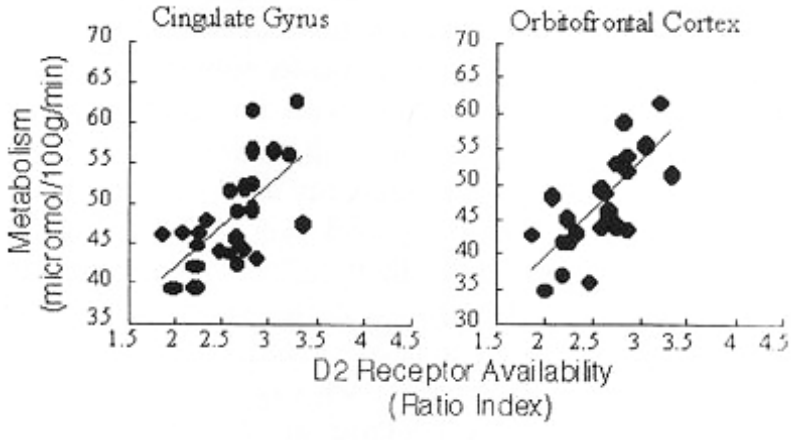

Figure 7: Relationship between regional brain glucose metabolism in cingulate gyrus and orbitofrontal cortex and dopamine D_2 receptor availability in the striatum in detoxified cocaine users. Reduced metabolism is clearly associated with reduced D_2 receptor availability (from Volkow & Fowler, 2000).

(Meyer & Quenzer, 2005). Although it is unclear whether reduced D_2 receptors in addicted individuals precede or result from chronic drug exposure, these autoreceptors certainly play a significant role in addiction. For example, reduced D_2 receptors in addicted individuals persist beyond detoxification, suggesting that this condition may be a predisposing factor (Dackis & O'Brien, 2005). This is further supported by the variability of D_2 binding across individuals and the fact that non-addicted individuals report significantly more pleasure after receiving stimulant drugs (Dackis & O'Brien, 2005). The existence of genetic factors, like those affecting intensity of reward, provide strong evidence for the biological basis of this disorder and the susceptibility model within the disease model of addiction. In addition, hypofrontality also lends credit to the exposure model within the disease model of addiction, as it also results from chronic drug exposure. Studies involving monkey subjects, for example, have yielded a decline in D_2 receptors after chronic drug administration (Dackis & O'Brien, 2005). D_2 autoreceptor downregulation is also associated with dopamine hypoactivity, which may serve as a marker for dopamine dysregulation, or the impairment of its physiological regulatory mechanisms, in addictive illness (Dackis & O'Brien, 2005). Unfortunately, research also suggests that hypometabolic activity of the orbitofrontal cortex in detoxified cocaine abusers is likely to involve disruption of other neurotransmitters in addition to dopamine, such as glutamate, serotonin, and GABA, which also play significant roles in the maintenance of a healthy nervous system (Volkow & Fowler, 2000). While cocaine, heroin, and alcohol increase striatal D_2 levels during intoxication, chronic exposure is associated with dopamine hypoactivity, reduced D_2 autoreceptors, and limbic activation during cue-induced craving, again consistent with the disease model of addiction, providing evidence for both the susceptibility and exposure models of this medical disorder (Dackis & O'Brien, 2005).

In addition to personality traits such as impulsivity and compulsivity, which contribute to the onset of addiction, several related genetic components and common genetic variants make some individuals genetically susceptible, or predisposed, to the disease of addiction. In fact, it is estimated that "genetic factors account for 30-60% of the overall variance in the risk for the development of

drug addictions" (Kreek et al., 2005). Generally, chronic exposure to a drug leads to persistent changes in the brain, including expression of genes or protein products, protein-protein interactions, neural networks, and neurogenesis and synaptogenesis (Kreek et al., 2005). Genetic factors are also involved in the alteration of pharmacodynamics, a drug's effect at its receptor, and pharmacokinetics, a drug's absorption, distribution, metabolism and excretion (Kreek et al., 2005). Overall, the genetics of addiction is quite influential and encompasses genetic variation in personality dimensions, comorbidity, and genetic factors that are associated directly with addiction (Kreek et al., 2005).

As discussed previously, personality traits such as impulsivity and risk taking are commonly associated with the disease of addiction. However, in addition to being influenced by neurological adaptations and imbalances, research strongly suggests that underlying genetic components contribute to these personal characteristics as well. Low levels of serotonin and its metabolites, for example, are associated with various forms of impulsivity (Kreek et al., 2005). More specifically, low levels of cerebrospinal fluid 5-hydroxylindolacetic acid (5-HIAAA), a major metabolite of serotonin, are related not only to impulsivity but also to aggression, depression, and early-onset alcoholism (Kreek et al., 2005). TPH1, a gene coding for the rate limiting enzyme in the production of serotonin, has a variant associated with reduced CSF 5-HIAA (Kreek et al., 2005). In addition to TPH1, a number of other genes are also associated with impulsivity, including SERT, DRD3, MAOA, 5-HT2A, and dopamine receptors D3 and D4 (the genes for these receptors are DRD3 and DRD4) (Table 2) (Kreek et al., 2005). Similar to impulsivity, risk taking, which is characterized by "behavior performed under uncertainty . . . without robust contingency planning," is also associated with addiction, and has underlying genetic mechanisms (Kreek et al., 2005). Novelty seeking, one aspect of risk taking, may be especially correlated with the progression from drug use to addiction. This trait is also associated with DRD4 receptor variants (Kreek et al., 2005). DRD4 receptors are members of the D_2-like family of G_i-coupled dopamine receptors, and are found in brain areas including the prefrontal cortex, hippocampus, dorsomedial thalamus, lateral septal nucleus, and hypothalamus (Kreek et al., 2005). Not coinci-

Table 2: Genes having one or more variants that have been reported to be associated with one or more addictions (from Kreek et al., 2005).

Gene	Protein	System	Chromosomal location	I	R	E	S	A	Drug	Status
OPRM1	μ opiod receptor	Opiod	6q24-q25	–	–	–	+	+	H/O; Alc	D/A[b]
OPRK1	κ opiod receptor	Opiod	8q11.2	–	–	–	–	+	H/O	D/A
PDYN	Preprodynorphin	Opiod	20pter-p12.2	–	–	–	–	+	C/S	D/A
TH	Tyrosine hydroxy-lase	Dopaminergic	11p15.5	–	–	+	–	+	Alc	D/A
DRD2	Dopamine recep-tor D2	Dopaminergic	11q23	–	–	–	–	+	Alc	D/A[b]
DRD3	Dopamine recep-tor D3	Dopaminergic	3q13.3	–	+	–	–	+	Alc;C/S	D/A[b]
DRD4	Dopamine recep-tor D4	Dopaminergic	11p.15.5	+	+	–	–	+	H/O;C/S; Alc	D/A[b]
DBH	Dopamine β-hy-droxylase	Dopaminergic	9q34	–	–	–	–	+	C/S	D/A
DAT (SLC6A3)	Dopamine trans-porter	Dopaminergic	5p15.3	+	–	–	–	+	Alc	D/A[b]
TPH1	Tryptophan hydroxylase 1	Serotonergic	11p15.3-p14	–	–	–	–	+	Alc	D/A[b]
TPH2	Tryptophan hydroxylase 2	Serotonergic	12q21.1	–	–	–	–	+	H/O; Alc	CSA; D/A[b]
HTR1B	Serotonin recepter 1B	Serotonergic	6q13	–	–	–	–	+	Alc;H/O	D/A[b]
HTR2A	Serotonin recepter 2A	Serotonergic	13q14-q21	–	–	–	–	+	Alc	CSA; D/A[b]
SERT (SLC6A4)	Serotonin trans-porter	Serotonergic	17q11.1-q12	+	–	+	–	+	H/O;Alc	D/A[b]
MAOA	Monoamine oxidase A	Catecholaminergic, Serotonergic	Xp11.23	+	–	+	–	+	Alc	D/A
COMT	Catechol-*O*-methyl transferase	Catecholaminergic	22q.11.2	+	–	–	+	+	Alc;H/O	D/A[b]
GABRA1	GABA receptor subunit α-1	GABAergic	5q34-q35	+	–	–	–	+	Alc	D/A[b]
GABRA6	GABA receptor subunit α-6	GABAergic	5q31.1-q35	+	–	–	–	+	Alc	D/A
GABRB1	GABA receptor subunit β-1	GABAergic	4p13-p.12	+	–	–	–	+	Alc	D/A
CHRM2	Muscarinic acetylocholine receptor M2	Cholinergic	7q35-q36	–	–	–	–	+	Alc	D/A[b]
CNR1	Cannabinoid receptor 1	Cannabinoid	6q14-q15	–	–	–	–	+	Alc;C/ SAlc	CSA; D/A[b]
FAAH	Fatty acid amide hydrolase	Cannabinoid	1p35-34	–	–	–	–	+	Alc	CSA
NPY	Neuropeptide Y	Neuromodulatory	7p15.1	–	–	–	–	+	Alc	CSA; D/A[b]

Gene	Protein	System	Chromosomal location	I	R	E	S	A	Drug	Status
ADH1B	Alcohol dehydrogenase 1B	Ethanol metabolism	4q22	–	–	–	–	+	Alc	D/A[b]
ADH1C	Alcohol dehydrogenase 1C	Ethanol metabolism	4q22	–	–	–	–	+	Alc	D/A[b]
ALDH2	Aldehyde dehydrogenase 2	Ethanol metabolism	12q24.2	–	–	–	–	+	Alc	D/A[b]
CYP2D6	Cytochrome CYP450	Drug metabolism	22q13.1	–	–	–	–	+	H/O	D/A
ANKK1	Ankyrin repeat and kinase domain-containing 1	Signal transduction (predicted)	11q23.2	–	+	–	–	+	Alc	D/A[b]

I: impulsivity, R: risk taking, E: environment, S: stress responsivity, A: addiction, H/O: heroin or opiate, Alc: alcohol, C/S: cocaine or stimulants, CSA: continued substance abuse, D/A: dependence or addiction.

dentally, the prefrontal cortex, as previously discussed, is the site of cognitive and executive function and decision making. Therefore, research suggests that an addict's inability to make good decisions regarding their substance abuse, and other life choices, may in fact be based on, or at least significantly influenced by a genetic, medical disorder.

Comorbidity, another phenomenon associated with substance dependence, is also related to the genetics of addiction. Defined as the diagnosis of a simultaneous but distinct disease process in an individual, significant comorbidity of drug abuse and addiction occurs with various personality and mood disorders (Meyer & Quenzer, 2005). Research has found that four psychiatric conditions, including depression, anxiety, antisocial personality disorder, and attention deficit/hyperactivity disorder, are "commonly present in and probably are involved in psychopathology or physiology of addiction to opiates and alcohol" (Kreek et al., 2005). The most common comorbid disorders are depression and anxiety, which exist in approximately 20-50% of people with alcoholism and cocaine and other stimulant disorders (Kreek et al., 2005). Interestingly, comorbidity of substance abuse with other psychiatric disorders is more common in women than in men, with the comorbid diagnosis more often being the primary one (Meyer & Quenzer, 2005). Research suggests that comorbidities may occur as a result of individuals who suffer from a mental illness attempting to self-medicate with illicit drugs (Volkow & Li, 2005). Another theory, although still lacking

sufficient evidence, proposes that early exposure to certain drugs of abuse may increase susceptibility to other mental disorders (Volkow & Li, 2005). While comorbidity remains controversial in regard to drug abuse and addiction, it is "likely to reflect overlapping environmental, genetic and neurobiological factors that influence substance abuse and mental illness" (Volkow & Li, 2005).

Finally, in addition to the genetic personality traits and comorbidity commonly observed in addicted individuals, a number of genetic factors directly associate with addiction, as well. Research conducted by The Collaborative Study on the Genetics of Alcoholism (COGA) highlighted "42 chromosomal regions that may be involved in vulnerability to drug use in African-Americans and European-Americans" (Kreek et al., 2005). All subjects involved in this study had polysubstance abuse, including nicotine and alcohol abuse or addiction. The study also showed that "at least 15 large chromosomal regions were shared with regions identified in one or more other linkage studies of alcoholism and nicotine addiction, suggesting that there may be general genetic factors for addiction" (Kreek et al., 2005). Additional studies implicate genetic variants in the development of opiate addiction as well. Variants and haplotypes of the μ opioid receptor gene, OPRM1, for example, are associated with opiate addiction (Kreek et al., 2005). An association between a distinct single nucleotide polymorphism and a specific haplotype of variants of the κ opioid receptor gene, OPRK1, has also been found (Kreek et al., 2005). A 68 base pair repeat in the promoter region of dynorphin, an endogenous ligand of the κ receptor, is also linked to cocaine abuse/dependence, and cocaine-alcohol dependence (Kreek et al., 2005). Variants in the genes coding for μ and κ receptors are quite significant as both of these receptors are important in the reinforcement of drug effects and reward. The μ receptor, for example, is widely distributed in the brain and spinal cord, and plays a significant role in reinforcement in the nucleus accumbens, a primary part of the limbic reward system (Meyer & Quenzer, 2005). OPRM1, OPRK1, and other genes mentioned above represent only a few of those that have been shown to play a role in the progression of drug abuse to substance dependence. A more complete list of genes having one or more variants associated with one or more addictions is found in Table 2, while Figure

8 describes the diverse contribution of genetic influences to initial drug use, abuse and addiction (Kreek et al., 2005).

In closing, it seems as though drug addiction is, in fact, much more than a simple cycle of reward and withdrawal. It involves complex neural imbalances and neurological adaptations that greatly influence personality traits associated with addiction, such as impulsivity and compulsivity. These characteristics, which involve the limbic system and prefrontal cortex, brain structures involved in regulating emotional responses, decision making, and risk/reward assessment, also have underlying genetic components, and have been shown to increase one's vulnerability to addiction. Genetic susceptibility, which accounts for 30%-60% of the variance for the risk of developing addiction, is also seen with comorbidity and individual variants directly associated with dependence, such as those affecting the opioid receptors involved in drug reinforcement and reward. Collectively, this research lends great credibility to the disease model of addiction, supporting the concept of sub-

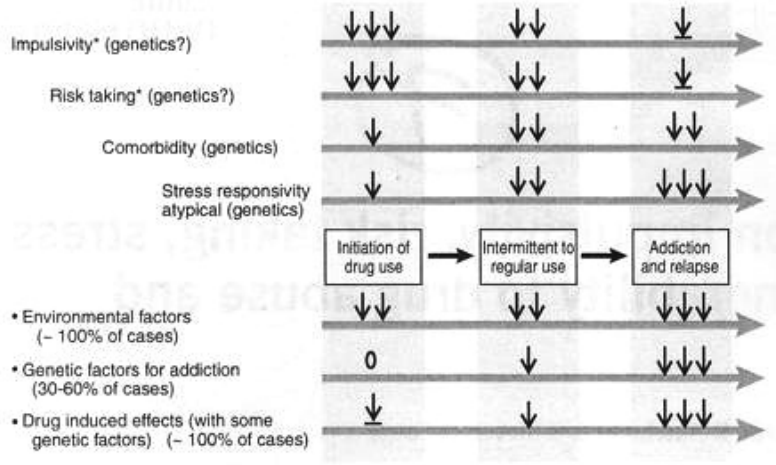

Figure 8: Diverse contribution of genetic influences to initial drug use, abuse, and addiction. It is suggested that impulsivity and risk taking contribute most to the initiation of drug use, while stress responsivity, environmental factors, genetic factors for addition, and drug induced effects are primarily responsible for the progression to addiction and likelihood of relapse (from Kreek et al., 2005).

stance dependence as a medical disorder, and one that should be treated as such. However, the disease model of addiction is still a somewhat controversial idea. Despite heavy research and persuasive findings, this model is not yet entirely conclusive.

As the child of a recovering addict, I still have questions that remain unanswered. For instance, when must a person take responsibility for her actions? When is one's behavior beyond her control? Where do we draw the line? I do not doubt the power of addiction, or the immense dedication and will required to overcome it. I realize that even the strongest of addicted individuals will oftentimes never reach complete and unfaltering recovery. Who would choose such a fate for herself? The answer is likely no one. But the truth is, each day people from diverse backgrounds and environments make the choice to use for the first time, putting themselves at potential risk for the full manifestation of this disease. Can individuals be held accountable for this initial decision? If addiction can be classified as a genetic disease, can it simply be avoided by abstinence? Given the evidence in support of the disease model of addiction, is this even plausible?

It seems there is no easy answer to these questions. However, I can easily say that addiction has touched my life. From the time I was ten to fourteen years old, I experienced adversity unlike anything I had ever known. My life, figuratively at least, was turned upside-down and I could not explain why. Yet despite my experiences, knowledge of my mom's addiction has been empowering. The next paragraph of my personal statement reads, "*It is to my hardships, my mom's addiction, my parents' divorce, and my family's experience on welfare, that I owe my fierce determination. It is these obstacles that have given me the ability to look at a bad situation and want to make it better, to want to make myself better, to want to do something great.*" I now can make healthy decisions for myself and aspire to much more in my own life. I will not become a victim to my mom's disease. I have no doubt that additional knowledge gained through continued research will also produce positive effects in the study of substance abuse and dependence. Understanding addiction is critical for promoting the health, safety and well-being of our family and friends. It is the key to education and prevention, and will likely provide insight on how to best, and most effectively,

treat addicted individuals, so that they may someday experience a complete and long-lasting recovery. With continued research, all of our questions may someday be answered. Elucidating the complex concept of addiction is no small task, but it is a worthy one. We must continue to support research, aim for greater understanding, and educate others about the underlying causes and dangers of drug addiction, so that no other mothers and daughters need experience the effects of this disease.

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