Why Can't We Say "No"?

The Struggle for Humanity to Renounce Reward

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Introduction

Before humans could build skyscrapers, forge steel, fry chicken, read books, and write blogs, they could differentiate between desirable and undesirable stimuli, or more simply: good and bad things. A forager in the forest is able to determine the ripeness of a fruit by its sweet or bitter taste, a child enjoys tactilely pleasing toys, and a businessman is much happier to be promoted than he is to be fired. We are instinctively prone, as are all living things, to gravitate toward rewarding things, things we deem "good". However, with the expansion of modern medicine, technology, and communication, our preferences are beginning to go beyond our basic needs. For the earliest of the *Homo sapiens*, life was considered "good" if you were able to survive infancy and childhood and eventually reproduce. For the modern human, a good life can be based upon many different and more elusive things: being financially comfortable, attaining an education, having a family, serving a community or aging well. This has allowed our species to diversify into different cultures, create new technologies, and engage more of our cerebral capacity than ever before. However, with these new standards for living a "good" life, unanticipated problems have arisen. Yet, before we can delve into our present problems, we must first understand the past.

A Brief History to Today

Once our species was surviving comfortably aside from the occasional plague or natural disaster, hierarchies began to form. Certain groups or families rose to power, tradesmen learned the unspoken rules of marketing, humans around the world forming niches and systems eventually resulting in civilization. Within these early societies were health specialists such as apothecaries, witchdoctors, shamans, and the many other terms they went by in different cultures. Without the benefits of industrialized chemical synthesizing techniques that we have today, they had to make due with Earth's own medicine: plants. Since humans learned to record information on the walls of caves or within the tombs of royals, we have seen use of many types of plants for their medicinal properties. The oldest recorded use of *Cannabis sativa* (commonly known as "marijuana") dates back to 2727 B.C. in ancient China, the use of the *Erythroxylon coca* plant (used to produce cocaine) can be traced back over 4,000 years, and the use of opium from the *Papaver somniferum* flower (commonly known as the "poppy") dates back as far as 3,400 B.C. in Mesopotamia. Ancient societies relying on the trade of these plants were wrought with war and conquest long before the existence of the modern day drug-trafficking cartels documentaries are so fond of portraying. It's clear our species has had a long and tumultuous relationship with all of these substances throughout history, and that doesn't seem to be changing. Rumors of the "drug epidemic" and "opiate crisis" are ever present in the news and talk, but what is the real data behind the words? To put it into perspective, in 2017 alone doctors wrote over 191 *million* prescriptions for opioids, while U.S. Customs and Border Protection seized over 1,500 pounds of trafficked fentanyl, equating to *680,390,000* regular doses (1mg/dose) and a street value of nearly seventy billion dollars. These statistics are only covering one branch of the tree—opioids in a sea of thousands of different types

of illicit drugs. The drug epidemic and resulting addiction crisis in America is ever escalating and unfortunately, we haven't found a way to combat it.

Deviating from our species' turbulent historical interaction with drugs, we look even further back in time at another universally "good" thing. Before the current era of widely accessible technology, efficient textile machines, and factories churning out new products by the second there was a clear standard by which wealth was judged: food. A commonly taught idea in primary schools is that wealthy people in history could often be identified by their body weight, and that excess fat was considered beautiful because it was a sign of wealth and a comfortable lifestyle. This was due to the fact that royals and noblemen were able to acquire food in excess, and thus obesity was a sign of their status and prosperity. The average man and woman looked upon this feature with envy, quite a different scenario than one might observe today. Today, nearly forty-percent of adults are considered overweight, amounting to over 1.9 billion humans in 2016. With such a large part of the population being overweight, ideals have changed to worship fitness and thin appearances—a beneficial change for our future physical health but not for our collective mental health. From an evolutionary perspective, our bodies are incredible machines that can store energy efficiently over long periods as well as ration what reserves we do have in times of famine. However, since long term food storage, processing, and preservation have become more effective and efficient than ever in recent years, certain populations of our species have run into a problem. We now have tasty treats easily accessible everywhere: in the train station, in schools, at events, in our cupboards, and even at elite sporting events like the Olympics—which is sponsored in part by fast food giant McDonald's. This ease of consumption and access has led us into the obesity epidemic, another example of something that once seemed "good" turning bad.

This brings us to a crossroads in current research. Humans have used drugs for thousands of years, and worshipped food for even longer. Scientists are beginning to question: are these two infatuations really all that different? Should we be looking at these diseases under the same pretenses? Could obesity and drug addiction work along the same neural pathways that lead people to lose all self-control and cave into craving? Should we use similar prevention strategies or model new treatments for one after successful ones for the other? Researchers have been hastily working to find answers to these questions before it's too late, and some may not be as simple as we once thought.

The Anatomy of Reward

As described earlier, humans tend to gravitate toward good things and avoid bad things. But what makes something good or bad? We evaluate the world around us with our five senses and this helps us determine the tastes we approve of, sounds that make us cringe, smells that make us hungry, plants that make us itch and environments that reduce our anxiety. We have all felt good and bad things, but what does this mean physiologically? Even more specifically, what does this mean on a neural level?

What nearly every process in the body boils down to is chemical interactions. Hormones course through our bloodstream helping us grow and develop, nutrients from food are absorbed in our gastrointestinal tract and integrated into our physique, and hemoglobin carries oxygen from the lungs to peripheral areas of our body allowing us to stay alive. In a similar fashion, the brain makes use of thousands of chemical interactions to function. The self-described most complex organ in the human body runs on molecules we get from our environment, and controls numerous systems through the use of electrical ion gradients and specialized chemicals called

neurotransmitters. These unique compounds are used to transmit information across the brain, neuron to neuron. One of the most universally well-known and discussed is dopamine—commonly referred to as our "pleasure" neurotransmitter, but more recently being associated with motivational salience and behavior.

Though it was first successfully synthesized in 1910, dopamine was first identified in the brain by Kathleen Montagu in 1957 and acknowledged as a neurotransmitter by Dr. Arvid Carlsson the same year. Dr. Carlsson's claim challenged the widely held belief of the time that dopamine was simply a precursor to the better studied norepinephrine and paved the way for subsequent research into the molecule's characteristics and system wide effects. The first data that claimed to find dopamine receptors in the brain (meaning dopamine could act on and effect things within the brain and therefore be irrefutably classified as a neurotransmitter) were published in 1972 by John Kebabian, Gary Petzold and Paul Greengard. Only three years before Carlsson's claim, James Olds and Peter Milner hypothesized the existence of a neural "reward system" after recognizing that rats would electrically stimulate specific areas of their brain—often ignoring necessary bodily functions including eating and drinking in favor of the stimulation up to the point of exhaustion and death. In 1964, Swedish scientists published evidence of localized dopamine within the lower brainstem, followed by Urban Ungerstedt publishing a stereotaxic map of the dopamine pathways in the rat brain in 1971. Over the next two decades, the structure and role of the dopamine pathway in the rat and human brains was further revealed. In 1986, Doctors Garrett Alexander, Mahlon DeLong and Peter Strick noted the integration of functionally separate areas of the basal ganglia and the cortex into at least four circuits, a groundbreaking rebuttal to the commonly accepted theory that the basal ganglia had only a motor circuit. In 1999 researchers from the Medical University of South Carolina examined one of these circuits and its role in adaptive behavior,

elucidating that particular areas of the basal ganglia were involved in different aspects of behavior. At the beginning of the new millennium, two Israeli scientists published a commentary verifying the role of the basal ganglia's influence on dopaminergic activity. In the nineteen short years since, researchers have become familiar with the dopamine pathway as a mediator of behavior, motivation, and whose dysfunction results in a wide array of cognitive, motor and psychological issues.

From these numerous dopaminergic pathways and systems, addiction and motivation researchers have converged on one known as the mesocorticolimbic system, a combination of the mesocortical and mesolimbic dopamine pathways. The mesolimbic pathway is widely regarded as a key contributor in natural reward seeking and behavior, as well as in dysfunctional and maladaptive behaviors such as addiction. The mesocortical part of the system extends from the brainstem into areas of the cortex commonly associated with decision making and executive functioning, whereas the mesolimbic aspect extends from the brainstem to the ventral striatum of the basal ganglia. The mesocorticolimbic system then consists of neuronal projections from the ventral tegmental area (VTA) of the midbrain to key regions, including: the Nucleus Accumbens (NAc) of the basal forebrain, the olfactory tubercle (that projects to the septum, amygdala and hypothalamus), the prefrontal cortex, the perirhinal cortex, and the cingulate cortex. This allows the mesocorticolimbic pathway to exert dopaminergic influence across a wide variety of neural structures, hence why its role in behavior is so significant.

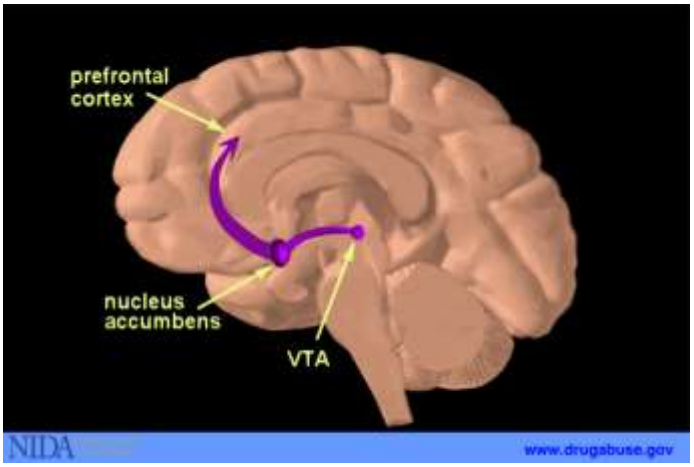

Figure 1. A simplified visual of the mesocorticolimbic dopamine pathway in the human brain beginning in the ventral tegmental area of the midbrain, travelling to the nucleus accumbens of the ventral striatum, and finally acting on the prefrontal cortex. Adapted from the National Institute of Drug Abuse at www.drugabuse.gov.

Dopamine and Incentives

What, then, is dopaminergic influence? We've just discussed dopamine's pathways in the brain—but what does it actually do, and how? Think about how you feel in particular situations such as finishing a great workout, enjoying your favorite food, winning an award for something you've worked hard on, accomplishing a long-term goal, or getting your paycheck. These are all deemed to be "rewarding stimuli" for humans—something we consider good. On a simplified neural level, we can attribute this feeling in part to the release of dopamine. When something good happens, one way that our brain responds is by releasing dopamine. If a stimulus or situation occurs often enough to the point that we become conditioned to expect the "reward", our brain will learn to release dopamine simply with the expectation of the reward. However, contrary to popular belief and pop-culture outlets, dopamine isn't necessarily telling you what is good and what is bad—in fact it has also been shown to be released in response to aversive or "bad" stimuli. Dopamine release doesn't increase hedonic characteristics of stimuli, and animals (including humans) without dopamine can still learn to like and dislike things. Instead, dopamine is now thought to convey *incentive salience*, or more simply, how bad an organism "wants" something. Under this

hypothesis, it is possible to be triggered by a particular cue (say, being in a place you had previously participated in drug use at) to "want" something you may have no memory of necessarily "liking," something you don't actually "like" and even something you do not "like" once you obtain it. So though dopamine may not affect whether or how much we like something, it certainly influences our craving and subsequent seeking of particular incentives.

Association and Memory

How does this "wanting" then translate into the apparent loss of control drug addicted and obese individuals experience? The answer lies in the associations that are formed with rewarding stimuli. An action that results in a reward (and subsequent dopamine release) is more likely to be repeated, likely due to associative learning of stimulus related cues. The linking of motivational significance to a previously unrelated cue was described by Tzschentke in 1998 when he noticed that rats preferred spending time in areas where they had received drug injections when compared to areas where they had received saline injections. Further research has shown that triggering cues can be anything from environmental setting to social context, and that these cues can enhance desire for the stimuli as well as elicit conditioned emotional responses. Similarly, the use of different drugs or substances results in different amounts of dopamine release. For example, cocaine can release around 100-300 units of dopamine, while methamphetamine can release an astounding 1200 units. This may explain in part why certain drugs have a higher abuse potential as well as why others are easier to quit once addicted. In order to understand this in terms of maladaptive drug and food behaviors, let's look at some common contexts for both. A methamphetamine user may be going to the same house or building every time they use the drug, meeting and using with the same social group, and even wearing similar clothing or maintaining a

pre-use routine. Once they try to stop using, these same places, habits, and friends will elicit emotional responses that increase their craving of the drug and make it more difficult to abstain, increasing their chances of relapse. Similarly, someone that experiences a chronically stressful environment (shift-workers, physicians, laborers) may use highly palatable foods as a form of anxiety reduction, or they may choose fast-food service after a long shift. Food causes release of dopamine in the brain, and in consequence these workers may begin to associate particular environments or emotions with the food—leading to an increase in how often they consume the associated food. Though not identical, these mechanisms of incentive association have continued to be a key theme in understanding these types of maladaptive behaviors.

Drugs or Obesity: Which is Worse?

Now that we have established a considerable understanding of the brain's reward system and dopamine's role, we can understand why drug addiction and obesity have been hypothesized to work through similar mechanisms. It may come as a surprise then, that even though drugs can release over twenty-times more dopamine than food and result in a more intense craving, obesity kills people at over five times the rate of drug overdose deaths. What, then, can explain the disparity between them?

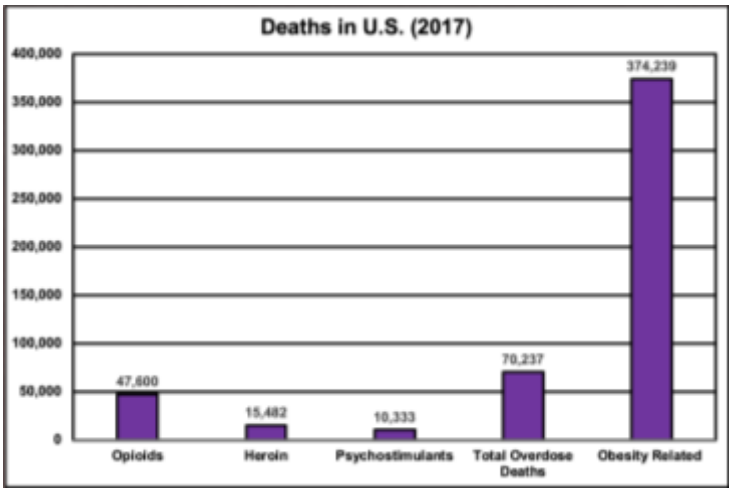

Figure 2. Overdose deaths for significant drugs in 2017 compared to total overdose deaths and total obesity related deaths. Adapted from https://www.wvdhhr.org/bph/oehp/obesity/mortality.htm and https://www.cdc.gov/nchs/products/databriefs/db328.htm.

Unfortunately for future treatment options, we cannot cast these two problems into the same category, based

on a variety of reasons. The first is that obesity has different types of social stigmas and ideas surrounding it than those associated with drug addiction. With the rise in concern about mental health, a "body positivity" movement has taken this country by storm. Unfortunately, with this newfound acceptance we have begun to ignore the distinction between healthy and unhealthy weights in favor of healthy mindsets. People have begun to call out institutions and brands for body shaming against larger women but in turn we have also come to be more accepting of unhealthy lifestyles. Another reason is that highly palatable foods such as those high in sugars, fats and salt are more widely available and financially accessible than their illicit counterparts. A McDonald's cheeseburger is one dollar and accessible twenty-four hours a day, whereas one quarter gram of methamphetamine is twenty dollars and difficult to access for the average person. Binge and fad diets are also widely acceptable, even though they are rarely effective and increase chances of "relapse" rather than teaching someone unhealthy habits.

Prevention of obesity can also be viewed as more difficult. We are exposed to sweets and treats as a reward at a young age—whether it be for cleaning our room or doing well in school. Fortunately, this doesn't tend to happen with drugs and physicians tend to be warier of prescribing certain drugs in particular to children. Starting drugs is usually associated with a more "personal" choice, whereas unhealthy food can be impossible to avoid. While obesity prevention programs in school can be seen as a newer occurrence, drug prevention programs have been funded for decades—including D.A.R.E., which was recently discontinued. Drug prevention is widely practiced in all forms of media as well, whether it be airing a commercial about the dangers of addiction or teaching people about the legal consequences they could face with a drug-related conviction.

We also receive a lot of input from our enteric nervous system, microbiome, hormones, certain nutrients and autonomic regulations when it comes to making decisions about food, whereas exogenous drugs are not factored into our decisions until we try them.

Another important distinction in analyzing these behaviors is the role of socioeconomic status. It may be more difficult for someone to make good decisions in particular situations than it is for others, especially when social groups and family structure are taken into account.

With these differences in mind, it is clear that there will not be a quick fix someday for both addiction and obesity. Both problems may work similarly through the reward pathway, but they are caused and influenced by different aspects of life. Their prevention and treatment should be approached separately, even though they may seem to be caused by the same dysfunction of the reward pathway. In conclusion, drug addiction and obesity are both large problems, not only in the United States, but around the world. Though they seemed to be surfacing as similar dysfunctions, they cannot be viewed the same way and in turn treatment and prevention must be approached separately. While researchers continue to delve into their potential cures we must do our best to educate ourselves and abstain from developing destructive habits.

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