“THEY TRIED TO MAKE ME GO TO REHAB”

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A Tribute to Amy Winehouse

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One wet and windy December evening in 2006, a 23-year-old Amy Winehouse arrived in Dingle, a fishing town of 2,000 souls in County Kerry, southwest Ireland, “at the edge of the known world before we found out that it was round,” as one resident describes it. There, in front of some 70 people gathered in the small St. James Church, Winehouse performed songs that have forever inscribed her in the musical firmament—“Back to Black,” “Tears Dry On Their Own,” “You Know I’m No Good.”

Singer Amy Winehouse performs in Dingle

With her second album “Back to Black” not even two months old, the English singer was in Dingle to record “Other Voices,” an Irish TV show that every winter brings musicians from all over the world to this remote corner of Europe. This month, a year after her premature death at 27 from alcohol poisoning, those few hours she spent in the town have been turned into a touching tribute to the tormented artist.

“Arena: Amy Winehouse—The Day She Came to Dingle,” by Irish director Maurice Linnane, brings together unseen footage from Winehouse’s heartfelt performance, archival recordings of her musical idols and the recollections of locals who met her that evening.

“We decided we would just tell a story of that day, of what happened when Amy came to Dingle,” says Mr. Linnane, whose film stays away from the rumors and controversies that surrounded the soul artist’s last years. “My rule was, if they weren’t in the room that day, they weren’t allowed to talk about it.”

So we hear about Winehouse from Paddy Kennedy, the Dingle bus driver who picked the singer up at the airport and thought she was Amy Winehouse’s daughter. “I hadn’t a clue who the lady was,” he recalls in the documentary. Mr. Linnane adds that she sang in the back of the bus, “half the way from Dingle to Cork.”

We hear from Adele Woodlock, a music producer on “Other Voices,” whom Winehouse asked to hold her hair while she backcombed it for her signature beehive style. “She came with her splindy, little legs and her mental hair, and sung her heart out, in Kerry, for us,” Ms. Woodlock says.
“As for Ms. Winehouse, her talent was as fierce as her heartache.”

– Sally Satel
The rat in question was placed in a large rectangular box with corners labeled A, B, C, and D and was allowed to explore freely. Whenever the rat went to corner A, Olds pressed a button that delivered a brief, mild electrical shock through the implanted electrodes. (Unlike the rest of the body, brain tissue does not have the receptors that allow for pain detection, so such shocks don’t produce a painful sensation within the skull.) After a few jolts, the rat kept returning to corner A and finally fell asleep in a different location. The next day, however, the rat seemed even more interested in corner A than the others. Olds and Milner were excited: They believed that they had found a brain region that, when stimulated, provoked general curiosity. However, further experiments on this same rat soon proved that not to be the case. By this time, the rat had acquired a habit of returning often to corner A to be stimulated. The researchers then tried to coax the rat away from corner A by administering a shock every time the rat made a step in the direction of corner B. This worked all too well—within five minutes, the rat relocated to corner B. Further investigation revealed that this rat could be directed to any location within the box with well-timed brain shocks—brief ones to guide the rat to the target location and then more sustained ones once it arrived there.
The next day...
**ingestion**

- Preferred for many drugs
- Easy and safe
- Carried via bloodstream
- Unpredictable dosage

**injection**

- Preferred by medical professionals
- Predictable: fast; strong drugs
- Drug users: IV injection
- Dangerous – allergic rxn or overdose.
**inhalation**

- Through the lungs into the capillaries
- Anesthetics; tobacco & marijuana
- Difficult to regulate dose
- Can damage lungs

**absorption**

- Mucous membranes
- Nose; mouth
- Snort cocaine
NICOTINE’S PATH TO THE BRAIN

Most cigarettes also contain ammonium hydroxide, To maintain neutral pH

From H. Lester, CalTech
Blood nicotine concentrations during and after a cigarette

![Graph showing blood nicotine concentrations over time](image-url)
CLASSIFICATION OF DRUG ACTIONS

- **stimulants**
  - Enhance and speed up CNS activity
  - Temporary effect → crash

- **depressants**
  - Slow down or impair CNS activity

- **Hallucinogens**
  - Distort sensory information processing
Drug Addiction, Dysregulation of Reward, and Allostasis

George F. Koob, Ph.D., and Michel Le Moal, M.D., Ph.D.

“Drug addiction is a chronically relapsing disorder that is defined by two major characteristics: a compulsion to take the drug with a narrowing of the behavioral repertoire toward excessive drug intake, and a loss of control in limiting intake (American Psychiatric Association 1994; World Health Organization 1992).

An important challenge for neurobiological research is to understand the neuroadaptive differences between controlled drug use and loss of control, and by extension, the molecular, cellular and system processes that lead to addiction (Koob and Le Moal, 1997).”
The spiraling distress/addiction cycle

- preoccupation
- anticipation
- wanting drug
- persistent psychological problem
- positive reinforcement
- binge
- intoxication
- taken in larger amounts than needed
- negative affect
- withdrawal
- persistent desire
- tolerance
- withdrawal
- social, occupational, recreational activities compromised
- addiction

Adapted from Koob & Le Moal (2001) Neuropsychopharmacology 24, 97–129
Drug Effects Over Time

- Administration Phase
- Active Phase
- Metabolism Phase

Drug Effects

Time

active drug → metabolism → inactive drug
ALTERING THE FUNCTION OF NEUROTRANSMITTERS CAN CHANGE BEHAVIOR.

agonist

mimics or facilitates the release

more dopamine released

antagonist

oppose or blocks the release

less dopamine released
Is there a common molecular pathway for addiction?

Eric J Nestler
Drugs of abuse

Diverse chemicals

Distinct targets & effects

Cause common effects:

Acute

Chronic

Characterized by:

Immediate reward \(\rightarrow\) repeated use \(\rightarrow\) addiction

Loss of control over drug use.
Negative emotional symptoms withdrawal.
MESOTELECEPHALIC DA SYSTEM

Nigrostriatal pathway

Mesocorticolimbic pathway
All drugs of abuse affect the limbic system.

Mesocorticolimbic system → dopaminergic neurons in the ventral tegmental area → NAc.
Examples of common effects on the VTA-NAc.

- **Stimulants** directly *increase* dopaminergic transmission in the NAc.
- **Opiates** do the same (indirectly) they inhibit GABAergic interneurons in the VTA, which *disinhibits* VTA dopamine neurons.
- **Opiates** also *directly* act on opioid receptors on NAc neurons.

Highly simplified scheme of converging acute actions of drugs of abuse on the VTA-NAc.
“On the basis of these common acute actions, one would expect that chronic exposure to drugs of abuse would also cause common chronic functional changes in the VTA-NAc pathway. Indeed, numerous common chronic adaptations have been described, examples of which are discussed in the next sections. Consistent with common mechanisms of addiction are the observations that certain drugs of abuse, under particular experimental conditions, can induce cross-tolerance and cross-sensitization to one another with respect to their locomotor activating and rewarding effects."
Highly simplified scheme of some common, chronic actions of drugs of abuse on the VTA-NAc

Under normal conditions – there are glutamatergic inputs to both the VTA and NAc neurons.

**Tolerance**: homeostatic response to repeated drug activation of the system

“Chronic exposure to any of several drugs of abuse causes an impaired dopamine system”

“It also becomes sensitized → more dopamine is released in response to the drug and its cues.

“Baseline levels of dopamine function are reduced, and normal rewarding stimuli may be less effective.”

Addiction also involves powerful emotional memories.

→ Amygdala

More recent work has established that several additional brain areas that interact with the VTA and NAc are also essential for acute drug reward and chronic changes in reward associated with addiction. These regions include the amygdala (and related structures of the so-called ‘extended amygdala’), hippocampus, hypothalamus and several regions of frontal cortex, among others. Some of these areas are part of the brain’s traditional memory systems; this has led to the notion, now supported by increasing evidence, that important aspects of addiction involve powerful emotional memories.

Rats will self-administer “drugs of abuse” – the animals are connected to an IV and have a choice of saline, food, or the drug of abuse (e.g. cocaine, amphetamine, heroin, whiskey, speed). **Within a few days, the animals are hooked!** They begin to display behaviors of addiction.

Rats will take drugs at the expense of normal activities— eating & sleeping—even dying of exhaustion or malnutrition. For the most addictive substances, rats will spend most of their waking hours working to obtain the drug. When the drug is no longer available they will hang-out by the lever that they used to deliver the drug. The pleasure is never forgotten.
Drugs take over the reward circuitry of the brain. A critical pathway is the projection from the ventral tegmental area (VTA) to the nucleus accumbens.

- **Mesolimbic DA**

- **No longer show interest in drugs of abuse.**

- **Amygdala**

- **Repeat the experience??**

**Lesions**

**“controller”**
N. Acc is modulating the activity of the limbic circuit

- **Amygdala**: Helps to determine if an experience is pleasurable or aversive—and whether it should be repeated or avoided—and helps to forge connections between an experience and other cues.
- **VTA-N. Acc.**: Communicates how rewarding an activity is.; the more rewarding an activity is the more it is likely to repeat it.
- **Frontal lobes**: Responsible to coordinate & process information and to ultimately determine behavior.
- **Hippocampus**: Involved in declarative memory formation of the experience—details include where, when, and whom it occurred.
Chemical Imbalance Theory of Mental Illness

Linked to basic body movement and emotions.

Mental & physical depression

Motivation

Anxiety

Pleasure seeking dysfunction

Linked to basic body movement and emotions.

Impulse & focus

Parkinson’s Disease

Sleep regulation

Extreme mood swings

OCD-like symptoms

Aggression

Suicidal thoughts

Susceptible to “cue triggers”
Criteria for Substance Dependence (DSM-IV)

- Preoccupation Anticipation
  - Preoccupation w/obtaining
  - Persistent physical or psychological problem
- Binge Intoxication
  - Taken in larger amounts than intended
- Withdrawal Negative Affect
  - Persistent desire
  - Tolerance withdrawal
  - Social, occupational or recreational activities compromised
  - Spiralling Distress
- Addiction

Koob & Le Moal (2001) Neuropsychopharmacology 24, 97–129
Dissecting the neural circuitry of addiction and psychiatric disease with optogenetics

Garret D. Stuber

The Ernest Gallo Clinic and Research Center, University of California, San Francisco, CA, USA

Optogenetics can modify neural activity in awake, behaving animals. An optical fiber delivers light to genetically targeted neurons. Illustration by Ethan Tyler.
Pathological gambling is linked to reduced activation of the mesolimbic reward system

Jan Reuter¹, Thomas Raedler², Michael Rose¹, Iver Hand³, Jan Gläscher¹ & Christian Büchel¹

By analogy to drug dependence, it has been speculated that the underlying pathology in pathological gambling is a reduction in the sensitivity of the reward system. Studying pathological gamblers and controls during a guessing game using functional magnetic resonance imaging, we observed a reduction of ventral striatal and ventromedial prefrontal activation in the pathological gamblers that was negatively correlated with gambling severity, linking hypoactivation of these areas to disease severity.
Gambling on dopamine

Dopamine neurons in the midbrain are thought to produce an error signal that could be important for learning to predict a reward. Now, it seems that the same neurons also signal the level of uncertainty in an experimental trial — which might even give us insight into why gambling is such a popular way to get rid of excess wealth.

Fiorillo and colleagues, writing in *Science*, describe experiments in which monkeys were conditioned with different visual stimuli, each of which had a different probability of being followed by a reward (a few drops of tasty fruit juice). So, for example, one of the stimuli was always followed by juice, whereas another was followed by juice on only a quarter of the trials. The monkeys learned these relationships — they would lick vigorously at the juice spout when they saw the ‘always rewarded’ stimulus, and the amount of licking decreased with the probability of reward.

Consistent with earlier work by the same group, dopamine neurons in the monkeys’ midbrains produced a stimulus-related signal that was stronger for stimuli that predicted reward more reliably, and a reward-related signal that was stronger when reward had not been reliably predicted. But the authors also saw a new signal — a more gradual increase in firing during the two-second interval between the onset of the stimulus and the potential reward that was greatest when there was the most uncertainty about whether a reward would be forthcoming.

When a stimulus is either always or never associated with reward, there is no uncertainty. By contrast, uncertainty is greatest when the probability of reward is 0.5, and this was when the sustained response of the dopamine neurons was the greatest. So it seems that, over the course of a trial, the same population of neurons codes two different aspects of the likelihood of reward: one that corresponds to the reward prediction error (shown previously by Waelti et al.), as proposed in formal learning theory by Rescorla and Wagner, and another that measures uncertainty.

This second signal also has correlates in learning theory. According to the Pearce–Hall theory, attention depends on uncertainty about reinforcers, and learning depends on attention. In a real situation, an animal’s
uncertainty about whether an action or event will be rewarding might just mean that the animal has insufficient information on which to base a prediction — so it will pay off to attend closely to the outcome. The dopamine neurons could be providing a signal that facilitates attention, and therefore learning.

Dopamine is closely associated with reward and addiction. The gradual increase in dopaminergic signalling in the presence of uncertainty might not be reinforcing, but if it is it could explain laboratory findings that animals prefer variable reward schedules over fixed ones. It could also, according to the authors, explain why gambling — in which rewards are, by definition, uncertain, and which is hard to explain by other means — is so popular and can even seem to be addictive.

Rachel Jones

References and links


Neural systems of reinforcement for drug addiction: from actions to habits to compulsion

Barry J Everitt & Trevor W Robbins

“...The change from voluntary drug use to more habitual and compulsive drug use represents a transition at the neural level from prefrontal cortical to striatal control over drug seeking and drug taking behavior as well as a progression from ventral to more dorsal domains of the striatum, involving its dopaminergic innervation. These neural transitions may themselves depend on the neuroplasticity in both cortical and striatal structures that is induced by chronic self-administration of drugs.”

Basal ganglia systems in ritualistic social displays: reptiles and humans; function and illness

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Abstract

Complex, situation-specific territorial maintenance routines are similar across living terrestrial vertebrates (= amniotes). Decades ago, Paul MacLean et al., at the Laboratory of Brain Evolution and Behavior of the National Institute of Mental Health, postulated that these are evolutionarily conserved behaviors whose expression is mediated by the similarly conserved amniote basal ganglia and related brain systems (BG systems). Therefore, they undertook studies in nonhuman primates and in small social lizards (the common green anole, Anolis carolinensis) to examine this idea.

MacLean et al. also postulated that when BG systems malfunction in humans, behavioral abnormalities result, some of them under the rubric of psychiatric illnesses. Obsessive–compulsive disorder (OCD) was singled out as one likely candidate.

In the last dozen years, functional brain imaging studies of OCD patients have validated the contention that this is, in fact, a condition involving dysfunctioning BG systems. Inspired by the MacLean group’s original investigations, my colleagues and I have now applied related functional imaging techniques in naturalistic experiments using Anolis to better understand BG systems’ roles in the mediation of complex behavioral routines in healthy amniotes. Here, I will review this functional imaging work in primates (man, and a little in monkey) and in lizards. I believe the literature not only supports MacLean et al.’s contentions about BG systems and behavior in general, but also validates Paul MacLean’s life-long contention that human behavioral medicine can profit from a broad comparative approach.

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MICROGRAPHS of nucleus accumbens neurons in animals exposed to nonaddictive drugs display dendritic branches with normal numbers of signal-receiving projections called spines (*left* and *center*). But those who become addicted to cocaine sprout additional spines on the branches, which consequently look bushier (*right*). Presumably, such remodeling makes neurons more sensitive to signals from the VTA and elsewhere and thus contributes to drug sensitivity. Recent findings suggest that delta FosB plays a part in spine growth.
Brains of OCD patients show:

(while resting quietly) elevation of activity in:
- Orbital frontal cortex (bilateral)
- Ventromedial caudate nucleus (right)

when provoked:
- Ventromedial thalamus

Orbitofrontal cortex and right striatal (head of caudate nucleus) over activity associated with OCD.

Correlation of Yale–Brown Obsessive–Compulsive Scale (Y-BOCS) score—a standard rating of OCD symptom severity—with FDG activity in right Cd. Patients studied with FDG-PET both before and after treatment with medication are graphed.
A representative axial view of the clusters of significant reduction of $[^{11}C]Rac$ binding potential in the basal ganglia of OCD patients evaluated during naive conditions (PET-I) and during fluvoxamine treatment (PET-II) in comparison with normal controls (unpaired t-test, p threshold <0.01).
The mean increase observed in our study is in line with rodent studies indicating an increase in central DA D2-like receptor function induced by repeated administration of SSRIs (Ainsworth et al, 1998a).

The same authors also reported an increase in D2 receptor mRNA and protein expression that was particularly evident in the shell region of rat nucleus accumbens (Ainsworth et al, 1998b).

$[^{11}\text{C}]$Rac binding has been proven to be sensitive to modification in extracellular concentration of exogenous or endogenous dopamine (Seeman et al, 1989; Laruelle, 2000a).

Thus, changes in the in vivo binding of $[^{11}\text{C}]$Rac could be related either to modifications in receptors expression or extracellular levels of dopamine. This property of $[^{11}\text{C}]$Rac binding, has been used, as an innovative strategy, to measure in living human subjects the modification in extracellular/synaptic dopamine concentration induced by pharmacological or behavioral stimulations (Laruelle, 2000b; Koepp et al, 1998).

A complex interaction between serotonin and dopamine system has been extensively described also using emission tomography techniques. In particular, serotonin neurons have been found to modulate striatal dopamine release (Dewey et al, 1995).

The basal firing of dopamine neuron rising from ventral tegmental area is negatively modulated by SSRIs (Di Mascio et al, 1998).
ALLOSTASIS

Homeostasis, in principle, corresponds to the mechanisms that maintain stability within the physiological systems and hold all the parameters of the organisms internal milieu within limits that allow an organism to survive (Bernard 1865; Cannon and Rosenblueth 1933; Sterling and Eyer 1988). It implied originally that i) deviations from normal set points are automatically corrected by local negative feedbacks, and ii) bodily organs are considered as functioning autonomously. Subsequently, homeostasis has been described as a self-regulating process for maintaining body parameters around a set point critical for survival (McEwen 2000). This includes multi-system coordination of the organism’s response to an acute challenge, including the brain, pituitary, autonomic system, and skeletomotor systems. However, while some of the parameters of the internal milieu are held constant (like body temperature), other parameters like stress hormones are varied within a wide range in an attempt to maintain homeostasis.

In contrast, the principle of allostasis proposes maintenance of stability outside of the normal homeostatic range, where an organism must vary all the parameters of its physiological systems to match them appropriately to chronic demands (e.g., reset the system parameters at a new set point) (Sterling and Eyer 1988). Allostasis refers to the integrative adaptive processes maintaining stability through change, a stability that is not within the normal homeostatic range. It implies that many, if not all, physiological functions are mobilized or suppressed, as reflected in a cascade of brain-organism interactions overriding local regulation. By controlling all the mechanisms simultaneously, the brain can enforce its command and introduce experience, memories, anticipation and re-evaluation of needs in anticipation of physiological requirements.

The allostatic model, because it involves the whole brain and body instead of simply local feedbacks, is far more complex than homeostasis. All parameters of a given domain (e.g., blood pressure, or in the central nervous system reward function) are controlled by numerous mutually interacting signals. When demands become chronic, the brain-body system tonically adapts at essentially all levels of organization implying widespread changes in set points, and entry into a relaxed condition may create an unpleasant state of withdrawal from one’s physiological regulation. Such changes in hormones, opioids, transmitters, and so on, provide a physiological basis for the individual to continue to seek a condition of high demand (Sterling and Eyer 1988), and a stabilized new level of activity far from homeostatic equilibrium. However, when chronic arousal, repeated stress and negative affective states impose prolonged regulations far from normality, there is no margin left for responding to additional challenges, no opportunity for relaxation, and no capacity for more responsiveness. This stabilized new level of activity far from homeostatic equilibrium forms an allostatic state. An allostatic state can be defined as a state of chronic deviation of the regulatory systems from their normal state of operation with establishment of a new set point.
Do ADHD Drugs Take a Toll on the Brain?

Research hints that hidden risks might accompany long-term use of the medicines that treat attention-deficit hyperactivity disorder.

E. S. Higgins (2009) Scientific American Mind
A few years ago a single mother who had recently moved to town came to my office asking me to prescribe the stimulant drug Adderall for her sixth-grade son. The boy had been taking the medication for several years, and his mother had liked its effects: it made homework time easier and improved her son’s grades.

At the time of this visit, the boy was off the medication, and I conducted a series of cognitive and behavioral tests on him. He performed wonderfully. I also noticed that off the medication he was friendly and playful. On a previous casual encounter, when the boy had been on Adderall, he had seemed reserved and quiet. His mother acknowledged this was a side effect of the Adderall. I told her that I did not think her son had attention-deficit hyperactivity disorder (ADHD) and that he did not need medication. That was the last time I saw her.

What is more, many people who have no cognitive deficits are opting to take these drugs to boost their academic performance. A number of my patients—doctors, lawyers and other professionals—have asked me for stimulants in hopes of boosting their productivity. As a result of these developments, prescriptions for methylphenidate and amphetamine rose by almost 12 percent a year between 2000 and 2005, according to a 2007 study.

With the expanded and extended use of stimulants comes mounting concern that the drugs might take a toll on the brain over the long run. Indeed, a smattering of recent studies, most of them involving animals, hint that stimulants could alter the structure and function of the brain in ways that may depress mood, boost anxiety and, contrary to their short-term effects, lead to cognitive deficits. Human studies already indicate the medications can adversely affect areas of the brain that govern growth in children, and some researchers worry that additional harms have yet to be unearthed.
Forbes

The Straight Dope on What Bath Salts Do to Your Brain and Why They're Dangerous

David S. Sarno, 09/11/2012

First, the name “bath salts” doesn’t refer to any single drug, but rather a group of substances with similar chemical properties. Most varieties contain either mephedrone or (MDPV) methylenedioxypyrovalerone. Both drugs are related to MDMA, an organic stimulant found in the Middle East and East African countries. What is illegal in the US because it contains cathinone, a Schedule I controlled substance according to the DEA.

Neither of these drugs are new; mephedrone has been bouncing around laboratories since the 1920s, MDPV since the late 1990s. Recreational use of the drugs is relatively new, dating back just a decade or so. Mephedrone is a stimulant and MDPV is both a stimulant and psychoactive drug. The qualifier “psychoactive” means that the drug crosses the blood-brain barrier and causes changes in neurochemical function, resulting in amplifying effects on mood, thought, perception and behavior.

Neither of these drugs are hallucinogens like LSD. Hallucinogens are psychoactive drugs, but not all psychoactive drugs are hallucinogens — the primary difference being that hallucinogens induce changes in perception that are significantly different than normal consciousness, not merely an amplification of conscious states we already experience.

So, for example, someone who takes MDPV may find himself feeling extremely paranoid and panicky, but he’s unlikely to believe that a giant lizard wearing a tuxedo is about to eat his cat.

(It bears noting, however, that since some varieties of bath salts are chemical gran bags containing any number of drugs, it’s certainly possible that hallucinogens are occasionally in the mix.)

The comparison between bath salts and ecstasy (MDMA) is based on the results of a study on rats showing that MDMA and mephedrone have similar effects on the neurotransmitters dopamine and serotonin. The study also suggests that the long-term effects of mephedrone are less harmful than ecstasy, because the drug doesn’t seem to deplete serotonin as severely as the favorite drug of ravers worldwide. But, and this is a big but, these are the results of one study on rats, and the researchers were careful to point out that much more research needs to be done before we can draw any conclusions about long-term effects.

Are bath salts addictive? Yes, they probably are, and for roughly the same reason that ecstasy is addictive — they cause the brain to limit reuptake of dopamine, which means more of the neurochemical is available in the brain and the brain really likes that. Over time the effect diminishes and more of the drug is required to keep the tail rolling.

Are bath salts addictive the way cocaine is addictive? No, probably not. The reason is that cocaine is an exceptionally addictive substance that appears to hook the brain in more than one way.
acetylcholine (ACh) - a neurotransmitter involved in memory and muscle contraction
agonist - a drug that mimics or facilitates the action of a particular neurotransmitter, thus enhancing its normal effects
alcohol - depressant drug derived from grain or fruit
amphetamines - stimulant drug that arouses the central nervous system and suppresses appetite
antagonist - a drug that opposes or blocks the action of a particular neurotransmitter
barbiturates - depressant drug used to induce sleep or reduce anxiety
caffeine - stimulant drug found in coffee, tea, and cola drinks
cocaine - a stimulant drug derived from the coca plant
depressants - psychoactive drugs that reduce neural activity and slow body functions
dopamine - the key neurotransmitter involved in drug addiction
endorphins - natural, opiate-like neurotransmitters linked to pain control and pleasure
hallucinogens - psychoactive drugs that distort perception and consciousness
heroin - depressant or narcotic drug that is three times more powerful than morphine
limbic System - a ring of brain structures located just below the cerebral hemispheres and involved in motivated behaviors and the experience of emotion.
LSD (lysergic acid diethylamide) - a powerful hallucinogen capable of producing vivid false perceptions and disorganization of thought processes
marijuana - a mild hallucinogen derived from the hemp plant
morphine - depressant or narcotic drug that is the main ingredient in opium; used as a powerful pain reliever
neurotransmitter - a chemical messenger of the central nervous system involved in the transmission of nerve impulses across the synapse to influence the action of another neuron
nicotine - stimulant drug found in tobacco products
norepinephrine - a neurotransmitter involved in arousal and alertness
opium - depressant or narcotic drug made from a crude extract of one type of poppy plant
physical dependence - a physiological need for a drug; indicated by the presence of withdrawal symptoms when the drug is not taken
psychoactive drugs - chemical substances that alter arousal, mood, perception, or behavior by affecting or mimicking the activity of neurotransmitters
psychological dependence - a strong craving to use a drug based on the desire to recapture the good feeling produced by the drug
serotonin - a neurotransmitter involved in sleep, emotions, and mood
stimulants - psychoactive drugs that excite neural activity and speed up body functions
tolerance - the decreasing effectiveness of a psychoactive drug that occurs with repeated use
withdrawal symptoms - the discomfort and distress that follow the discontinued use of addictive drugs
Two years ago the city of Copenhagen offered to supply addicts with heroin. Local politicians hoped that the move would keep addicts from committing crimes and frequenting emergency rooms. Junkie heaven? Not quite. Only a small fraction of city’s addicts signed up. The rest, program officials said, found the give-away program too regimented.

Judging from his self-portrait in “Memoirs of an Addicted Brain,” Marc Lewis was once that kind of addict. He was hooked on subterfuge and defiance. He stole drugs, forged prescriptions and traveled black markets—for heroin and other mind-altering substances. He was arrested, he overdosed, he betrayed loved ones. And then he did it again and again until he decided not to.

Mr. Lewis’s book is the newest addition to a popular genre, the addiction memoir. What distinguishes his entry is that he tells much of his story from the perspective of his brain, a “bristling, bustling, neural metropolis,” as he calls it. Mr. Lewis, as it happens, is a developmental neuroscientist.

Mr. Lewis grew up in middle-class Toronto in the 1950s and 1960s. He was an insecure teen, he tells us, puzzled and hurt by his parents’ insistence that he attend an American boarding school. Bullied by his classmates, he turned to alcohol, cough medicine and marijuana for relief. He graduated with honors, though, and went on to attend the University of California, Berkeley—where he tuned in, turned on and dropped out. After a year or so in Southeast Asia floating through opium dens in Calcutta, he was back in Berkeley to finish college and then pursue doctoral work in psychology. For about 10 years, he went in and out of full-blown addiction to narcotic painkillers and stimulants—and the Ph.D. he inhaled was put on hold.

During this period, Mr. Lewis says, he learned that his brain “was accessible, mutable. I could change its chemistry, its balance. I could knock it out of one orbit and into another, if I tried, if I found the right substance.” Scotch, for example, soothed him. Why, exactly? As he can now detail: Alcohol molecules affect “inhibitory neurons,” which in turn cause other neurons to “remain buffered from each other, focused on the task at hand.” LSD has a different effect. It “opens everything up so that even the tiny details of perception mushroom, layer by layer, an elaborate mandala. The
What Alcohol Really Does to Your Brain.

What happens once that vodka cranberry works its way through your bloodstream and hits the control center behind your eyes?

An example of an inhibitory neurotransmitter is **GABA**, which reduces energy levels and calms everything down. Drugs like Xanax and Valium (and other benzodiazepines) increase GABA production in the brain, resulting in sedation. Alcohol does the same thing by increasing the effects of GABA. This, by the way, is one reason you don’t want to drink alcohol while taking benzodiazepines; the effects will be amplified, and that can slow your heart rate and respiratory system down to dangerous levels.

So what we just discussed accounts for the depressant effects of alcohol: it suppresses the excitatory neurotransmitter glutamate and increases the inhibitory neurotransmitter GABA. What this means for you is that your thought, speech and movements are slowed down, and the more you drink the more of these effects you’ll feel (hence the stumbling around, falling over chairs and other clumsy things drunk people do).

But here’s the twist: alcohol also increases the release of dopamine in your brain’s “reward center.” The reward center is the same combination of brain areas (particularly the **ventral striatum**) that are affected by virtually all pleasurable activity, including everything from hanging out with friends, going on vacation, getting a big bonus at work, ingesting drugs (like cocaine and crystal meth), and drinking alcohol.

By jacking up dopamine levels in your brain, alcohol tricks you into thinking that it’s actually...