The Neurological Basis of Addiction

Implications for Treating Substance Abuse

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Learning Objectives

- By the end of this activity, participants will be able to -
  - Describe the normal structure and function of the brain as it relates to addiction
  - Describe salient brain changes that occur as a result of addiction
  - Understand the implications of such changes in the treatment of substance abuse

Presentation Outline

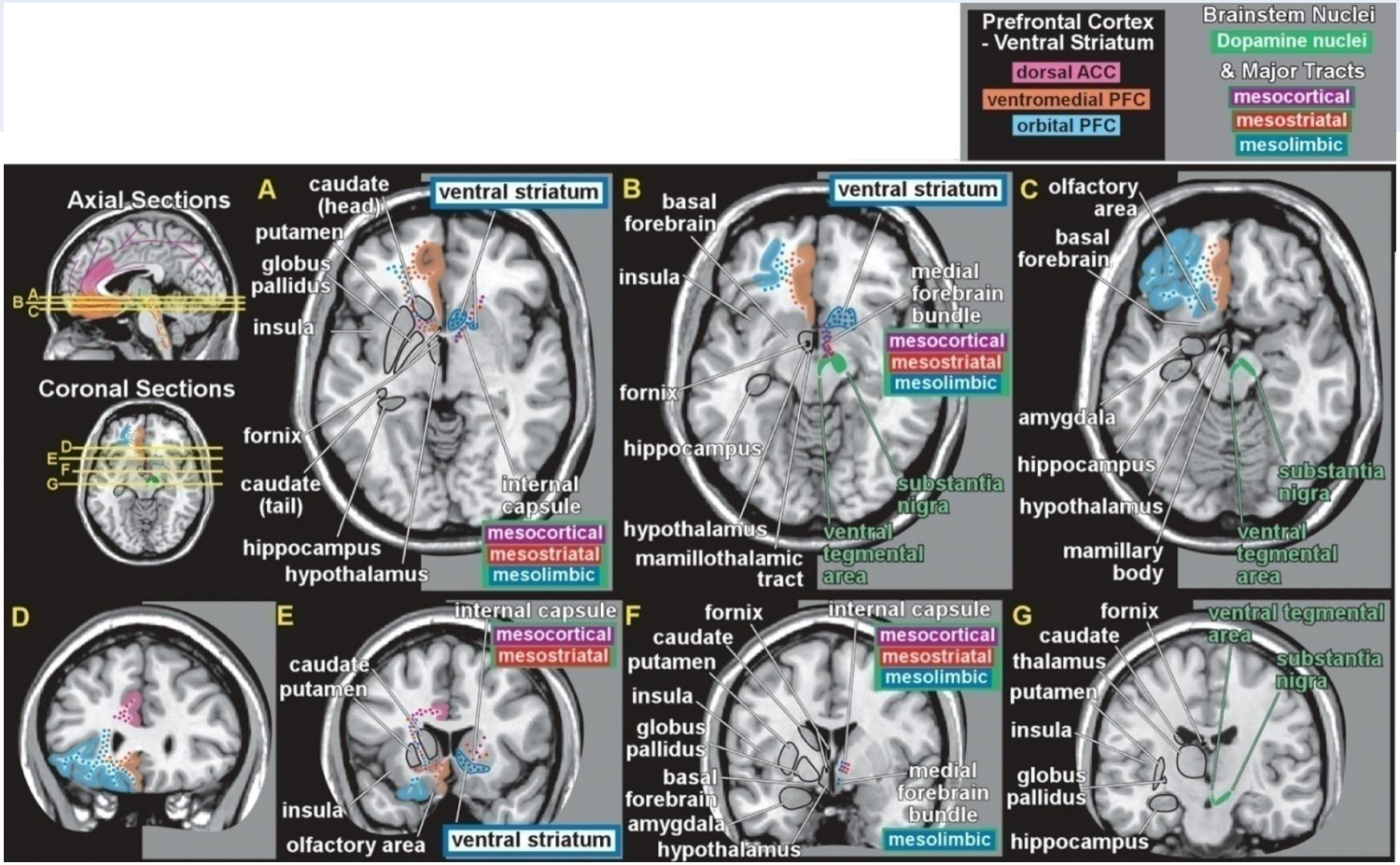
- Neurobiology of Addiction
  - Neuroanatomy
  - Circuitry of Reward
- Substance Use Disorders
  - Definition of Addiction
  - How Neural Dysfunction Maintains Addiction
  - Stages of Addiction
  - Implications for Treatment

Neuroanatomy

- The Human Nervous System
  - CNS - The Brain and Spinal Cord
  - PNS – Peripheral Motor and Sensory Nerves
  - ANS – Autonomic Nerves, Sympathetic vs Parasympathetic

Neuroanatomy

- CNS Anatomy -
  - Anatomy of the Brain
    - The brain is a complicated structure
    - Has important structures on the surface and embedded within it
      - It is really helpful (but possibly difficult) to think in 3-D
    - Has many interacting parts, both grossly and microscopically
    - No one is absolutely sure about how these parts interact
    - The brain is plastic, i.e. structure and function can change with various forms of stimulation, both biological and psychological
    - All of the above factors have a part to play in understanding addiction



COVER and FIGURE 1. Approximate portions of the prefrontal cortex (PFC), important for reward, are color-coded (dorsal anterior cingulate cortex [ACC]: pink; ventral PFC: orange; orbital PFC: blue) on the left side of axial (A–C) and coronal (D–G) MRIs. Approximate extent and locations of major midbrain dopamine nuclei important for reward (dark green) and the major dopaminergic tracts (mesocortical: purple; mesostriatal: red; mesolimbic: dark blue) are color-coded on the right side of axial (A–C) and coronal (D–G) MRIs.

Neuroanatomy

- The Brain
  - Composed of Gray Matter (Nerve Cell Bodies) and White Matter (Nerve Cell Extensions [Axons])
  - Lies at upper end of spinal cord
  - Is the seat of consciousness, cognitive function, perception and communication, plays central role in determining human behavior

Neuroanatomy

- Moving craniocaudally
  - Cerebral Hemispheres
    - Cerebral cortices (Surface areas of gray matter)
  - White matter tracts
    - Corpus Callosum
    - Fornix
    - Medial Forebrain Bundle
  - Ventricles (Collections of CSF in Brain)

Neuroanatomy

- Continuing on our downward course
  - Basal ganglia (Areas of gray matter embedded deep within the brain)
  - Thalamus, Hypothalamus, Pituitary Gland, Pineal Gland

Neuroanatomy

- And even further down…
  - Brainstem
    - Midbrain
    - Pons
    - Medulla Oblongata
  - Cerebellum
    - Vermis
    - Hemispheres

Neuroanatomy

- Expanding on the Main areas involved in addiction
    - Cerebral cortices
        - **Prefrontal cortices**
        - Sensory areas
        - Motor areas
        - Associational cortices
        - **Insular cortex**
        - **Entorhinal cortex**

Neuroanatomy

- Expanding on the main areas involved in addiction
    - Medial Forebrain Bundle
        - **Mesocortical tract**
        - **Mesolimbic tract**
        - Nigrostriatal tract
        - Tuberoinfundibular tract

Neuroanatomy

- Expanding on the main areas involved in addiction
  - Basal Ganglia
    - Caudate, Putamen, Globus Pallidus, **Nucleus accumbens** (located between caudate and putamen), **Ventral Pallidum**
    - Lentiform Nucleus = Putamen plus Globus pallidus
    - Corpus Striatum = Lentiform nucleus plus Caudate
    - Neostriatum /Dorsal Striatum/Striatum = Caudate plus putamen
    - Ventral Striatum = Nucleus accumbens, the ventral olfactory tubercle, and ventral caudate and putamen

Neuroanatomy

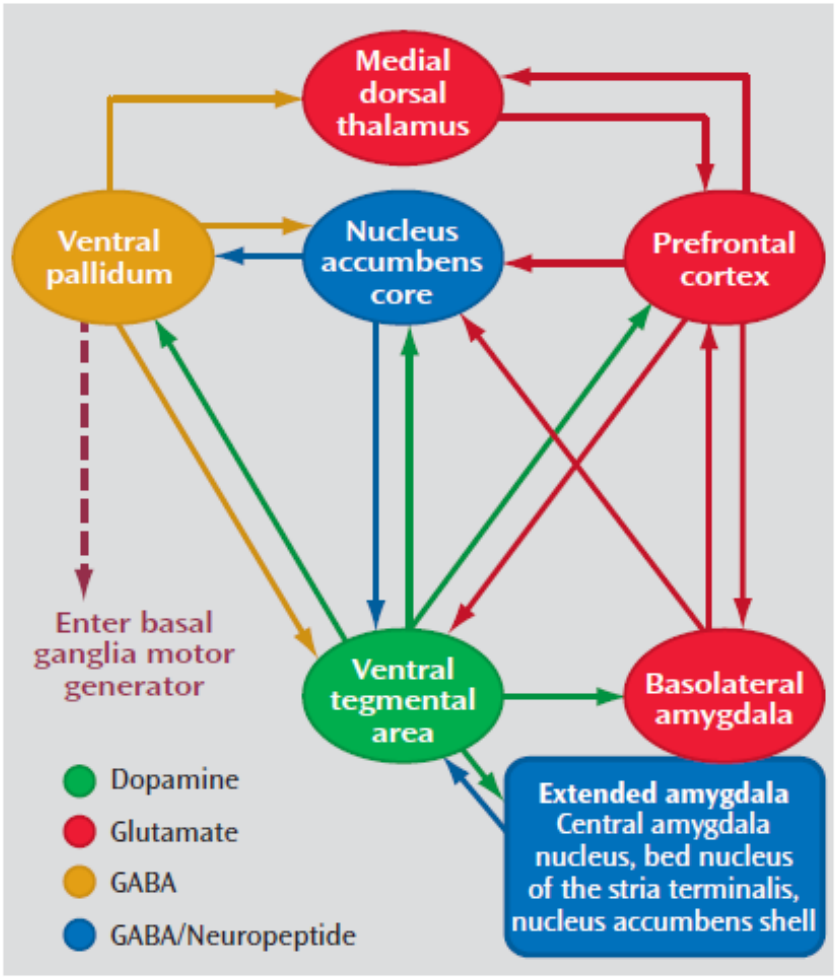
- Expanding on the Main areas involved in addiction
  - Thalamus
    - Divided into three regions that are anatomically defined by a "Y" shaped bundle of nerve fibers termed the internal medullary lamina.
      - Anterior, lateral and medial subdivision of the thalamus.
        - » The anterior thalamic nucleus has a single nucleus, the anterior nucleus
        - » The medial portion of the thalamus contains **the medial dorsal nucleus** (MD; also called the dorsal medial nucleus - DM) as well as smaller midline nuclei (located right beneath the wall of the third ventricle).
        - » The lateral region is subdivided into ventral and dorsal tiers each of which contain subnuclei.
    - Relays motor and sensory signals to the cerebral cortex

Neuroanatomy

- Brainstem
  - Midbrain
    - **Ventral Tegmental Area**

Neurocircuitry

FIGURE 1. Neural Circuitry Mediating the Activation of Goal-Directed Behavior



Taken from "The Neural Basis of Addiction: A Pathology of Motivation and Choice", Kalivas and Volkow, (Am J Psychiatry 2005; 162:1403–1413)

Reward Circuitry

- Rewarding effects of acute drug administration depends on increased DA release in nucleus accumbens
- Motivationally relevant event causes VTA to release DA throughout circuit (especially to nucleus accumbens and PFC)
  - DA then serves 2 functions
    - Alerts one to presence of novel important stimulus, thereby promoting learning
    - Alerts organism to possible appearance of a familiar important stimulus on basis of associated environmental stimuli

What is Addiction?

- Open discussion

DSM 5

- Addiction –
  - “The essential feature of a substance use disorder is a cluster of cognitive, behavioral, and physiological symptoms indicating that the individual continues using the substance despite significant substance-related problems.”
  - “[Addictive substances] produce such an intense activation of the reward system that normal activities may be neglected. Instead of achieving reward system activation through adaptive behaviors, drugs of abuse directly activate the reward pathways.”
  - “The pharmacological mechanisms by which each class of drugs produces reward are different, but the drugs typically activate the system and produce feelings of pleasure, often referred to as a “high.” “

DSM 5

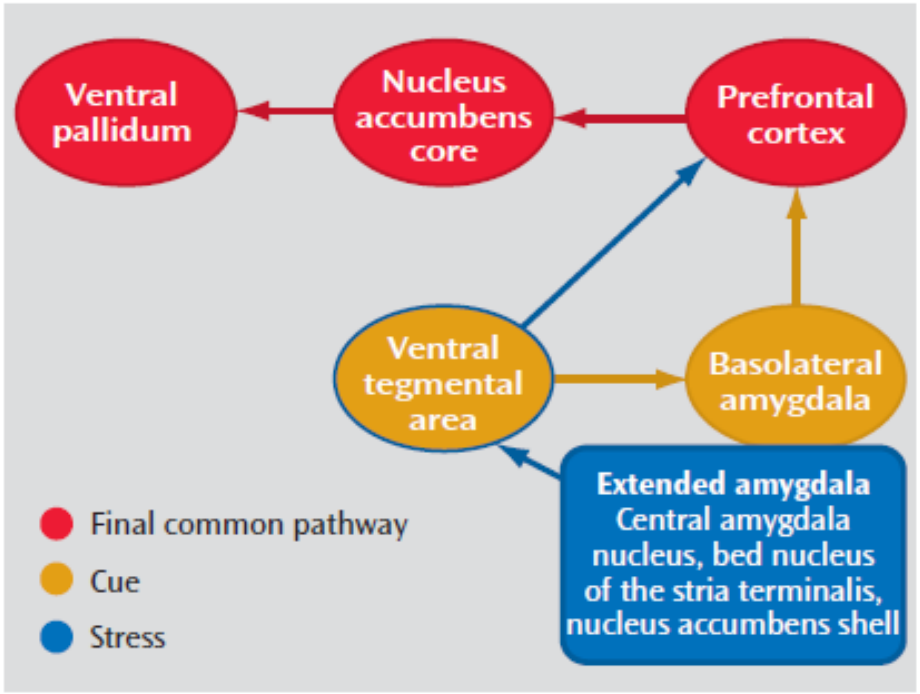
- Addictive substances –
  - Alcohol, Tobacco, Cannabis, Hallucinogens and PCP, Sedative/Hypnotic/Anxiolytic, Opioids, Inhalants, Stimulants
  - DSM 5 also recognizes gambling disorder (pathological gambling)

DSM 5

- Criteria for substance addiction –
  - Impaired control
  - Social impairment
  - Risky use
  - Pharmacological criteria

Circuit Dysregulation

FIGURE 2. Neural Circuitry Mediating Drug Seeking[a]



[a] The series projection from the prefrontal cortex to the nucleus accumbens core to the ventral pallidum is a final common pathway for drug seeking initiated by stress, a drug-associated cue, or the drug itself (which increases dopamine release in the prefrontal cortex).

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Circuit Dysregulation

- Dysregulation of reward circuit (Fig. 1) is induced by repeated use of addictive drugs, establishing behaviors characteristic of addiction (e.g. Fig. 2)

Drug Seeking

- Can be reinstated by –
  1. Cue previously associated with drug delivery
  2. Mild stressor
  3. Single dose of drug

Drug Seeking

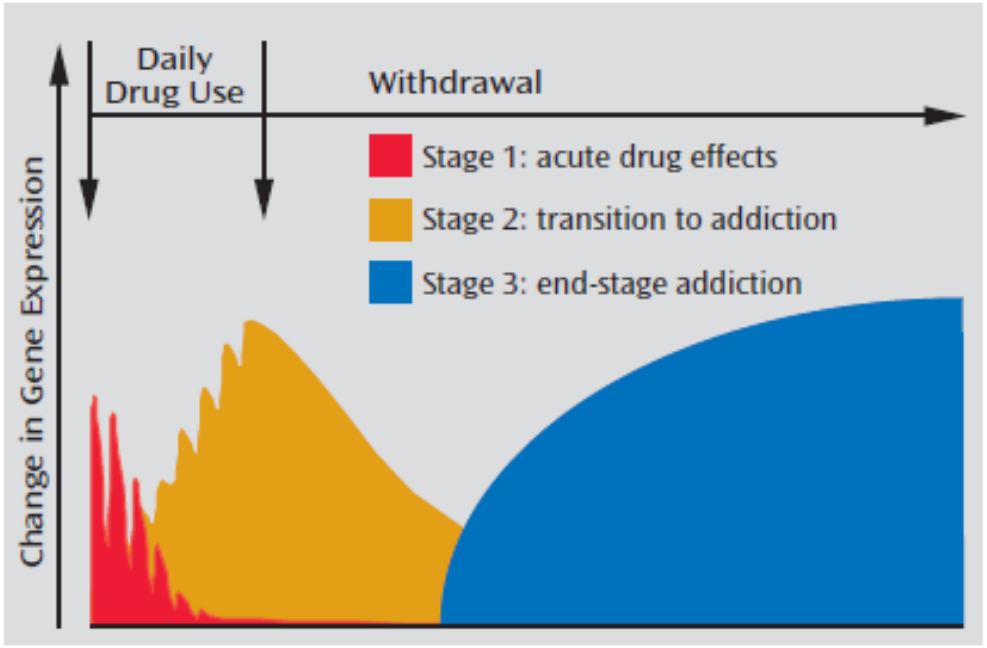
- Prefrontal Cortex
  - Necessary for drug seeking
  - Craving associated increase in prefrontal activity is on the background of reduced activity when pt is drug free
  - Activation of anterior cingulate and OFC is inhibited in experimental situations of biologically relevant rewards e.g. sexual cues
  - These observations indicate that prefrontal dysregulation is involved in the greater value of stimuli assoc with drug availability over those assoc with biological rewards

Drug Seeking

- Dopamine Transmission
  - Necessary for drug seeking
  - Reinstatement of drug seeking depends on DA release into the PFC and amygdala, not the nuc accumbens

Stages of Addiction

FIGURE 4. The Three Stages of Addiction[a]



[a] Acute drug effects occur widely in dopamine terminal fields in the circuit shown in Figure 1. Neuroadaptations mediating the transition from recreational drug use to addiction endure for a finite period after discontinuation of repeated drug administration and initiate the changes in protein expression and function that emerge during withdrawal and underlie the behavioral characteristics of end-stage addiction, such as craving, relapse, and reduced ability to suppress drug seeking.

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Stages of Addiction

- Drug high and initiation of addiction is caused by DA release into the nucleus accumbens
- Repeated drug use causes gradual recruitment of PFC and its glutamatergic efferents to the nucleus accumbens
- Switch from impulsive to compulsive use

Stages of Addiction

1. Acute Drug Effects
   - Supra-normal DA release throughout circuit
   - Causes neuroplastic changes that persist for hrs to days after drug use
2. Transition to Addiction
   - Due to changes in neuron function that accumulate with repeated admin of drug and decrease over days to weeks after stopping drug use

Stages of Addiction

1. End-Stage Addiction
   - Due to enduring cellular changes
   - Vulnerability to relapse endures for years
   - Changes in protein content/function here often become greater with increasing periods of withdrawal

Implications for Treatment

- Open discussion