Addiction: diseased brain, divided will, or restless heart?

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Editor's Note

Judith Toronchuk (PhD McGill) teaches physiological psychology for Trinity Western University. She has published on affective neuronal selection and both the phylogeny and ontogeny of affective social behaviour. She describes for us here the latest developments and challenges in the science of addiction for our society and Christian faith. That focus calls for our attention with opioid, marijuana, nicotine, gambling, porn, and alcohol addictions staggering our society. Toronchuk's essay is intended as an invitation. Readers are encouraged to take up one of the insights or questions, or maybe a related one that was not mentioned, and draft an article (typically about 5,000-8,000 words) that contributes to the conversation. These can be sent to Dr. Toronchuk at toronchu@twu.ca . She will send the best essays on to peer review and then we will select from those for publication in an Addiction theme issue of *Perspectives on Science and Christian Faith*. The lead editorial in the December 2013 issue of *PSCF* outlines what the journal looks for in article contributions. For best consideration for inclusion in the theme issue, manuscripts should be received electronically before 31 October 2017.

Looking forward to hearing your perspectives,

James C. Peterson
Editor of *Perspectives on Science and Christian Faith*

Fentanyl is so deadly that funeral directors in the Vancouver area are advised to carry the antidote naloxone (Narcan) because of OD risk just from handling victims.[1] Just 2 mg of this synthetic opioid can be lethal. In 2016 in British Columbia 922 people died of drug overdose (60% from fentanyl)[2] leading Canada's Health Minister to declare this epidemic the nation's greatest public health crisis.[3] In one year deaths from overdose have nearly doubled and now account for three times those of vehicular accidents.[4] The fentanyl crisis is in a way iatrogenic due to physician overprescription of opioid pain medication. When prescriptions run out or are limited, users often turn to cheaper illicit drugs such as heroin. On the street fentanyl is even cheaper and users are often unaware that what they buy as heroin or oxycondone to smoke, snort or inject is substantially fentanyl.[5] As of Jan. 2017 fentanyl's analogue carfentanil, a sedative for

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1 http://vancouversun.com/health/local-health/fentanyl-funeral Retrieved Jan. 23, 2017.

2 British Columbia Coroner's Service, "Illicit Drug Overdose Deaths in BC" Posted Feb. 17, 2017 at http://www2.gov.bc.ca/assets/gov/public-safety-and-emergency-services/death-investigation/statistical/illicit-drug.pdf.

3 www.theglobeandmail.com/news/national/canada-seeks-warnings-on-opioids-amid-rising-deaths/article33700593/ Retrieved Jan. 23, 2017.

4 www.cbc.ca/news/canada/british-columbia/a-year-of-overdoses-7-charts-that-show-the-scope-of-b-c-s-drug-crisis-1.3910246 Retrieved Jan. 23, 2017.

5 US Justice Dept., Drug Enforcement Administration "National Drug Threat Assessment Summary" Nov 2016: 65-70.

bison and elephants, has also been appearing on Vancouver's streets.[6] As little as 20 micrograms can be fatal to a human.

In the US opioid overdose deaths due to fentanyl and prescription drugs have also skyrocketed. Drug poisoning deaths in the US are now at their highest recorded level outnumbering deaths by firearms, motor vehicle crashes, suicide, and homicide.[7] Overdose from controlled prescription opioids (mostly hydrocodone and oxycodone) account for 52 deaths per day.[8] Second only to marijuana use, prescription opioid use is greater than that of cocaine, heroin and methamphetamine combined. Healthcare costs in the US for prescription drug abuse are estimated at over $25 billion annually plus $25.5 billion in lost productivity.[9] Startling as these statistics are, the CDC reports that tobacco use remains the leading preventable cause of disease, disability, and death in the US—contributing to 1 in every 5 deaths.[10] Alcohol use disorders are among the most common mental disorders with 36% of adult males in the US meeting the criteria for disorder at some time in their lives.[11] Alcohol, tobacco and illicit drug use account for 12% of worldwide mortality.[12] Meanwhile new synthetic drugs are being rapidly designed; e.g. the use of "spice", a potentially lethal synthetic cannabinoid has reached epidemic proportions in parts of the UK.[13]

One of the strengths of *Perspectives* is gathering together authors and readers from multiple disciplines to tackle questions that are far more complex than any one of us can address. In the following pages, without assuming readers have a background in this area, I will introduce what we know of addiction at the neuroscience level, with particular emphasis on the disordered findings in the brain. I will then raise some questions about our understanding of the physical, psychological and spiritual aspects of addiction and how we as individuals and a society might react. My intention is that this essay will trigger both responses to those questions, as well as

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6 www.cbc.ca/news/canada/british-columbia/carfentanil-confirmed-metro-vancouver-1.3962548 Retrieved March 13, 2017.

7 DEA, "National Drug Threat" *v.*

8 Ibid., 25.

9 Ibid., 38.

10 National Institute on Drug Abuse Blog Team. Tobacco, Nicotine, & E-Cigarettes Retrieved from https://teens.drugabuse.gov/drug-facts/tobacco-nicotine-e-cigarettes on April 20, 2017.

11 Reviewed in J.P. Connor, P.S. Haber and W.D.Hall, "Alcohol Use Disorders," *Lancet* 387 (2016) 988-998.

12 UN Office on Drugs and Crime *World Drug Report* (Vienna: UN, 2016) estimates 5% of adults worldwide used illicit drugs in 2014 and 29 million suffer from drug use disorders.

13 www.dailymail.co.uk/news/article-4302806/Spice-synthetic-drug-turns-users-living-dead.html Retrieved March 13, 2017.

generate other questions that I have not thought to ask, allowing us to integrate insights from biological, psychological and theological perspectives.

The disease model currently favored by neuroscientists states that substance and behavioral addictions are recurring disorders of the brain originating in genetic components and/or brain developmental changes.[14] 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 instead the centrality of psychosocial and environmental factors as well as spiritual and moral origins.[15] An integrated physical, psychological and spiritual approach will be required to deal with the spectrum of behaviors — from substance use to compulsive internet porn and gaming — now identified as having underlying neural properties.[16]

Motivational Mechanisms

Addictions[17] arise when the motivation, emotional and executive control systems of the brain which are necessary for survival become hijacked by external factors. Genes, protein expression, neuronal circuits, neurodevelopment, individual behaviors, and societal conditions all interact to produce both normal and disordered desires, however, the common mechanism involves increased sensitivity to the neurotransmitter dopamine (DA).[18] The ability to learn and repeat behaviors that result in food, drink and successful social encounters depends on the mesolimbic

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[14] The medical model is supported by Volkow and others at NIDA. See Volkow *et al.*, "Neurobiologic Advances"; and N.D. Volkow and G. Koob, "Brain Disease Model of Addiction: Why is it so Controversial?" *Lancet Psychiatry* no.2 (2015): 677-679. The model is disputed by W.D. Hall, A. Carter and C. Forlini, "The Brain Disease Model of Addiction: Is it Supported by the Evidence and has it Delivered on its Promises?" *Lancet Psychiatry* 2 (2015):105–10.

[15] A Christian view is provided by Ken Dunnington *Addiction and Virtue: Beyond the Models of Disease and Choice.* (Downer's Grove: IVP, 2011). Some other possible perspectives are provided by B. K. Alexander, *The Globalization of Addiction: A Study in Poverty of the Spirit*. (Oxford, UK: Oxford University Press, 2008); Gabor Maté, *In the Realm of Hungry Ghosts: Close Encounters with Addictions* (Berkeley: North Atlantic Books, 2010).

[16] See for example: N.D. Volkow, G.F. Koob, A.T. McLellan, "Neurobiologic Advances from the Brain Disease Model of Addiction," *New England Journal of Medicine* 374 (2016):363-71; J. Frascella, M.N. Potenza, L.L. Brown and A.R. Childress, "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; W. M. Struthers, *Wired for Intimacy: How Pornography Hijacks the Male Brain.* (Downer's Grove: IVP, 2009).

[17] The National Institute on Drug Abuse (NIDA) defines addiction as "characterized by compulsive drug seeking and use, despite harmful consequences." The DSM5 used by clinicians refers to "substance use disorders" rather than addiction. NIDA (2016). Media Guide. Accessed Feb. 22, 2017 at www.drugabuse.gov/publications/media-guide. Many sources no longer consider tolerance, or withdrawal to be integral to addiction. See E.J. Nestler, S.E. Hyman, D.M. Holzman and R.C. Malenka, *Molecular Neuropharmacology: A Foundation for Clinical Neuroscience* 3rd ed. (New York: McGraw-Hill Medical, 2015) 380, 381.

[18] This occurs specifically in the nucleus accumbens (NAc), a sub-cortical forebrain structure coding for salience of rewards and their cues.

dopamine system which extends from the ventral tegmental area (VTA), where dopaminergic neurons originate, to the nucleus accumbens (NAc) and the orbitofrontal cortex, as well as other limbic structures.[19] This pathway was first associated with reward in 1954 when my thesis advisor Peter Milner discovered that rats will press a lever up to 2000 times per hour to receive electrical stimulation there.[20] Although many pleasurable behaviors including eating, drinking, listening to relaxing music, social and sexual interactions are accompanied by dopamine release, the early idea of a brain *pleasure* center located in NAc turned out to be too simplistic. More precisely DA release here flags an event as worth attending to and the cues associated with it worth *learning*. Reward has both "wanting" and "liking" components because, as addicts come to realize, one can "want"something that one does not really "like". Thus dopamine (DA) release in NAc produces "wanting" by focussing attention on the associated stimuli.[21] At the same time the memory of reinforcement decreases activity in the cortical executive circuits which normally provide inhibitory behavioral control.[22] The most recent hypothesis is that DA release is time-locked to unexpected or novel stimuli and acts as a reward prediction signal.[23]

Psychostimulants, opiates, ethanol, cannabinoids and nicotine all either directly or indirectly produce bursts of dopamine release in the NAc 3 to 5 times greater than normal reinforcers.[24] In order to understand the processes giving rise to reinforcement we will first describe the basic mesolimbic DA response to psychostimulants such as cocaine, methamphetamine, MDMA and "bath salts"[25] which directly affect the NAc. The increased bursting activity produced by psychostimulant drugs is on its own necessary and sufficient to promote reinforcement directly. Additional dopamine-independent processes, reviewed below, are needed to indirectly activate the DA response to the presence of opiates, ethanol, cannabinoids and nicotine.[26]

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[19] The VTA is located in the ventral midbrain; prefrontal cortex participates in valuation of motivational goals and cognitive control of behavior. See Nestler *et al.*, *Neuropharmacology,* 152, 159, 382 for a fuller description of the pathway.

[20] J. Olds and P.M. Milner, "Positive Reinforcement Produced by Electrical Stimulation of Septal Area and Other Regions of Rat Brain," *Journal of Comparative & Physiological Psychology* 47(1954): 419-427.

[21] K. C. Berridge and T. E. Robinson, "Parsing Reward," *TRENDS in Neurosciences* 26 (2003):507-513.

[22] N.D. Volkow, J.S. Fowler and G.-J. Wang, "The Addicted Human Brain: Insights from Imaging Studies," *The Journal of Clinical Investigation* 111 (2003):1444-1451.

[23] N.D. Volkow and M. Morales, "The Brain on Drugs: From Reward to Addiction," *Cell* 162 (2015): 712-725.

[24] Ibid.

[25] 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.

[26] R. C. Pierce and V. Kumaressan, "The Mesolimbic Dopamine System: The Final Common Pathway for the Reinforcing Effect of Drugs of Abuse?" *Neuroscience and Biobehavioral Reviews* 30 (2006): 215-238.

The VTA receives reciprocal innervation from widespread limbic areas involved in memory, emotion, attention and motivation. 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.[27] 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 DA available in the synapse to stimulate the postsynaptic cell is increased. Slow, longer lasting release of DA stimulates the higher affinity D2 receptors which sustain motivation. Large supraphysiologic bursts of DA stimulate the lower affinity D1 receptors[28] signalling reward and drug "highs".[29] Most cells in NAc also receive multiple inputs regarding stimulus salience from many limbic areas via dopamine, glutamate, endocannabinoids and other inputs. Conditioning to salient cues can be induced by DA bursts large enough to activate the D1 receptors. Stimuli associated with the drug thus become conditioned and eventually these stimuli trigger phasic release of DA from the VTA.[30]

Although DA accounts for the direct reinforcement effect of all substances of abuse, several complex factors control the release of DA by the VTA neurons which are themselves normally under tonic inhibition due to the transmitter GABA.[31] The timing of DA bursts is likely controlled by VTA local interneurons and other GABA-releasing axons from those ventral brain regions involved in evaluation of rewards, attention, arousal and memory.[32] The release of DA is increased by glutamate released in the VTA by dorsal raphe cells.[33] Serotonin (5-HT) from dorsal raphe cells plays a lesser but more complex role. One type of serotonin receptor[34] (5HT2C) in the VTA seems to decrease stimulant-induced reinforcement, while another (5HT1B) indirectly increases DA release by disinhibition of $GABA_A$ receptors.[35] Endogenous opioids (including endorphins) and endogenous cannabinoids (endocannabinoids) also interact in complex ways

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

[28] Dopamine has at least 5 types of receptors labeled D1 to D5, which produce different molecular effects.

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

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

[31] GABA stands for γ-amino butyric acid, the most common inhibitory transmitter in the brain. It binds with 2 basic types of receptors, $GABA_A$ and $GABA_B$.

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

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

[34] Serotonin (5-HT) has at least 16 subtypes of receptor.

[35] This material is reviewed in Pierce and Kumaresan, "Final Common Pathway".

with the DA 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.

Opiate drugs, including the synthetics heroin and fentanyl, and semi-synthetics such as oxycodone (Oxycontin), are direct opioid receptor agonists. They work by mimicking the effects of the neuromodulatory endogenous opioids, specifically endorphins and enkephalins which bind to μ opioid receptors[36]. Reinforcing effects are mostly due to activation of these μ receptors which are plentiful in both VTA and NAc. One effect of μ receptor stimulation is to inhibit GABAergic neurons in the VTA which in turn disinhibits DA release in the NAc. Opioid drugs also stimulate the NAc directly via receptors on the NAc cells. Naturally occurring endorphins decrease sensitivity to pain, increase relaxation, and cause drowsiness by blocking the brainstem area (locus coeruleus) which responds to arousing stimuli.

Ethanol has widespread complex pharmacological effects, although the mesolimbic DA system is the major contributor to the rewarding effects. Ethanol also has complex interactions with GABA, serotonin (5HT), endorphins, endocannabinoids, glutamate and nicotinic receptors. In low doses ethanol interacts with a subset of $GABA_A$ receptors on inhibitory interneurons which control VTA cells, resulting in increased release of DA. In higher doses it can decrease K+ currents at $GABA_B$ receptors on VTA cells causing disinhibition which further increases DA release.[37] 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. Blocking certain receptors for glutamate[38] contributes to these inhibitory effects. Stress-related circuits including those of corticotropin-releasing hormone (CRH) and neuropeptide Y are also eventually affected contributing to the adverse effects of ethanol withdrawal by producing anxiety and depression. Recent evidence suggests that direct administration of acetaldehyde, the breakdown product of ethanol, also has a rewarding effect on

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[36] There are 3 basic types of opioid receptor: μ, κ, and δ. κ receptors in NAc bind with the 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.

[37] Pierce and Kumaressan, "Final Common Pathway".

[38] There are several types of glutamate receptor including NMDA, AMPA and kainate. Ethanol blocks NMDA and kainate receptors. The role of NMDA and AMPA receptors in learning is discussed below.

the DA system (via D2 receptors) and activates the stress system by increasing CRH levels which increases cortisol.[39]

The main psychoactive ingredients in cannabis are Δ^9 tetrahydrocannabinol (Δ^9 THC) and cannabidiol (CBD) which mimic the effects of endocannabinoids such as anandamide and 2-AG at endocannabinoid receptor sites.[40] Cannabinoid 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 from VTA interneurons. After prolonged use glutamate-dependent synaptic plasticity which is required for memory encoding can be disrupted and consequently Δ^9 THC impairs learning.[41] It also has psychoactive effects and increases anxiety. On the other hand CBD can facilitate learning and reduce anxiety and when taken together with Δ^9 THC may ameliorate its harmful effects especially on memory. However, the levels of Δ^9 THC in street cannabis has risen 3 fold over the last 20 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 that most users experience.

Endocannabinoids affect neurodevelopment by interacting directly with the glutamate pathways which play a major role in two processes prevalent during adolescence i.e. the development of axonal connections and the process of pruning irrelevant synapses. Adolescent exposure to Δ^9 THC alters the normal maturational fluctuations of glutamate receptors which lead to decreases in DA activity in adulthood and increased levels in stress-related signalling. The hippocampus, involved in long-term memory, has been shown in neuroimaging studies to have decreased volume in regular cannabis users, although the presence of CBD in addition to Δ^9 THC (in hair samples) had an ameliorating effect.[42] Other neuroimaging studies show decreased volume in the

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[39] A. Brancato, G. Lavanco, A. Cavallaro, F. Plescia and C. Cannizzaro, "Acetaldehyde, Motivation and Stress: Behavioral Evidence of an Addictive *ménage à trois,*" *Frontiers in Behavioral Neuroscience* 11 (2017) article 23.

[40] The information on cannabis is reviewed in H. V. Curran, T.P. Freeman, C. Mokrysz, D. A. Lewis, C.J. Morgan and L.H. Parsons, "Keep off the Grass? Cannabis, Cognition and Addiction." *Nature Reviews Neuroscience* 17 (2016):293-306.

[41] See also M. Colizzia, P. McGuirea, R.G. Pertweeb and S. Bhattacharyya, "Effect of Cannabis on Glutamate Signalling in the Brain: A Systematic Review of Human and Animal Evidence" *Neuroscience and Biobehavioral Reviews* 64 (2017): 359-381.

[42] Reviewed in V. Lorenzetti, N. Solowij and M. Yucel, The Role of Cannabinoids in Neuroanatomic Alterations in Cannabis Users" *Biological Psychiatry* April 1, 2016; 79:e17–e31 www.sobp.org/journal.

orbitofrontal cortex.[43]The effects on cognition may therefore be dependent on the maturational state of the brain with adolescents being most vulnerable.[44] Although the addictiveness of marijuana has been debated in the past, the consensus now is that it does have addictive potential. The estimated chance of dependence after first exposure to cannabis is 8.9%, compared with 20.9% for cocaine, 22.7% for alcohol and 67.5% for nicotine.[45]

Nicotine, in spite of 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.[46] It activates HPA axis and can block nociceptive pain. There are at least 12 genetically diverse nicotinic Ach subtypes which bind together in various groups of five distributed throughout the nervous system. Nicotine directly stimulates some of these receptors and depending on the site of action and subtype of receptor alters release of DA, norepinephrine, 5-HT, glutamate, GABA and endogenous opioids.[47] Stimulation of α4β 2 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.[48] The opioid antagonist naltrexone decreases nicotine use, providing further support for the suggestion that endogenous opioids contribute to nicotine reinforcement.

Development of addiction: changes in emotion and control

Addiction involves a shift from impulsive action learned via the mechanisms of positive reinforcement discussed above to compulsive action learned through negative reinforcement via

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[43] F. M. Filbey, S. Aslan, V.D. Calhoun, J.S. Spence, E. Damaraju, A. Caprihan and J. Segall. "Long-term effects of Marijuana Use on the Brain," *Proceeding of the National Academy of Sciences* 111(2014):16913-16918.

[44] Reviewed in Curran *et al.* "Keep off the Grass?" and Lorenzetti The Role of Cannabinoids in Neuroanatomic Alterations in Cannabis Users. *Biological Psychiatry* 79(2016):17-31.

[45] C. Lopez-Quintero, *et al.* "Probability and Predictors of Transition from First Use to Dependence on Nicotine, Alcohol, Cannabis, and Cocaine: Results of the National Epidemiologic Survey on Alcohol and Related Conditions (NESARC)," Drug and Alcohol Dependence. 115(2011): 120–130

[46] Nestler *et al. Neuropharmacology*. p. 378, 385.

[47] F. Berrendero, P. Robledo, J.M. Trigo, E. Martin-Garcia and R. Maldonado, "Neurobiological Mechanisms Involved in Nicotine Dependence and Reward: Participation of the Endogenous Opioid System", Neuroscience and Biobehavioral Reviews 35 (2010):220-231; S. Kishioka, N. Kiguchi, Y. Kobayashi and F. Saika, "Nicotine Effects and the Endogenous Opioid System" *Journal of Pharmacological Science* 125 (2014): 117-124; Nestler *et al. Neuropharmacology*. p. 385, 86.

[48] Dynorphin is an endogenous opiate that binds to κ opiate receptors and is hypothesized to mediate negative emotional states.

dysregulation of the reward circuits and recruitment of stress responses.[49] Thus, in addition to changes in motivation, there are changes in affective mechanisms and ability to regulate behavior. The stages of addiction have been described as 1) binge/intoxication 2) withdrawal/ negative affect and 3) preoccupation/anticipation ("wanting").[50] The initial bursts of DA during intoxication cause positive reinforcement which eventually leads to learning drug cues. The normal molecular basis of learning in the brain is based on the repeated simultaneous activation of NMDA and AMPA glutamate receptors which leads to increased synaptic efficacy due to long-term structural changes in synapses and dendritic spines. One effect is to change the ratio of AMPA to NMDA receptors resulting in increased sensitivity to glutamate. It is through this mechanism (called long-term potentiation) that cues associated with the drug become conditioned.

Epigenetic changes occur in gene expression following chronic drug use due to modulation of gene transcription caused by transcription factors CREB (cAMP response element binding protein) and ΔfosB.[51] Initial use of opiates inhibits the cAMP pathway, which recovers and increases during withdrawal. This upregulation of CREB in the NAc leads to increased activation of the gene which codes for the endogenous opiate dynorphin. Dynorphin inhibits the VTA and with it further DA release, and also facilitates anxiety-like states. Activation of the extended amygdala (associated with fear and negative affect) by the VTA leads to negative emotion, the activation of stress systems and decreased sensitivity to natural rewards. Amygdala activation also produces changes in the HPA system including increased CRF, ACTH and cortisol.[52] Stress responses occur more easily which then facilitates craving and relapse. Chronic use of drugs leads to decreased subjective reward and tolerance to the drug due to adaptation to the high levels of DA. Tolerance necessitates greater amounts of the drug to produce a "high". The altered set-point in the reward system with accompanying sensitization to stress has been called the "dark side" of addiction.[53] To prevent withdrawal and irritability, individuals become focussed on compulsively seeking more of the drug (chronic "wanting").

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[49] G.F. Koob and M. Le Moal, "Addiction and the Brain Antireward System," *Annual Review Psychology* 59 (2008):29-53; N.D. Volkow G.J.Wang, J.S. Fowler, D.Tomasi F. Telang "Addiction: Beyond Dopamine Reward Circuitry" *Proceedings National Academy of Science U.S.A.* 108 (2011):15037-42.

[50] G.F. Koob and N.D. Volkow, "Neurocircuitry of Addiction," *Neuropsychopharmacology Reviews* 35, (2010): 217–238.

[51] Transcription factors control the rate of gene expression.

[52] HPA stands for hypothalamic-pituitary-adrenal axis, CRF for corticotrophin releasing factor which is released by the hypothalamus, and ACTH for adrenocorticotropic hormone released by the pituitary under the control of CRF and which in turn causes release of cortisol from the adrenals.

[53] Koob & Le Moal, "Brain Antireward System".

Build up of the transcription factor ΔfosB in the D1 neurons eventually causes longer-term epigenetic changes. When the expected drug is not forthcoming ΔfosB suppresses dynorphin causing increased sensitivity in the reward path. In contrast to tolerance the result is now sensitization in which less drug is needed to activate the mechanisms of "wanting". Elevated ΔfosB can remain for months acting as a "molecular switch for addiction".[54] The individual becomes focussed on relieving withdrawal rather than experiencing the positive rewarding effect of the drug. "Wanting" now occurs in the absence of "liking". Depressive disorders and compulsive running have also involve accumulation of ΔfosB. The processing of salience attribution and the ability to self-control both require dopamine release and the presence of receptors that will bind to it in the prefrontal cortex. However neuroimaging reveals reduced DA activity in the prefrontal cortex due to reduced density of D2 receptors in addicted individuals (with the exception of cannabis).[55] Due to impaired prefrontal control, the ability to inhibit risky behaviors and delay reward is reduced, and flexibility in making further behavioral choices is impaired.

Risk factors

One puzzling question is why some users of drugs, alcohol and tobacco become dependent but others do not. Although exact incidence varies with the type of substance, only about 10% of individuals using drugs or alcohol become addicted, and 50-70% of that risk is attributable to several genetic factors involving various transmitter systems.[56] As with many mental disorders, a large number of genes and combinations of genes, plus epigenetic factors, are implicated making it difficult to identify specific addiction-related alleles. In addition childhood and adult trauma, adolescent use, and comorbid mental health conditions all increase risk of dependence.[57]

Although vulnerability to substance abuse is polygenic, knowledge of genetic variations may provide useful tools for future treatment strategies. Genetic coding influences drug risk via two types of protein-based mechanisms: the psychoactive effects occur via receptor mechanisms; and the ability to metabolize external substances and clear them from the body is controlled by enzymes. Genetic influences on receptors include various alleles for $GABA_A$ receptors which play a role in many sorts of addictions including alcohol. A protective factor against alcohol

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[54] E.J. Nestler, M. Barrot and D.W. Self, "Delta FosB: a Sustained Molecular Switch for Addiction," *Proceedings of the National Acadademy of Sciences U.S.A.* 98(2001):11042-1146.

[55] N.D. Volkow, J.S. Fowler, and G.-J. Wang "The Addicted Human Brain: Insights from Imaging Studies"J. Clin. Invest. 11:(2003):1444–1451; Volkow and Morales, "Brain on Drugs".

[56] Nestler, "Cellular Basis of Memory for Addiction,"*Dialogues in Clinical Neuroscience* 15 (2013) 431-443.

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

abuse is provided by those variants of the genes for alcohol dehydrogenase and acetaldehyde dehydrogenase which allow build up of acetaldehyde with accompanying unpleasant side effects. The risk for nicotine addiction is increased by numerous polymorphisms in the genes which encode the various nicotinic acetylcholine receptor subunits. Nicotine addiction is also affected by genes for the enzyme that breaks down nicotine in the liver, allowing classification of individuals into slow or fast metabolizers. 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.[58] Research on genetic variations of the CB1 cannabinoid receptor has been inconsistent.

The term "Reward Deficiency Syndrome" (RDS) was coined by Blum and his coworkers in 1996 to suggest that genetic difference in the dopamine receptor system are involved in addiction and impulsive disorders.[59] Carriers of the A1 allele of the D2 receptor gene have 30%–40% fewer D2 receptors available for dopamine signalling. Dysfunction in the DA receptor system has been associated with alcohol use disorders, substance abuse, obesity, pathological gambling and several other disorders. Neuroimaging studies show that individuals with lower density of D2 receptors find stimulant drugs more pleasant than those with high density presumably due to increased sensitivity caused by fewer receptor sites. Individuals with alcohol use disorders have reduced levels of D2 receptors in the NAc region either predisposing to, and/or as a result of, increased ethanol intake. Baseline levels of D2 receptors are also affected by stress and in monkeys by stress-associated social hierarchies. Thus D2 levels influencing the predisposition to drug use could be controlled by both genetic factors and, via epigenetics, by environmental factors.[60] The recurring theme of lowered dopamine action may explain why most abusers of alcohol have another substance use disorder—at least half use tobacco and 1/3 other drugs.[61] In theory measurement of D2 density or genetic markers for D2 receptors could provide a marker for the risk of substance abuse.

Other risk factors for alcohol and other substance abuse disorders are known to include early use, lack of parental monitoring, childhood mood disorders, impulsivity, and living in a culture that encourages drinking to intoxication. Peer use is one of the strongest predictors for adolescent use

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[58] Demers *et al.*, "Pharmacogenetics".

[59] K. Blum, P J Sheridan, R C Wood, E R Braverman, *et al.*, "The D2 dopamine Receptor Gene as a Determinant of Reward Deficiency Syndrome" *Journal of the Royal Society of Medicine* 89(1996); K. Blum, A.L.C. Chen, J. Giordano, J. Borsten, T.J.H.Chen, M. Hauser, *et al.* "The Addictive brain: All Roads Lead to Dopamine," *Journal of Psychoactive Drugs* 44 (2012): 134–143.

[60] Volkow and Morales, "Brain on Drugs"

[61] Connor *et al*., "Alcohol Use Disorders".

of alcohol. It has long been known that early environment plays a role even in the development of morphine self-administration in animals.[62]

Behavioral Addictions

The neurophysiological mechanisms for uncontrolled gambling, internet use, gaming, pornography and sexual acting out are largely the same as those elicited in psychoactive substance abuse. Obesity, overeating, and compulsive shopping are now also being researched along these lines.[63] Many of these behavioral disorders share similarities with substance abuse including preexisting vulnerabilities in failed regulation of the mesolimbic DA system by frontal regions. Evidence for DA involvement in behavioral addictions includes the fact that DA agonists given to some Parkinson's patients can trigger compulsive gambling, sex, and shopping. Even though the intense euphoria of romantic relationships is a common human experience, it also shares many facets of addiction because the basic circuitry for romantic love and attachment necessary for survival of the species is the same circuitry co-opted by drugs.

Gambling disorder (GD) is the first non-substance disorder that has been classified by the DSM-5 in the category of "Substance Related and Addictive Disorders". Similar to drug use both D2 and μ opioid receptors are implicated and opioid antagonists have shown the most promise as drugs of treatment. As with alcohol use disorders deficits exist in executive functions decision making and inhibitory control because of diminished activation of the ventromedial prefrontal cortex control mechanisms.[64] As with substance abuse fixations, tolerance and withdrawal occur. The heritability of pathological gambling estimated from twin studies is 50-60% similar to alcohol and substance abuse with which there is high co-morbidity.[65] It shares genetic vulnerability factors with antisocial behaviours, alcohol dependence and major depressive disorder and 96% of individuals with lifetime GD have at least one other lifetime psychiatric disorder.

Binge eating and obesity have also come under scrutiny because obsessive and compulsive eating share disruptions in transmitter and hormone systems which overlap normal systems for

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[62] B. Alexander, R. Coambs, P. Hadaway P. "The Effect of Housing and Gender on Morphine Self-administration in Rats," *Psychopharmacology* (Berl) 58 (1978): 175–79.

[63] Reviewed in Frascella, *et al*., "Carving Addiction".

[64] Reviewed in D.S. Lobo and J.L. Kennedy "Genetic Aspects of Pathological gambling: a complex disorder with shared genetic vulnerabilities,"*Addiction* 104(2009):1454–1465.

[65] Connor *et al*., "Alcohol Use Disorders".

food reward and the disordered systems associated with drug reward. [66] Chocolate cravers show greater activation in many reward areas activated in drug craving. DA release in the NAc varies as a function of food palatability and an inverse relationship has been reported between D2 receptors and BMI.[67] It has been suggested that reduced DA levels occur in the obese leading to overeating of highly palatable foods as compensation for reward deficiency. Endogenous cannabinoids and opioid systems in interaction with the DA system also 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 brain sensitivity to the rewarding effects of various drugs.[68] The rewarding effects of food, particularly food 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.

Internet gaming disorder is now included in the current diagnostic manual used by psychologists (DSM5) under the heading of "Conditions for Further Study". It could be argued that other internet use including cybersex, online relations, shopping and information searching can also be addictive. ASAer William Struthers has done a fine job setting out the case for the addictive properties of internet pornography.[69] The findings for all the internet disorders are consistent with neuroimaging, neurobiological and psychological models of substance disorder.[70] Certain prefrontal functions such as executive control are related to symptoms of internet addiction. While watching game-related pictures heavy internet gaming users shows similar fMRI activation patterns in both NAc and orbitofrontal cortex as do substance abusers. Structural changes in parts of prefrontal cortex may be related to loss of control. Grey matter reductions in orbitofrontal regions and alterations in the DA system have also been reported in those given to excessive internet gaming. This should hopefully lead in the future to development of new treatments for internet and other behavioral addictions.

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[66] D. Tomasi and N.D. Volkow, "Striatocortical Pathway Dysfunction in Addiction and Obesity: Difference and Similarities." *Critical Reviews in Biochemical and Molecular Biology* 48(2013):1-19.

[67] G.-J. Wang, N.D Volkow, P.K. Thanos, and J.S. Fowler, "Similarity Between Obesity and Drug Addiction as Assessed by Neurofunctional Imaging: A Concept Review. *Journal of Addiction Disorders* 23 (2004):39-53.

[68] Volkow *et al*., 2016.

[69] W. M. Struthers, *Wired for Intimacy: How Pornography Hijacks the Male Brain.* (Downer's Grove: IVP, 2009).

[70] M. Brand, K.S. Young and C. Laier. "Prefrontal Control and Internet Addiction: A Theoretical Model and Review of Neuropsychological and Neuroimaging Findings." *Frontiers in Human Neuroscience* 8 (2014): article 375; T. Love, C. Laier, M. Brand, L. Hatch and R. Hajela, "Neuroscience of Internet Pornography Addiction: A review and Update" *Behavioral Sciences* 5 (2015): 388-433.

In the fight against both drug and behavioral addictions, treatment strategies might be best focussed not only on reducing the rewarding effects of addictive use and behaviors, but increasing the rewarding effects of other stimuli, and on increasing cognitive control provided by the cortex. Treatments that provide individuals with social support which itself produces natural levels of dopamine, rather than supraphysiologic bursting, seem to show greatest promise. In particular the various 12 step programs which utilize continued social support can be combined with medical treatments and cognitive therapy. Multiple approaches are needed to address a multifactorial problem.

Biological, psychological and theological perspectives on addiction all suggest different answers to questions about treatment, prevention and legislation. As those meant to bring God's shalom to the world, I believe Christians need to contribute to the public discussion. As we seek solutions some questions worth considering include: What constraints should there be on prescribing addicting pain medication to non-addicts? What about substitute drugs for addicts? Should heroin be legalized for maintenance? Is it morally acceptable to reduce the risk of disease with safe injection sites and needle exchange programs? If opioid antagonists become easily available will it prevent deaths or merely encourage greater use of opioids? Should cannabis be legalized? What about the far deadlier nicotine?[71] What programs if any, beyond 12-step programs, can churches provide? Are there supporting facilities that churches can provide for recovering addicts? What sorts of preventive methods can government take that will actually work? Is it morally justifiable to cut back insurance coverage for addiction treatment for those who cannot afford it?[72] And how can churches be involved in providing safe, affirmative environments for young people?

Theological and spiritual questions are basic in this discussion and because we are embodied moral agents we need to ask: What is the spiritual meaning of addiction? How should Christians understand behavioral addictions? Are we discussing a continuum which stretches from normal, necessary behaviors of eating, romantic love, attachment and social behavior to disordered behaviors and to the disfunctionality that we label addiction? Does this mean the very nature of being human carries a level of risk for us all? Augustine in his *Confessions* describes his sexuality, need for love, and need for adulation in terms reminiscent of behavioral addictions. Systems that evolved for survival are not easy for most people to control. Was it in recognition of

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[71] The claim was made by a US politician that *only* 30% of smokers die of smoking-related diseases. Although statistics on long-term use of cannabis are not clear, lower addictive potential hence less compulsive use suggests lower mortality than alcohol or tobacco. WHO estimated that in the 20th c. 180 million people were killed by tobacco. *WHO Report on the Global Tobacco Epidemic: The MPOWER Package,* (Geneva:WHO, 2008).

[72] P.D. Friedman, C.M. Andrews and K. Humphreys, "How ACA Repeal Would Worsen the Opioid Epidemic" *New England Journal Medicine*, 376:e16 (March 8, 2017).

this tendency that Augustine on becoming bishop refused to allow women to enter his residence? Bill W, the co-founder of AA, ("Hello, I'm Bill. I'm an alcoholic.") died of emphysema from his smoking addiction.[73]

In contrast to the disease model many therapists have suggested that addiction is basically an attachment disorder induced by attempts at self-repair.[74] Augustine's transparency on his divided will echoes Paul's dilemma in Rom. 7. What are the implications of this restless that we face, and how do we find hope for long-term grace and healing transformation that requires a lifetime of the Spirit's work?

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[73] B. K. Alexander, *The Globalization of Addiction: A Study in Poverty of the Spirit*. (Oxford, UK: Oxford University Press, 2008).

[74] Frascella, *et al.*, "Carving Addiction". Gabor Maté, *In the Realm of Hungry Ghosts: Close Encounters with Addictions* (Berkeley: North Atlantic Books, 2010).