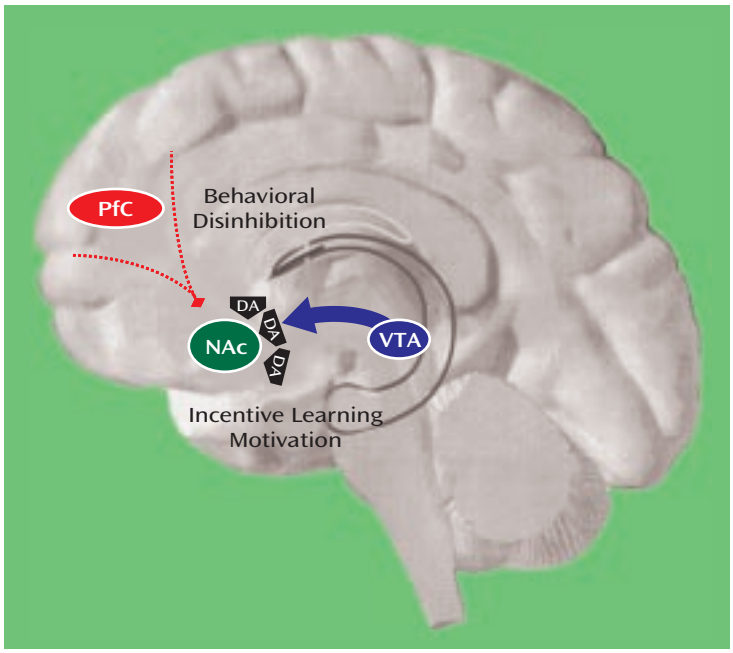
Drug Dependence and Addiction



Addiction-related changes in cortical and subcortical systems involved in regulating addictive behavior in the nucleus accumbens (NAc): chronic drug and alcohol abuse is associated with hypofrontality in several regions including the prefrontal cortex (PfC) in human studies and long-term depression in cortico-accumbal synapses in animals. Conversely, dopamine neurons in the ventral tegmental area (VTA) exhibit sensitized responses to drugs and drug-related environmental stimuli in animal studies. The weakening of cortical glutamatergic input is thought to contribute to behavioral disinhibition (impulsivity), whereas enhancement of dopamine input is thought to facilitate incentive learning and motivational responses to relapse-inducing stimuli. These changes may persist for at least 1 month into abstinence in dependent patients.

Neural Substrates

The loss of control over drug use that characterizes addiction develops progressively over time as a result of drug-induced changes in the brain. Chronic substance use leads to the behavioral and neurobiological changes referred to as dependence and can be diagnosed according to the clinical criteria in DSM-IV. The characteristics of addiction include escalating drug intake, impulsive and compulsive drug use, increased drug craving, and withdrawal symptoms following drug cessation. Drug dependence has been successfully modeled in animal preparations by observing behavioral correlates of clinical addiction in humans such as increased drug taking and drug craving in withdrawal, a process that has provided methods to study the neural substrates of drug dependence and addiction. The most reproducible finding in drug addiction is that abused substances activate the mesolimbic dopamine system, which reinforces both natural and pharmacologic rewards. The mesolimbic dopamine system consists of dopamine-containing neurons in the ventral tegmental area (VTA) and their axonal projections to terminal fields in the nucleus accumbens (NAc) and prefrontal cortex (PfC). Opiates, psychostimulants, alcohol, nicotine, and cannabinoinds all act on this system to increase synaptic levels of dopamine (DA) during their drug action. Opiates increase dopamine, among other mechanisms, by removing the tonic inhibitory influence of GABAergic interneurons on dopamine-containing cells. Low or moderate levels of alcohol disinhibit dopamine neurons directly. Nicotine acts on nicotinic cholinergic receptors to depolarize dopamine neurons. Amphetamines release dopamine, and cocaine blocks the reuptake of dopamine. Phencyclidine and other psychotomimetics attenuate the excitatory glutamatergic inputs into the nucleus accumbens that regulate GABAergic inhibition of dopamine-containing cells. For natural rewards, like food or sex, dopamine is also released acutely but not in a sustained fashion. Dopamine release, in turn, leads to neuronal plasticity that may underlie incentive learning and long-term memories that contribute to craving in human addiction. Its neural basis is now being studied using modern molecular techniques.

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