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Article

Addiction: Diseased Brain, Divided Will, or Restless Heart?

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Addictive disorders lay a heavy burden on global medical resources while continuing to devastate personal lives at an alarming rate. Complex interrelated risk factors, including biological, psychological, sociological, cultural, and spiritual factors, must be considered as churches and communities address the individual and societal problems. This article will consider multiple causes of substance and behavioral addiction and reflect on the issue of determinism versus free will. I will take the position that addicts, as all persons, are simultaneously constrained by their embodied nature and yet free to respond to God's grace. The disease model and the choice model are not in opposition: rather, the brain changes that occur during addiction give rise to habits and compulsions which, nevertheless, can be broken as new habits are formed through both divine grace and grace offered by supportive others. Multiple approaches are needed to address a multifactorial problem.

Addiction rates around the world continue unabated while church, society, and individuals struggle to respond in an efficacious manner. Since 2014, the US and Canada have had the highest per capita consumption of opioids (combined prescription and illicit) in the world. The addiction and overdose burden primarily afflicts young males; in the US in 2016, opioids were responsible for 20% of deaths among those aged 24 to 35.[1] The US Centers for Disease Control and Prevention (CDC) reports that tobacco use in the US remains the leading preventable cause of disease, disability, and death—contributing to one in every five deaths.[2] Globally, the World Health Organization (WHO) estimated that, in the twentieth century, 180 million people were killed by tobacco.[3] Why do people choose to endanger their health, livelihood, family, and even life itself to consume addictive substances?

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Addictive behavior illustrates the age-old ontological conundrum of whether human behavior is essentially determined, at various levels and by multiple factors, or freely engaged in by the individual. The disease model, supported by substantial neurophysiological research, states that substance addictions[4] are recurring disorders of the brain, originating in genetic components and neuroplasticity.[5] Evidence is now accumulating that an entire spectrum of behaviors—including compulsive gambling, eating, and viewing of pornography—have underlying genetic and neural similarities with substance abuse.[6] However, because not all users develop addiction, and most addictions remit without treatment, this medical model has been called into doubt by those who stress psychosocial and environmental influence as well as spiritual and moral factors.[7] In this article, we will discuss each of these factors in turn and attempt a holistic response.

Neural Mechanisms of Addiction

For organisms to learn and successfully repeat behaviors that result in survival of

the individual and the species, certain brain mechanisms for motivation, emotion, and executive control must be activated.[8] Substance abuse occurs when these normal mechanisms become overwhelmed due to repeated, supranormal phasic activation by particular external substances. Pleasurable behaviors including eating, drinking, music, video games, and social and sexual interactions are all accompanied by release of the neurotransmitter dopamine in the nucleus accumbens (NAc), a small subcortical area in the ventral striatum which codes for salience of rewards and reward cues. This area, part of the limbic system, is rich in dopamine receptors, and it sends output to forebrain areas responsible for attention, memory, and executive control. The current view of most researchers is that most abused substances promote, by direct or indirect means, rapid phasic bursts of dopamine release three to five or more times greater than that provided by nonaddictive reinforcers which produce more tonic release.[9] The universal dopamine theory of addiction is the most prevalent theory among researchers, although others propose that addiction involves disruptions of multiple transmitters and that different drugs produce different neural adaptations as discussed below.[10]

Dopamine release in NAc flags an event as worth *attending to* and the cues associated with it as worth *learning* so that the rewarding behavior may be repeated. After it was discovered in 1954 that rats will press a lever thousands of times per hour to receive electrical stimulation at this location in the brain, it was proposed that the NAc was a "pleasure center," but this is now seen as too simplistic. The ability to learn and remember the salient cues predicting rewards depends on an extensive neural pathway which extends from the midbrain ventral tegmental area (VTA) where dopaminergic neurons originate, to the NAc where dopamine is released, then to the orbitofrontal cortex which participates in evaluation and executive control, and finally to other structures involved in memory and emotions. Dopamine released by VTA axons into synapses in NAc attaches briefly to receptors on NAc neurons and then is rapidly taken up again into the releasing axons by means of molecular transporter molecules.[11] Cocaine blocks these transporter molecules, whereas amphetamine and its derivatives cause the transporters on the dopaminergic axons to run in reverse. In either event, the dopamine available in the synapse to stimulate the postsynaptic cell is increased. Reward has both "wanting" and "liking" components because, as addicts come to realize, one can "want" something that one does not really "like"; thus the NAc should not be simplistically referred to as the brain's "pleasure center."

Dopamine release in NAc produces "wanting" rather than "liking" by focusing attention on the stimuli already associated with reward.[12] At the same time, the memory of reinforcement causes decreased activity in the frontal cortical executive circuits which normally provide inhibitory control over behavior.[13] The most recent hypothesis is that dopamine release is time-locked to unexpected or novel stimuli and acts as a reward prediction signal.[14] This mechanism underlies learning of the behaviors necessary to provide a mammal with food, drink, and social partners, and results in the long-term structural changes in synapses which normally underlie learning. The mechanism functions as it should if the organism learns, for example, where food is available and repeats whatever behavior procured it. The problem arises when supraphysiological bursts of dopamine produced by addictive substances cause attention, emotion, and motivation to focus exclusively on drug-related cues. Psychostimulants such as cocaine, methamphetamine, MDMA, and "bath salts" directly affect the NAc.[15] The increased bursting activity produced by these drugs is necessary and sufficient on its own to promote reinforcement directly. Evidence indicates that indirect processes, reviewed below, which often involve endogenous opioid or cannabinoid receptors, are needed to indirectly activate the dopamine response to the presence of opiates, ethanol, cannabis, and nicotine.[16] Dopamine is of primary importance in stimulant addiction and cue-triggered craving for opioids, but perhaps the endogenous opiates and GABA[17] systems play the primary role in producing satisfaction ("liking" as opposed to "wanting") in opioid and cannabis addiction.[18]

Nonaddictive behaviors cause the slow, lengthy release of dopamine in NAc, stimulating high affinity D2 receptors which sustain moderate levels of motivation necessary to procure and consume rewards.[19] Large rapid bursts of dopamine stimulate both D2 and lower affinity D1 receptors which signal expectation of reward and cause drug "highs." Activity in the midbrain VTA itself is influenced by reciprocal innervation from widespread limbic and lower-level areas involved in memory, emotion, attention, and

motivation. Most cells in the NAc also receive multiple varied inputs regarding stimulus salience from widespread limbic areas via dopamine, glutamate, endocannabinoids, and other inputs. Conditioning to salient cues can be induced by dopamine bursts large enough to activate the D1 receptors. Stimuli associated with the drug thus become conditioned and eventually trigger phasic release of dopamine from VTA onto the NAc. The VTA neurons are themselves normally under tonic inhibition due to the transmitter GABA.[20] The timing of dopamine bursts is likely controlled by VTA local interneurons and other GABA-releasing axons from those ventral brain regions, subject to neuroplastic changes, which are involved in evaluation of rewards, attention, arousal, and memory. Among the changes in the brain associated with repeated drug use are altered firing patterns in VTA and its input areas due to cellular-level mechanisms which normally accompany learning.

Endogenous opioids (including endorphins) and endogenous cannabinoids (endocannabinoids) interact in complex ways with the dopamine system in natural and drug-produced hedonic responses along with additional transmitters, many involved in eating and satiety.[21] In addition, the release of dopamine is increased by glutamate released in the VTA by dorsal raphe cells.[22] Serotonin (5-HT) from dorsal raphe cells also plays a lesser but more complex role. One type of serotonin receptor[23] ($5\text{-}HT_{2C}$) in the VTA seems to decrease stimulant-induced reinforcement, while another ($5\text{-}HT_{1B}$) indirectly increases dopamine release by disinhibition of $GABA_A$ receptors.[24] Endogenous opioids and endogenous cannabinoids also interact in complex ways with the dopamine system in natural and drug-produced hedonic responses. Other transmitters and modulators involved in natural rewards, including leptin, insulin, galanin, neuropeptide Y, substance P, and melanocortins, also influence the system. Many of these substances are involved in regulation of eating. In summary, the control of dopamine release is complicated and much more research will be necessary to paint a complete picture.

Opiate drugs, including heroin, fentanyl, and oxycodone, stimulate opioid receptors directly. Most opioid abusers start with prescription drugs but soon discover less expensive alternatives on the street.[25] When prescriptions run out or are limited, users often turn to cheaper illicit drugs such as heroin. However, fentanyl is even cheaper than heroin, and users are often unaware that what they buy on the street as heroin or oxycodone may be substantially fentanyl.[26] Fentanyl, in combination with street drugs, was responsible for over 80% of the more than 1,420 overdose deaths in British Columbia in 2017.[27] Synthetic opioids mimic the effects of these neuromodulatory endogenous opioids by binding to μ opioid receptors, which are plentiful in both VTA and NAc.[28] One effect of μ receptor stimulation is to release the "brakes" in the VTA by disinhibiting normal inhibitory modulation GABAergic neurons in the VTA, which in turn disinhibit dopamine release in the NAc. Most of the reinforcing effects of opioid drugs are due to direct stimulation of μ receptors on the NAc cells. Naturally occurring endorphins decrease sensitivity to pain, increase relaxation, and cause drowsiness by blocking the brainstem area (locus coeruleus) that responds to arousing stimuli. Hence, opioids reduce both anxiety and pain, and normally function to promote positive feelings brought on by contact and social interaction. The effect that endorphins have on cortical emotional systems helps explain why relational loss is perceived in humans as similar to pain and panic. Social pain in humans, separation distress in animals, and the affective component of physical pain all involve the anterior cingulate cortex and the insula; furthermore, μ opioid receptors are implicated in each of these types of pain.[29]

Alcohol use disorders are among the most common mental disorders, with 36% of adult males in the US meeting the criteria for the disorder at some time in their lives.[30] Ethanol has widespread complex interactions with GABA, serotonin (5-HT), endorphins, endocannabinoids, glutamate, and nicotinic receptors, although the major contributor to pleasurable sensations is the mesolimbic dopamine system. It also acts on the inhibitory GABA interneurons which normally act as "brakes" controlling VTA cells, thereby indirectly producing increased release of dopamine in NAc.[31] Ethanol's facilitation of the inhibitory transmitter GABA in widespread areas of the brain leads to muscle relaxation, decreased anxiety, decreased behavioral inhibition, and eventually loss of consciousness. Stress-related circuits, including those of corticotropin-releasing hormone (CRH) and neuropeptide Y, are also eventually affected, contributing to the adverse effects of ethanol with-

drawal by producing anxiety and depression. In adolescents, alcohol alters the development of grey and white matter and disrupts pathways involved in attention, verbal learning, visuospatial processing, and memory. In rodents, this causes decreased cognitive flexibility, behavioral inefficiency, increased anxiety, impulsivity, and risk-taking, as well as impaired neurogenesis and epigenetic alterations as further discussed below.[32]

The main psychoactive ingredients in cannabis are Δ-9-tetrahydrocannabinol (Δ-9-THC) and cannabidiol (CBD) which mimic the effects of endocannabinoids at their receptor sites.[33] Cannabiniod receptors are one of the most abundant receptors occurring throughout the brain, and activation produces a variety of effects on hunger, nausea, memory, sensation, and subjective perception of time. Similar to endocannabinoids, Δ-9-THC is believed to indirectly decrease inhibition on dopaminergic neurons by inhibiting GABA release in the VTA. After prolonged use, synaptic plasticity required for encoding of memory can be disrupted, and therefore learning can be impaired, especially during periods of brain development or reorganization.[34] Δ-9-THC also has psychoactive effects and increases anxiety, whereas CBD can facilitate learning and reduce anxiety, and when taken together with Δ-9-THC may ameliorate its harmful effects, especially on memory. Unfortunately, the levels of Δ-9-THC in street cannabis has risen threefold over the last twenty years while that of CBD has declined to negligible levels. Legalization has been suggested as a way to standardize and control the ratio of Δ-9-THC to CBD and therefore reduce possible harms caused by cannabis.[35]

Endocannabinoids affect neurodevelopment by interacting directly with the glutamate pathways which play a major role in two processes prevalent during adolescence—the development of axonal connections and the process of pruning irrelevant synapses. Adolescent exposure to Δ-9-THC thus alters the normal maturational fluctuations of the glutamate receptors which underlie learning mechanisms, leading to decreases in dopamine activity in adulthood and to increased levels in stress-related signaling. In regular cannabis users, the hippocampus (involved in long-term memory) has decreased volume, although CBD in addition to Δ-9-THC may ameliorate this effect.[36] Neuroimaging studies also reveal decreased volume in the orbitofrontal cortex, a major area for executive control.[37] Because the effects of cannabis on cognition seem dependent on the maturational state of the brain, adolescents appear to be the most vulnerable to neural changes.[38] The present consensus is that cannabis has addictive potential, although the risk of dependence after first exposure has been reported at 8.9%, compared with higher rates of 20.9% for cocaine, 22.7% for alcohol, and 67.5% for nicotine.[39] Although statistics on long-term use of cannabis are not clear, lower addictive potential than alcohol or tobacco, and hence less-compulsive use suggests lower mortality.

Nicotine, despite its high-addictive potential in humans, differs from most other drugs in that it produces reinforcement without euphoria and is less strongly reinforcing in animals.[40] It activates the hypothalamic-pituitary-adrenal (HPA) axis which governs the body's stress response and can block pain from the stimulation of nerve cells. Nicotine directly stimulates certain types of acetylcholine receptors and, depending on the site of action and subtype of receptor, alters release of dopamine, norepinephrine, serotonin, glutamate, GABA, and endogenous opioids.[41] Stimulation of α4β2 subunits of the nicotinic receptors on dopaminergic neurons in NAc contributes to the rewarding effect. The endorphin/μ opioid system, glutamate, and endocannabinoid systems are also implicated. Consistent with reports that stress increases cigarette smoking, activation of the dynorphin/κ opioid system associated with stress and negative states may be involved in nicotine dependence and withdrawal.[42] The opioid antagonist naltrexone decreases nicotine use, further supporting the hypothesis that endogenous opioids contribute to nicotine reinforcement.

Behavioral Addictions

The neurophysiological mechanisms for uncontrolled gambling, internet use, gaming, pornography, and sexual acting out have been shown to be remarkably similar to those elicited in psychoactive substance abuse. Obesity, overeating, and compulsive shopping are now being researched along these lines.[43] Many of these behavioral disorders share similarities with substance abuse, including preexisting vulnerabilities due to failed regulation of the mesolimbic dopamine system by frontal regions. Dopamine agonists can trigger in some Parkinson's patients

compulsive gambling, sex, and shopping, further suggesting that dopamine dysregulation may be involved in these behaviors. Even the intense euphoria and attentional focus of romantic relationships share many facets of addiction because the basic circuitry for romantic love and attachment necessary for survival of the species shares the same circuitry co-opted by drugs.[44] Is it possible that there is a continuum which stretches from normal, necessary behaviors of eating, romantic love, attachment, and social behavior, through mildly disordered behaviors, which then finally ends in the disfunctionality of addiction? If so, this might mean that addiction, rather than being a disease afflicting only some, is a risk factor carried by all.

Gambling disorder (GD) is the first nonsubstance disorder classified by the American Psychiatric Association in the *Diagnostic and Statistical Manual of Mental Disorders, 5th Edition: DSM-5* in the category of "Substance-Related and Addictive Disorders." Both D2 and μ opioid receptors are implicated in GD, and opioid antagonists such as naloxone are the most promising drugs of treatment. As with drug abuse, deficits exist in executive functions, decision making, and inhibitory control because of diminished activation of the ventromedial prefrontal cortex control mechanisms.[45] Similarly, fixations, tolerance, and withdrawal also occur. The heritability of pathological gambling, estimated from twin studies, is similar to alcohol and drug abuse. GD also shares genetic vulnerability factors with antisocial behaviors, alcohol dependence, and major depressive disorder, as well as having a 96% comorbidity rate with lifetime psychiatric disorder.

Obsessive and compulsive eating share disruptions in transmitter and hormone systems, which again overlap normal systems for food reward and the disordered systems associated with drug reward.[46] Chocolate cravers show greater activation in many reward areas which are also activated in drug craving. Dopamine release in the NAc varies as a function of food palatability, and an inverse relationship has been reported between D2 receptors and BMI.[47] One suggestion is that reduced dopamine levels occur in the obese, promoting overeating of highly palatable foods as compensation for reward deficiency. Endocannabinoid and endorphin systems normally interact with the dopamine system to help regulate food intake. Furthermore, chemical signals involved in normal satiety and hunger (i.e., leptin, insulin, ghrelin) not only influence the sensitivity of the brain dopamine system to the rewarding effects of food, but also modulate sensitivity to the rewarding effects of various drugs.[48] The rewarding effects of foods, particularly those rich in fat and sugar, can trigger neuroadaptations in brain reward, stress circuitry, and prefrontal control systems that are similar to those produced by addictive drugs. As stated above, mechanisms which evolved for survival are difficult for most people to control.

Internet gaming disorder is included in the current diagnostic manual, *DSM-5,* under the heading of "Conditions for Further Study." William Struthers presents the case for the addictive properties of internet pornography,[49] but other internet activities such as cybersex, online relations, shopping, and surfing may also be addictive. The findings for all the internet disorders are consistent with neuroimaging and with neurobiological and psychological models of substance disorder.[50] Game-related pictures elicit fMRI activation patterns in both NAc and in the orbitofrontal cortex of heavy-internet-gaming users that are similar to those found in substance abusers. Grey matter reductions in orbitofrontal regions and alterations in the dopamine system have also been reported in excessive internet gaming users.

Genetic and Epigenetic Influences

Genetic variations in the dopamine system have been correlated with substance abuse, obesity, pathological gambling, and several other disorders.[51] Neuroimaging studies show that individuals with lower density of D2 receptors find stimulant drugs more pleasant than those with high density. Nevertheless, not all of these low-density people become addicted, and fully 33% of all people have the allele associated with addiction. One puzzling question is why some users of drugs, alcohol, and tobacco become dependent, but others do not. Exact incidence varies with the type of substance, but only about 10% of individuals using illegal drugs or alcohol become addicted, even though 30%–70% of that risk may be attributable to genetics.[52] As discussed in this issue by Robin Rylaarsdam, because large numbers and combinations of genes, plus epigenetic factors, are implicated, it is difficult to identify specific addiction-related alleles and any one allele may increase a person's risk factor by only a very small percentage.[53]

Genetic coding influences drug risk via two types of mechanisms: (1) the psychoactive effects are influenced by receptors; and (2) the ability to metabolize external substances is controlled by enzymes. Variants of GABA receptors may be implicated in many sorts of addictions, including alcohol. The risk for nicotine addiction is increased by numerous polymorphisms in the genes that encode the various nicotinic receptor subunits. Genetic variants of the μ opioid receptor have been found which modulate the effectiveness of the opioid antagonist naltrexone and which are also associated with relapse of alcohol abuse.[54] Regarding the second mechanism, a protective factor against alcohol abuse is provided by those variants of the genes for alcohol dehydrogenase and acetaldehyde dehydrogenase, which result in unpleasant side effects, as Rylaarsdam notes. Nicotine addiction is also affected by variants of genes for the enzyme that breaks down nicotine in the liver.

The term "Reward Deficiency Syndrome" (RDS) was coined in 1996 to suggest that genetic differences in the dopamine receptor system might be involved in addiction and impulsive disorders.[55] Carriers of the A1 allele of the D2 receptor gene have 30%–40% fewer D2 receptors available for dopamine signaling. Dysfunction in the dopamine receptor system has been associated with several disorders, including alcohol and substance abuse, obesity, and pathological gambling. Neuroimaging studies show that individuals with lower density of D2 receptors find stimulant drugs more pleasant than those with high density, perhaps due to increased sensitivity caused by fewer receptor sites. Individuals with alcohol-use disorders have reduced levels of D2 receptors in the NAc region, but the causal genetic relationship is not clear. Because D2 receptor levels are also affected by stress (and in monkeys by stress-associated social hierarchies), D2 levels influencing the predisposition to drug use could be epigenetically influenced by environmental factors.[56] However, the recurring theme of reduced dopamine activation may explain why most abusers of alcohol have another substance use disorder: at least one-half use tobacco; and one-third, other drugs.[57] Clearly the vulnerability to substance abuse is polygenic and influenced by the environment; nevertheless, understanding of genetic variations may someday provide useful tools for treatment strategies.

Neuroplasticity in Emotion and Control Circuits: Dividing of the Will?

The concept of divided will introduced by Augustine addresses Paul's dilemma in Romans 7:18. As Augustine states it,

> This partial willing and partial non-willing is thus not so bizarre, but a sickness of the mind, which cannot rise with its whole self on the wings of truth because it is heavily burdened by habit. There are two wills, then, and neither is the whole: what one has the other lacks.[58]

This passage from his *Confessions* echoes the common experience of addicted persons so aptly described as burdened by habit that they often want, but do not want, a drug or behavior. "Wanting" something and "liking" it are not the same, but this is only one example of dual-process thinking. The concept of the divided mind has been popularized by Daniel Kahneman in *Thinking, Fast and Slow* which characterizes two brain systems: one—unconscious, instinctive, and emotional; and the other—conscious, logical, and deliberative.[59] Both systems are necessary for normal adult thought, but, in certain situations, the rapid unconscious system gives rise to thought habits which become difficult to break. This insight from Kahneman suggests a useful way to think about addiction in terms of habit driven by unconscious systems.

Repeated use of addictive substances eventually restructures the synaptic pathways from the NAc and VTA, causing an increase in the number of stimulated dendrites, while other usual reinforcers come to stimulate fewer dendrites.[60] The incentive salience system of the NAc can motivate for short-term, but not long-term goals. As attention becomes more narrowly focused on the drug, long-term changes occur in motivation, emotion, and executive control. Due to physiological adaptation to the high levels of dopamine, chronic use of a drug often leads to a decrease in the subjective feeling of pleasure, and increasingly greater amounts are necessary to produce the same "high." Eventually substance abusers try to avoid the distress, irritability, and restlessness of the decreased dopamine release by compulsive pursuit of the substance. Thus changes in motivation are accompanied by changes in emotional mechanisms. The memory of substance reinforcement also decreases activity in the frontal cortical executive circuits that normally

provide inhibitory control over all adult behavior and allow adults to consciously make wise decisions. Whenever frontal cortex is damaged or its output decreased, the ability to voluntarily regulate behavior becomes impaired. Behavioral control shifts from the prefrontal areas involved in conscious decisions to the dorsal striatum, which is involved in habitual motor patterns.[61]

Allostatic dysregulation of the reward circuits, along with the recruitment of stress responses, gives rise to addiction through a shift from *impulsive* action learned via the mechanisms of positive reinforcement, to *compulsive* action learned through either negative reinforcement or habit formation.[62] The initial bursts of dopamine during intoxication cause positive reinforcement, which eventually leads to learning drug cues. The normal molecular basis of learning is based on the repeated activation of synapses, leading to increased efficacy due to long-term facilitation in synapses and dendrites. These normal mechanisms of learning allow cues associated with the drug or behavior to become conditioned and behavioral habits to form.

Following chronic drug use, epigenetic changes occur in gene expression in the NAc, causing increased activation of the gene that codes for dynorphin.[63] Unlike other endogenous opiates, dynorphin inhibits the VTA and further dopamine release, and it also facilitates anxiety-like states. The VTA then activates the amygdala (associated with fear) leading to negative emotions, activates stress systems, and decreases sensitivity to natural rewards. Hormones, such as cortisol, that enhance stress responses are released; and the heightened feeling of stress facilitates craving and relapse. Chronic use decreases subjective reward and often leads to tolerance due to adaptation to increased dopamine, necessitating greater amounts of the drug to produce the usual "high." This sensitization to stress is referred to as the "dark side" of addiction because individuals become focused on compulsively seeking more of the drug to prevent withdrawal and irritability. "Wanting" now occurs in the absence of "liking." Eventually longer-term epigenetic changes occur in the brain. Dynorphin then comes to be suppressed during abstinence, and sensitivity returns to the reward path. This new sensitization means that less drug is now needed to activate the mechanisms of "wanting." These epigenetic changes can remain for months.[64]

Depressive disorders and compulsive running also involve similar epigenetic changes. The processing of cue salience and the ability to exert self-control both require dopamine release and the presence of receptors in the prefrontal cortex; however, neuroimaging shows reduced dopamine activity in this area in addicts due to reduction in D2 receptors (with the exception of cannabis users).[65] Due to impaired prefrontal control, the ability to inhibit risky behaviors and delay reward is reduced, and flexibility in making further choices is impaired. This sensitization to drug cues can also cause craving in abstinent former users. Cues associated with the drug, such as paraphernalia, places, and people, increase anticipatory activity in the sensitized NAc and related areas and reinstate craving. This mechanism helps explain the increased risk of overdose death when a former addict suddenly uses their previously accustomed dose.

Emotional and motivational systems that evolved to promote survival are difficult to control with conscious effort. Marc Lewis has provided a developmental-learning model of addiction which attempts to bridge the gap between the false dichotomy of disease and choice models.[66] Habits form as activity in the NAc restructures and over time strengthens activity in the dorsal striatum (motor program area) and amygdala (emotion center). Axons normally grow from the ventral striatal area of NAc to the dorsal striatum as habits form.[67] Automatization of habits frees up cognitive processes for other things, allowing us to drive and talk at the same time. This shift in activation also occurs when an addiction forms. The repetitive strengthening of this pathway over time can lead to habits of drug use and eventually to compulsion similar to obsessive-compulsive disorder (OCD)—which primarily involves the dorsal striatum—as attention becomes modified by drug use and focused on drug cues.[68] At the same time, the executive control pathways from the prefrontal cortex become disengaged. These well-researched brain changes lead many researchers to classify addiction as a disease, but Lewis, a developmental neuropsychologist, sees it as an extreme form of processes normally used in learning.

These normal modifications of the brain are reversible, leaving open the possibility of unlearning if new habits are formed. Furthermore, as in OCD, these changes occur in pathways below consciousness,

causing them to seem irrational even to the addict. Augustine wrote of his struggle, "Any sort of habit is bondage."[69] Lewis contends that brain changes are normal rather than genetically preprogrammed and depend on feedback from the environment. The mutually reinforcing repetitions of certain behaviors, especially during childhood, also play a role in the development of anxiety and depression. And the brain self-organizes as learning occurs and as habits emerge.

Animals, children, addicts, and those with damaged prefrontal connectivity find delaying rewards difficult because they have less executive control over the dorsal striatum from the prefrontal cortex than do normal human adults. Adolescence is a time of brain reorganization during which the prefrontal areas are last to develop all their connections. The NAc, amygdala, and dorsal striatum develop earlier than prefrontal areas; this leads to imbalances in activation during adolescent development.[70] Dopaminergic axons continue to grow from the striatum to the prefrontal cortex during adolescence, and target choice appears to be malleable.[71] Top-down regulation of these striatal areas increases as the frontal cortex develops. The result of this temporary imbalance is that adolescents have even less top-down control of the lower areas associated with emotion, reward, and habit than younger children, leaving them especially vulnerable to the effects of addictive drugs.

Psychological Factors

The neurophysiological and genetic data help explain why addiction is so difficult to treat; however, we are not fully determined mechanisms, and so other factors must be considered. A study of over 12,000 individuals reported probability estimates of life-time remission from dependence at 84% for nicotine, 91% for alcohol, 97% for cannabis, and 99% for cocaine.[72] Median time to remittance was 26 years for nicotine, 14 for alcohol, 6 for cannabis, and 5 for cocaine. Although we can describe many risk factors, including age, gender, ethnicity, education, and presence of personality disorders that affect risk, nevertheless, addiction is not usually life-long. Most Viet Nam vets who used drugs (about 90%) stopped after their return. The dopamine receptors influencing predisposition to drug use are likely controlled not only by genetic factors, but also by environmental factors, including social stress.[73]

It has long been known that early environment plays a role even in the development of morphine self-administration in animals.[74] Childhood trauma and neglect have been shown to affect the course of neurological development of the brain as the circuits involved in reward anticipation and emotional regulation are changed.[75] The final configuration of the mammalian brain is due to sculpting by experience during development and is particularly malleable during periods of neural development. Childhood patterns of personality development become entrenched due to neuronal plasticity and can underlie depression and anxiety disorders.[76]

In a review of the effects of maltreatment and maternal deprivation on the brain, developmental neuropsychiatrist Martin Teicher asserts, "Maltreatment-related childhood adversity is the leading preventable risk factor for mental illness and substance abuse."[77] Maltreatment alters brain development and affects the structure of prefrontal and orbitofrontal cortical areas, amygdala, and hippocampus which are involved in, among other things, emotional regulation and anticipation of rewards—things that are crucial for avoiding addiction. It is also associated with reduced response to anticipated rewards in parts of the striatum, perhaps leading to enhanced risk for addiction.

The well-known research by John Bowlby and Mary Ainsworth, dating from the 1950s, showed that in order to thrive infants must not only be fed, but must also be in an emotionally satisfying, nurturing relationship with a stable caregiver in order to develop emotional regulation.[78] Addiction could thus be seen as an attachment disorder with attempts at self-repair in traumatized individuals.[79] Self-medication may thus represent an adaption to uncontrollable environmental factors that leads to loss of stability, loss of relationships, and loss of self. The basic circuitry for romantic love and attachment, which is evolutionarily prepared for survival of the species, includes and overlaps the circuitry co-opted by drugs, particularly opiates; and dopamine is also a major contributor to pair bonding in animals. Augustine, too, according to his own account in *Confessions,* suffered childhood abuse.

In order to fully understand the addiction crisis, individual stress and trauma must also be located in a wider social context. Peer use is one of the strongest

predictors for adolescent use of alcohol. According to addiction specialist Gabor Maté, adolescents whose primary relationships are with peers do not easily learn emotional attunement with others because their peers are equally emotionally immature and cannot model appropriate emotional control. A child's lack of emotional attunement with her caregiver is exacerbated by the lack of support given to the mother by the extended family, tribe, or community. Sociologist Peter Berger claims society, created by humans, acts back on human creators who then become the objectified products of society, often losing individual identity in the process.[80] This entails a form of self-objectification that forces individuals to construct their own identity. As the framework of tradition and the support of known community are diminished in modern society, individuals become isolated from their traditional base and social roles.[81] The mechanisms of social dislocation foster addiction as families are uprooted, and people turn inward because they no longer feel connected.[82] Socioeconomic status in humans and animals has been correlated with D2/D3 receptor availability in the striatum; and, as seen above, density of these receptors is lower in addicted humans, although the causal relationship here is unclear.[83]

When given a choice between cocaine and food, or cocaine and sweetened water or milk, most primates and rats choose the tasty substance, even when it is nonnutritive.[84] Self-administration by animals in bare cages pressing levers for intravenous drugs might, in fact, be partly a function of boredom and lack of choice. While boredom and loneliness are common in dislocated individuals, the greater problem in modern culture is loss of meaning. Psychiatrist Viktor Frankl asserted in 1946 that addiction along with depression and aggression are due to a feeling of emptiness and meaninglessness he called the "existential vacuum."[85] External substances provide focus and identity for individuals who lack self-identity and a sense of control over their otherwise uncontrollable lives. While social conditions are not responsible for addiction in any one individual, they lower the playing field for all, and the vulnerable succumb as they seek to temporarily fill the excruciating void.

Social and Cultural Factors

Although much of the medical model has been largely confirmed, it does not always take social context into account. The concept of addiction as disease is reified, according to sociologist Robert Granfield, by insisting that individuals are sovereign entities able to make choices apart from cultural context.[86] As he wryly notes, addiction is not an equal opportunity disease; some individuals are more vulnerable than others. Those constrained at the bottom of the social order have less choice to "just say no."

In a historical analysis of addictions, Bruce Alexander argues that prevalence tends to wax and wane, with periods of social chaos, such as the decline of the Greek and Roman empires, characterized by addictive behaviors.[87] Plato argued that the main cause of alcohol abuse in Greece was the structure of society itself. In what Plato called "just societies," addiction is rarely problematic, but in tyrannical societies almost everyone succumbs. Alcoholism, Alexander claims, was also a serious problem in the declining Roman Empire as evidenced by Augustine's description in *Confessions* of his mother's early behavior.

The present period is also a time of social chaos and inequality. The economically depressed regions of the US South and Appalachia are among the most drug-afflicted areas. While not dealing specifically with addiction, J.D. Vance's *Hillbilly Elegy* sheds light on the problems caused by community disruption and dislocation of families.[88] A study on mortality rates in the US shows that rates among white working-class males without tertiary education are unexpectedly rising, while they continue to decrease among better educated males, white females, and nonwhite individuals.[89] The authors of this study assert that the increase is due to alcohol- and drug-related deaths plus suicide—diseases of despair. Indeed, addiction has become a worldwide problem as the UN estimates that 5% of adults worldwide used illicit drugs in 2014, and 29 million suffer from drug use disorders. Alcohol, tobacco, and illicit drug use account for 12% of worldwide mortality.[90]

Technology and consumerism tend to interact in a complexity of ways to produce, sustain, and in turn be supported by substance use. Opiates were advertised and mass marketed in patent medicines in the late nineteenth and early twentieth centuries, allowing them to become acceptable to the public at that time. For example, the evangelical reformer William Wilberforce used the tincture of opium known as laudanum daily for 45 years, ostensibly for stomach pain. The fentanyl crisis is partly iatrogenic

due to physician overprescription of opioid pain medication. Oxycontin makers indulged for profit in fraudulent claims about the nonaddictiveness of their products.[91] Modern advertising is complex, potentially ambiguous, and affects all of us. It is well known that the tobacco industry continued to relentlessly promote cigarettes even after evidence showed them to be addictive. A 1979 report for Reynolds Tobacco discussed industry plans to enlist the venerable sociologist Peter Berger in their campaign against antismoking publicity.[92] In 1991 Berger produced a report, paid for by Philip Morris, in which he appealed to personal liberty to smoke, arguing that antismoking publicity would discourage liberty to smoke, in spite of the known health and social costs of smoking.[93] Arguing in favor of freedom of choice, some politicians continue to speak out against big government regulation of the tobacco industry, but they, in contrast, reject legalization of less-addicting cannabis. The point here is that social, economic, and political factors beyond the control, and sometimes even awareness, of the individual play definite roles in the choice of addictive substance.

Harm reduction policies of providing safe injection sites, needles, Narcan kits, and methadone have been controversial among those who see them as exchanging one opioid for another or as encouraging addicts to continue their habits without consequence. The continued use and development of overdose reversal methods such as naloxone; use and development of methadone and other treatment drugs; and development of alternative medications, including cannabinoids, to relieve pain are supported by Francis Collins and his colleagues at the National Institutes of Health (NIH).[94] Daniel Mallinson, in this issue, presents policy options for both governments and the church in light of both evidence-based science and social ethics.[95] Catholic scholar Irene Pettus points out the harms that overzealous Christian attitudes have inflicted on drug abusers, as well as on those in chronic and terminal pain who cannot access controlled medicines.[96] In her view, churches that hold attitudes of rejecting not only drug users but also harm reduction, have damaged individuals and groups when they ought instead to play a prophetic role, ministering to the marginalized and criminalized. She reminds us that pain-reducing opiates are largely unavailable to non-Western people, even for terminal illness, partly because of policies based on fear of addiction.

Meaning vs. Despair: Restless Hearts

At one time addiction was seen as a moral or spiritual problem, rather than as a physical problem. Addicts were counselled to find moral and spiritual strength to just abstain. Turning aside from the view of universal sinfulness, AA tends to classify the alcoholic as the victim of a disease yet within a framework that has moral and spiritual implications.[97] Not all agree that AA is the most effective form of treatment, but it does work for many, partly because members develop new habits through the support of a strong social network which provides unconditional love and grace no matter how many times they relapse. Of course, support, community, love, and grace are what we should also expect to find within the body of Christ. Social support itself produces natural levels of dopamine, and treatments that provide individuals the slow release of dopamine associated with social support rather than supraphysiologic bursting, do seem to show the greatest promise. In particular, the various 12-step programs that utilize continued social support can be combined with medical treatments and cognitive therapy.[98] Kent Dunnington, in this issue, sees AA as the best recovery regimen because it aims for a humble reconstitution of the self in the face of the challenges of accepting one's own guilt, shame, and failure while building a new identity.[99] Addicts often lack the self-identity needed to trust or invest in their future self. Its development, however, is undercut by guilt, shame, and failure. The admission of powerlessness over alcohol and the need to cast one's self on a higher power reflect how difficult it is for prideful creatures to ask for grace. Dunnington avers that 12-step programs allow addicts to see self-hood as grace received, by learning to the rest in the unconditional love of others.

Nevertheless, AA leads to a theological challenge—one can either recognize the Creator as revealed in Jesus Christ, or define AA's "higher power" as one likes, thereby turning one's life over to an essentially self-created divinity.[100] Acknowledging the present emphasis on widespread behavioral addictions, Linda Mercadante asks if AA's insistence on total abstinence is a new form of effortful Pelagianism. Previously we were all sinners; now we are all diseased. She points out that addiction and sin are fellow travelers, but not to be equated. This conclusion is echoed in this issue by Janet Warren reminding us

that we all do need development of our self-narrative, because we all face difficulty in acceptance of our guilt, shame, and failures.[101]

In *Confessions* Book X, Augustine describes his sexuality, need for love, and need for adulation in terms reminiscent of behavioral addictions. On becoming bishop, he even refused to allow women to enter his residence.[102] He also describes his post-conversion attempts to not enjoy the taste of food or the music of hymns, seemingly replacing his earlier addictions with what psychologist Bruce Alexander considers moralistic obsession. The tendency to merely replace one addiction with another is common, and as stated above, comorbidity is high. Although AA's cofounder Bill Wilson gave up alcoholism, he struggled as a chain smoker until his death from smoking-related emphysema. Alexander opines that Augustine cured his addiction by adopting a different, more preferable and healthier, form of addiction that provided him with both social support and ecstatic experience. A valid question here might be if addiction to religion is possible. Religion can become, like addiction, just another way to gain control of one's life. Dunnington notes that addiction to God is indeed possible if religion is grounded in a desire to control God.[103] True submission recognizes that even our relationship with God is possible only through grace—in thankfully accepting who we are and accepting God's grace.

Paul's dilemma in Romans 7:15–19 illustrates the moral problem of willing to do one thing, but doing the opposite. Morality has to do with actions, right and wrong, whereas spirituality has to do with the intent of the heart and openness to God's action in one's life (Rom. 8:1–8). Rather than a form of controlling life by means of religion, spirituality involves relationship with God. True relationship occurs in freedom rather than self-abnegation, honestly accepting that we are less than what we wish we were. We cannot control our lives or God's opinion of us, but we must accept grace and unconditional love.

Habitual substance abuse changes circuits in the brain and decreases frontal cortical activity because epigenetic changes are fostered by habitual substance abuse. Habit formation provides one of many examples of how the mind and the brain in mutual relationship grow together and shape each other. An addict becomes more and more trapped in a vicious spiral because repetition of a behavior creates pathways in the brain like ruts in an unpaved road. On the other hand, cortical thickness can be physically increased through meditation, and studies have shown that prayer also affects the brain.[104] Thus spiritual disciplines can form habits that enable us to become progressively more of what God intends. As new habits are formed, step by small step, old pathways in the brain become progressively less activated and newer pathways are gradually strengthened. Functional imaging has shown that rational cognitive strategies that lead to reduction of craving for both food and nicotine can produce activation in the prefrontal-striatal pathway, as well as reduced activation in the ventral striatum.[105] Imaging studies also show that, even though addiction results in loss of grey matter in the frontal cortex, the volume of grey matter in the frontal pathways increases again after months or years of abstinence.[106] The brain is always changing in response to the stimulation it receives. New synaptic growth can allow us to renew our minds. Spiritual disciplines can form new habits. Over time, perhaps, relationship with God may even reverse the neural damage done by abusive relationships with a parent or spouse.

Recovery, however, can be slow because it requires repeated instantaneous decisions to resist craving in spite of competition between the striatal habit system and the frontal control system. The competition for activation will replay again and again, requiring a long series of moment by moment choices. Drugs such as buprenorphine or methadone can make each decision point a little easier by satisfying the ventral striatum's craving mechanism. Each decisive moment of temptation, however, will contain a measure, sometimes very small, of free will with which one can grasp the proffered grace. We must avoid both Pelagian perfectionism of moral responsibility, and Manichean determinism of external factors, while recognizing that we are surrounded at each moment by God's prevenient grace reaching out to enable choices as we reach out in return. Paul's injunction in Romans 12:2 to be transformed by the renewal of the mind is intended for all of us, not just addicts, and it extends by the Spirit's gracious work over our entire lifetime.

Notes

[1]T. Gomes, et al., "The Burden of Opioid-Related Mortality in the United States," *JAMA Network Open* 1, no. 2 (2018): e180217, doi:10.1001/jamanetworkopen.2018.0217.

[2]National Institute on Drug Abuse Blog Team, "Tobacco, Nicotine, & E-Cigarettes," accessed April 20, 2017, https://teens.drugabuse.gov/drug-facts/tobacco-nicotine-e-cigarettes.

[3]World Health Organization, *WHO Report on the Global Tobacco Epidemic: The MPOWER Package* (Geneva: WHO, 2008).

[4]The National Institute on Drug Abuse (NIDA) defines addiction as "characterized by compulsive drug seeking and use, despite harmful consequences." The American Psychiatric Association in *Diagnostic and Statistical Manual of Mental Disorders, 5th Edition: DSM-5* (Arlington, VA: American Psychiatric Association, 2013) refers to "substance use disorders" rather than addiction. See NIDA, "Drug Misuse and Addiction," in *Drugs, Brains, and Behavior: The Science of Addiction*, July 20, 2018, accessed August 22, 2018, https://www.drugabuse.gov/publications/drugs-brains-behavior-science-addiction/drug-abuse-addiction.

[5]The medical model is supported by researchers at NIDA, e.g., Nora D. Volkow, George F. Koob, and A. Thomas McLellan, "Neurobiologic Advances from the Brain Disease Model of Addiction," *New England Journal of Medicine* 374, no. 4 (2016): 363–71; and Nora D. Volkow and George Koob, "Brain Disease Model of Addiction: Why Is It So Controversial?," *Lancet Psychiatry* 2, no. 8 (2015): 677–79. The model is disputed by, e.g., Wayne Hall, Adrian Carter, and Cynthia Forlini, "The Brain Disease Model of Addiction: Is It Supported by the Evidence and Has It Delivered on Its Promises?," *Lancet Psychiatry* 2, no. 1 (2015): 105–10.

[6]For example, Volkow, Koob, and McLellan, "Neurobiologic Advances"; Joseph Frascella et al., "Shared Brain Vulnerabilities Open the Way for Nonsubstance Addictions: Carving Addiction at a New Joint?," *Annals of the N.Y. Academy of Sciences* 1187 (2010): 294–315; and William M. Struthers, *Wired for Intimacy: How Pornography Hijacks the Male Brain* (Downers Grove, IL: InterVarsity Press, 2009).

[7]Kent Dunnington, *Addiction and Virtue: Beyond the Models of Disease and Choice* (Downers Grove, IL: InterVarsity Press, 2011); Bruce K. Alexander, *The Globalization of Addiction: A Study in Poverty of the Spirit* (Oxford, UK: Oxford University Press, 2008); and Gabor Maté, *In the Realm of Hungry Ghosts: Close Encounters with Addictions* (Berkeley, CA: North Atlantic Books, 2010).

[8]Discussed in Judith Toronchuk and George F. R. Ellis, "Affective Neuronal Selection: The Nature of the Primordial Emotion Systems," *Frontiers in Psychology* 3 (2012): article 589.

[9]Nora D. Volkow and Marisela Morales, "The Brain on Drugs: From Reward to Addiction," *Cell* 162, no. 4 (August 13, 2015): 712–25, http://dx.doi.org/10.1016/j.cell.2015.07.046.

[10]David J. Nutt et al., "The Dopamine Theory of Addiction: 40 Years of Highs and Lows," *Nature Reviews Neuroscience* 16, no. 5 (2015): 304–12; and Aldo Badiani et al., "Addiction Research and Theory: A Commentary on the Surgeon General's Report on Alcohol, Drugs, and Health," *Addiction Biology* 23 (January 23, 2018): 3–5.

[11]Neurotransmitter receptors are proteins embedded in neural membranes to which transmitters briefly bind. Transporters are embedded proteins which actively move transmitters across membranes.

[12]Kent C. Berridge and Terry E. Robinson, "Parsing Reward," *TRENDS in Neurosciences* 26, no. 9 (2003): 507–13.

[13]Nora D. Volkow, Joanna S. Fowler, and Gene-Jack Wang, "The Addicted Human Brain: Insights from Imaging Studies," *The Journal of Clinical Investigation* 111, no. 10 (2003): 1444–51.

[14]Volkow and Morales, "Brain on Drugs."

[15]MDMA ("Ecstasy" or "Molly") has properties similar to both methamphetamines and hallucinogens. "Bath salts" are synthetic cathinones (found in the khat plant) with stimulant properties.

[16]R. Christopher Pierce and Vidhya Kumaresan, "The Mesolimbic Dopamine System: The Final Common Pathway for the Reinforcing Effect of Drugs of Abuse?," *Neuroscience and Biobehavioral Reviews* 30, no. 2 (2006): 215–38.

[17]GABA stands for γ-amino butyric acid, the most common inhibitory transmitter in the brain. It binds with two basic types of receptors, $GABA_A$ and $GABA_B$.

[18]Nutt et al., "The Dopamine Theory"; and Badiani et al., "Addiction Research and Theory."

[19]Dopamine has at least five types of receptors (D1 to D5) with somewhat different properties.

[20]Volkow and Morales, "Brain on Drugs."

[21]The actual effect of opioids on the dopamine system is still somewhat disputed according to Badiani et al., "Addiction Research and Theory."

[22]The dorsal raphe is involved in emotion, perhaps linking addiction and mood. Glutamate is the most common excitatory transmitter in the brain.

[23]Serotonin (5-HT) has at least sixteen subtypes of receptor.

[24]This material is reviewed in Pierce and Kumaresan, "The Mesolimbic Dopamine System."

[25]NIDA, "Prescription Opioids and Heroin," National Institute on Drug Abuse website, posted January 17, 2018, accessed April 9, 2018, https://www.drugabuse.gov/publications/research-reports/relationship-between-prescription-drug-heroin-abuse/prescription-opioid-use-risk-factor-heroin-use; and Francis S. Collins, Walter J. Koroshetz, and Nora D. Volkow, "Helping to End Addiction Over the Long-Term: The Research Plan for the NIH HEAL Initiative," *Journal of the American Medical Association* 320, no. 2 (2018): 129–30, doi:10.1001/jama.2018.8826.

[26]U.S. Department of Justice, Drug Enforcement Administration, "2016 National Drug Threat Assessment Summary," November 2016, 65–70, https://www.dea.gov/sites/default/files/2018-07/DIR-001-17_2016_NDTA_Summary.pdf.

[27]CBC News, "More Than 1,420 People Died of Illicit-Drug Overdoses in B.C. in 2017, The 'Most Tragic Year Ever': Coroner," posted January 31, 2018, accessed March 25, 2018, http://www.cbc.ca/news/canada/british-columbia/overdose-deaths-bc-2017-1.4511918.

[28]There are three basic types of opioid receptors: μ, κ, and δ. κ receptors in NAc bind with endogenous dynorphin and play a role in withdrawal as discussed below. Opioid antagonists such as naltrexone are somewhat effective in reducing both alcohol and nicotine use, confirming the involvement of opioid receptors in the rewarding effect of these drugs.

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[32]Linda Spear, "Effects of Adolescent Alcohol Consumption on the Brain and Behavior," *Nature Reviews Neuroscience* 19, no. 4 (2018): 197–214.
[33]See H. Valerie Curran et al., "Keep Off the Grass? Cannabis, Cognition and Addiction," *Nature Reviews Neuroscience* 17, no. 5 (2016): 293–306 for review of the research literature.
[34]M. Colizzia et al., "Effect of Cannabis on Glutamate Signalling in the Brain: A Systematic Review of Human and Animal Evidence," *Neuroscience and Biobehavioral Reviews* 64 (2017): 359–81.
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[41]Fernando Berrendero et al., "Neurobiological Mechanisms Involved in Nicotine Dependence and Reward: Participation of the Endogenous Opioid System," *Neuroscience and Biobehavioral Reviews* 35, no. 2 (2010): 220–31; Shiroh Kishioka et al., "Nicotine Effects and the Endogenous Opioid System," *Journal of Pharmacological Science* 125 (2014): 117–24; and Nestler et al., eds., *Molecular Neuropharmacology*, 385–86.
[42]Dynorphin is an endogenous opiate that binds to κ opiate receptors and is hypothesized to mediate negative emotional states.
[43]See Frascella et al., "Shared Brain Vulnerablities."
[44]Toronchuk and Ellis, "Affective Neuronal Selection."
[45]Reviewed in Daniela S. S. Lobo and James L. Kennedy, "Genetic Aspects of Pathological Gambling: A Complex Disorder with Shared Genetic Vulnerabilities," *Addiction* 104, no. 9 (2009): 1454–65.
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[52]Eric Nestler, "Cellular Basis of Memory for Addiction," *Dialogues in Clinical Neuroscience* 15, no. 4 (2013): 431–43.
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[57]Connor, Habor, and Hall, "Alcohol Use Disorders."
[58]Augustine, *The Confessions*, Part 1, Vol. 1, ed. John E. Rotelle, O.S.A. (New York: New City Press, 1997), Book VIII.9.21, 201.
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