Gambling Disorder: A Disease for Multiple Contexts

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Disclosures

- Dr. Moberg has nothing to disclose.

Objectives

- Discuss the relevant neurobiology
- Comparisons and contrasts between substance use disorders and process addictions with a focus on gambling
- Expansion of what is known regarding gambling into other process addictions including treatment

What do we know?

- We know less about process addictions than chemical addictions.
- We know more about gambling than the other process addictions.
- Dopamine, a chemical that plays a role in chemical addictions, also plays a role in gambling disorder. There is evidence for involvement of other neurotransmitters as well.
- The mesolimbic and mesocortical systems are involved in both chemical and gambling disorders.
- Parkinson's disease patients provide an interesting model to study some process addictions.

THE REWARD SYSTEM: THE CORE

Similarities

- Early age of onset
- Chronic relapsing patterns
- Many resolve on their own
- Tension or arousal before
- Relief during (“high”)

Grant et al., 2010

Is gambling disorder a dopamine deficiency disorder?

- Low dopamine levels may be baseline
- Low dopamine levels may be the result

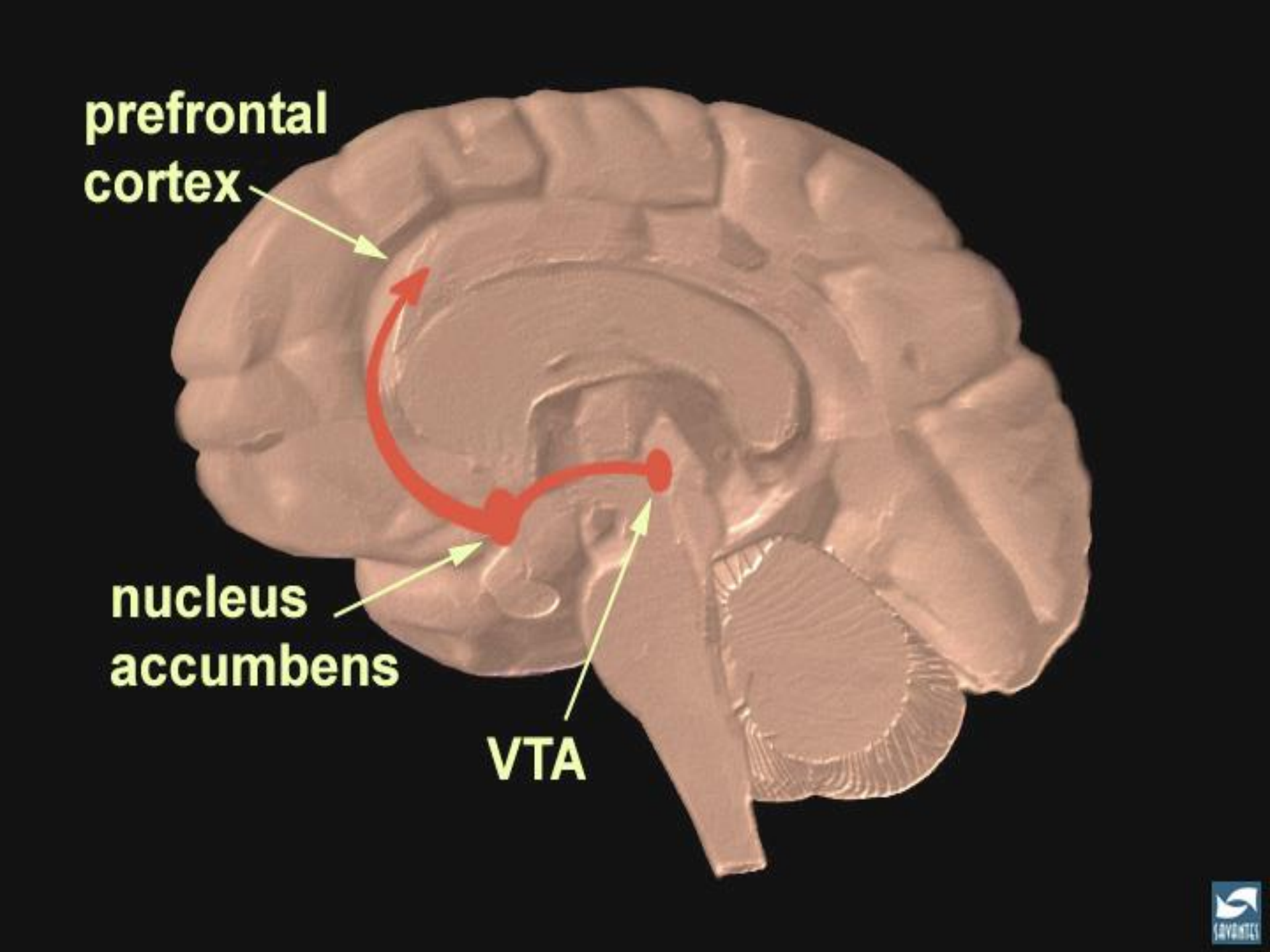
- …and the results are equivocal in gambling

Probst & Eimeren, 2013

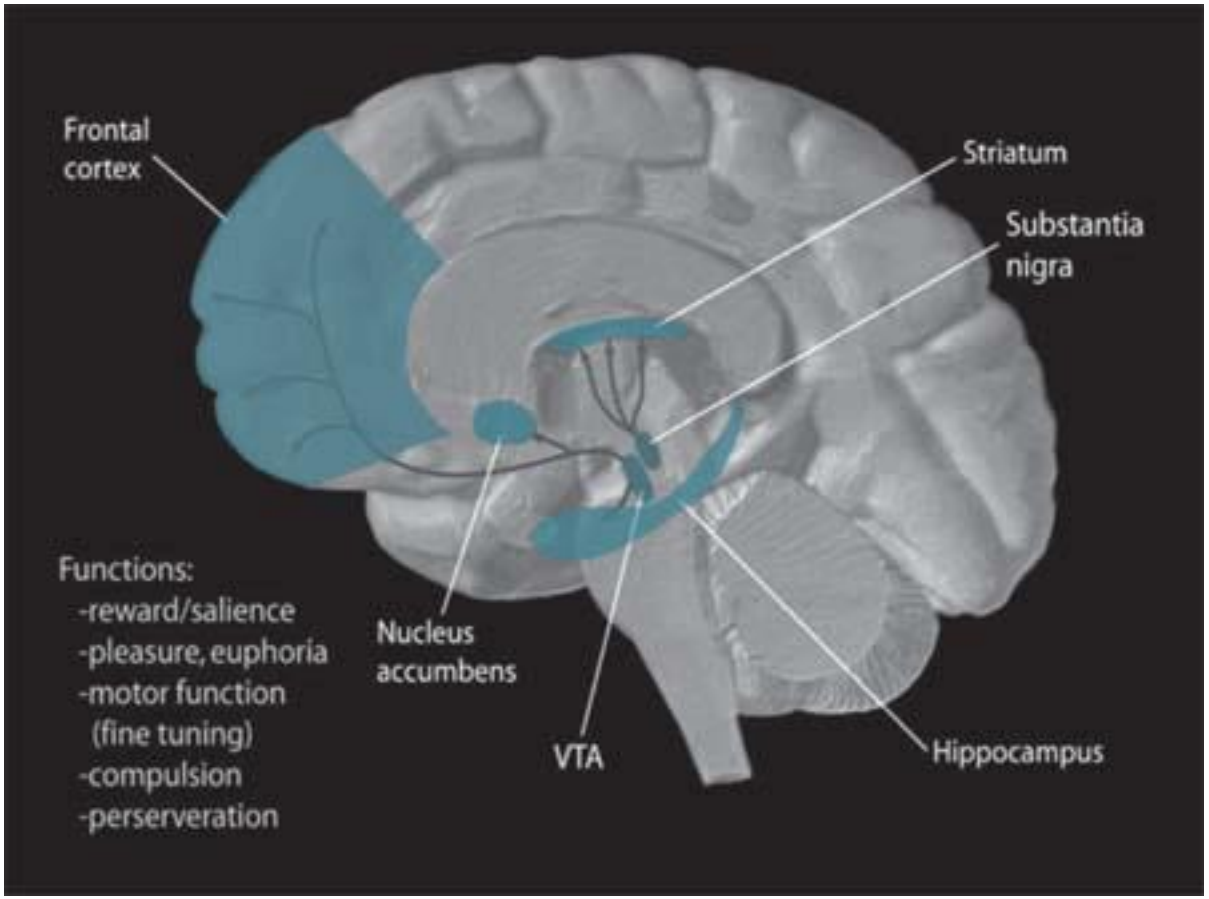
Salience attribution

- Stronger activation of reward system following cues
  - Drugs
  - Unclear with gambling

Probst & Eimeren, 2013

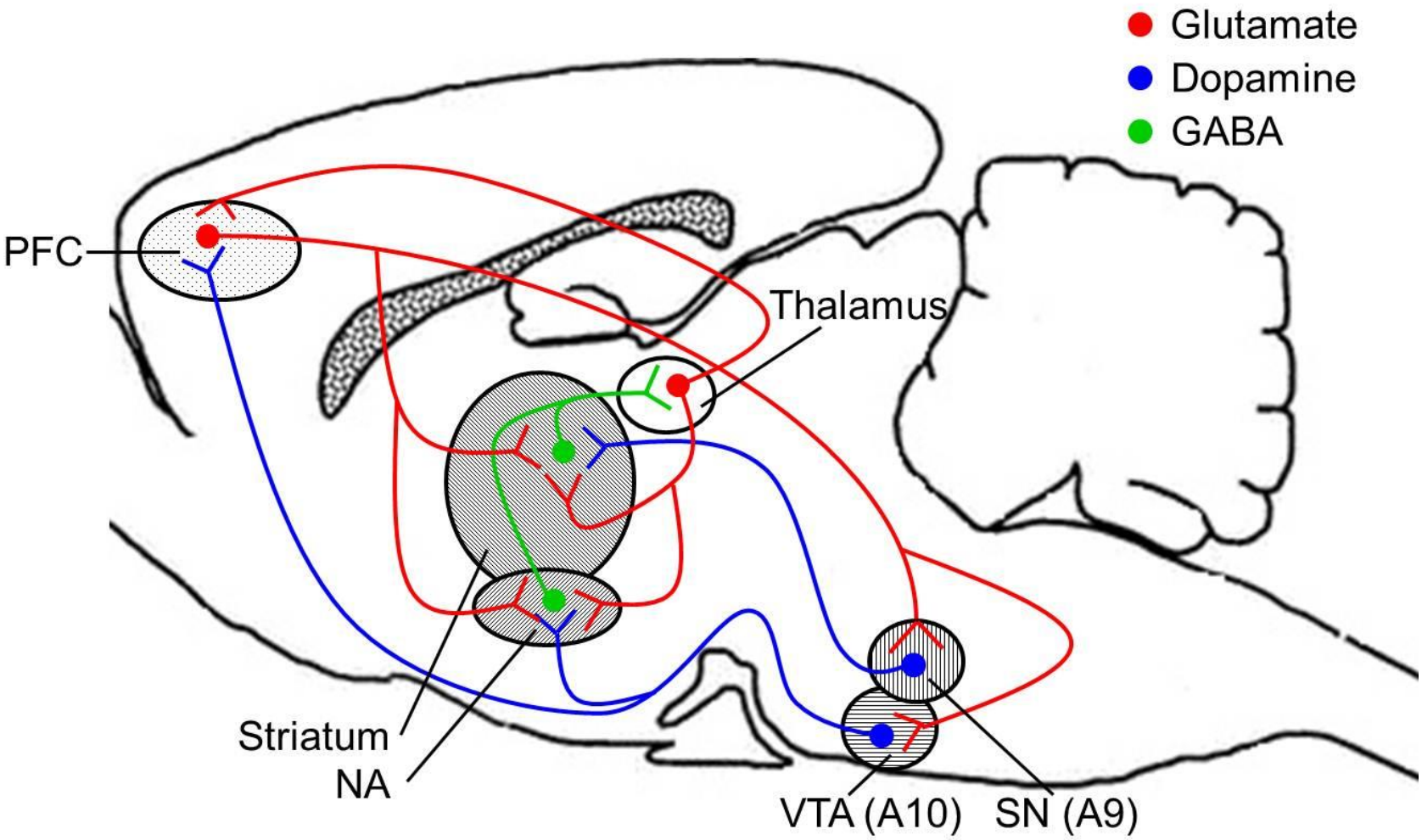

prefrontal
cortex
nucleus
accumbens
VTA

Adding another dopamine circuit



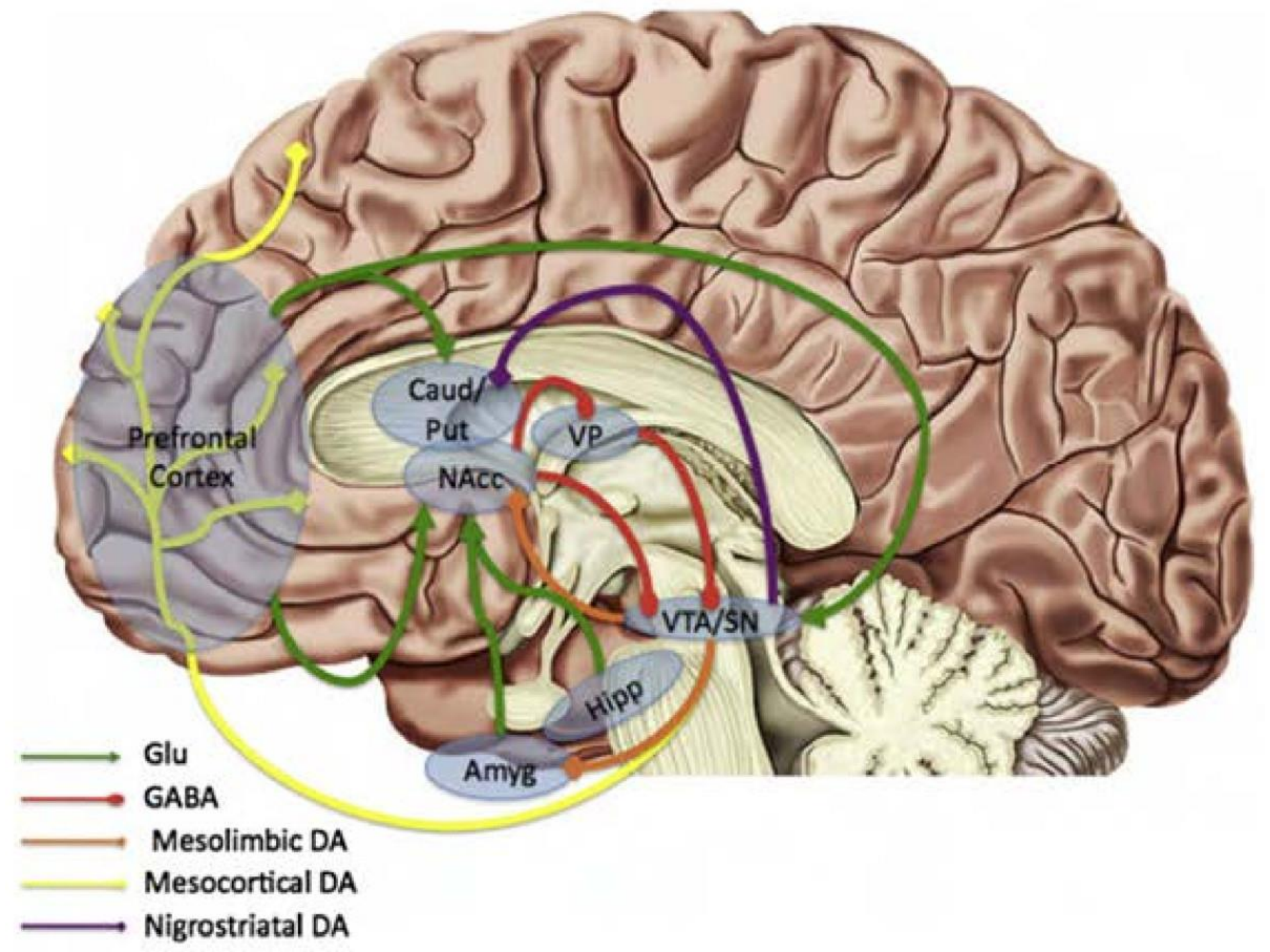
VTA to NA: reward pathway
SN to dorsal striatum: coordination of motor function

Dopamine and glutamate interactions
Miller et al., 2013



Relevant areas of the brain

- Reward and reinforcement
  - Ventral tegmental nucleus
  - Ventral pallidum
  - Nucleus accumbens
- Memory
  - Hippocampus
  - Amygdala
- Executive function
  - Pre-frontal cortex
- Coordination of movement and behavior
  - Substantia nigra
  - Dorsal striatum

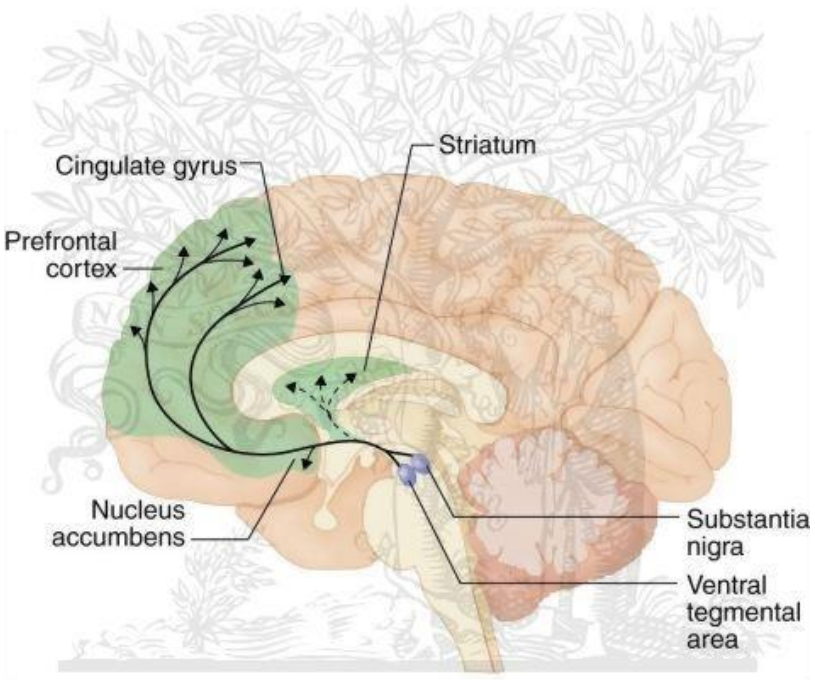

Prefrontal Cortex
Caud/ Put
VP
NAcc
VTA/SN
Hipp
Amyg
Glu
GABA
Mesolimbic DA
Mesocortical DA
Nigrostriatal DA

Executive functions

- Differentiate among conflicting thoughts
  - Good vs. bad
  - Better vs. best
  - Same vs. different
  - **Future consequences of current activities**
  - Differentiate between conflicting thoughts
  - **Working toward a defined goal**
  - **Expectation based on actions**
  - **Behavioral inhibition**
  - Social “control”

Neuroanatomical hypothesis Cilia 2010 and 2011

- Is gambling disorder a neural disconnectivity disorder?
- 3 populations
  - Parkinson's disease + gambling (group 1)
  - Parkinson's disease w/o gambling (group 2)
  - Normal controls (group 3)
- Single Photon Emission Computed Tomography (SPECT)
- Normal connection between anterior cingulate cortex and striatum
  - Anterior cingulate cortex—error detection (visualized by increasing activity)—**losing**
  - Striatum—shifts behavior in the context in increasing errors—**stopping**
- Shifting strategy abnormal in group 1
- Conclusion: behaviors don't change despite errors



Cingulate: error detection

Striatum: coordination of motivation with behavior

Implicated neurotransmitters

- Norepinephrine—arousal and excitement
- Serotonin—impulse control
- Dopamine—rewarding and reinforcing aspects
- Opioids—pleasures and urges
- Cortisol—stress responsivenes
- Glutamate—cognitive functioning and flexibility

Potenza, 2013

Where does dopamine fit in?

- Reward deficiency hypothesis
  - Vulnerable individuals have low D2 receptor density and have a need for strong reinforcers.
  - Blum et al., 1996.
- Sensitization theory (salience attribution)
  - Vulnerable individuals are sensitized to triggers and cues after repeated use.
    - Robinson & Berridge, 2008.
- Impaired response inhibition and salience attribution
  - Low D2 receptor density creates vulnerability and is maintained by salience attribution.
    - Goldstein & Volkow, 2002.

Reuter et al., 2005; Grant et al., 2006; Grant et al., 2010; van Holst et al., 2010, Karim & Chaudhri, 2012; Probst & Elmeren, 2012; Joutsa et al., 2012; Grant et al., 2013; Potenza et al., 2013; Potenza, 2013

Another dopamine observation

- Dopamine agonists and antagonists have been linked to gambling behaviors.

Potenza, 2013

Dopamine dysregulation syndrome
Normal motor function

- Dopamine cell bodies in substantia nigra
  - Project to:
    - Dorsal striatum
- Result: control of fine motor movements

Fenu et al., 2009

Dopamine dysregulation syndrome
Impaired motor function

- Dopamine deficient cell bodies in substantia nigra
  - Project to:
    - Dorsal striatum
- Result: poor control of fine motor movements

Dopamine dysregulation syndrome
Normal reward function

- Dopamine cell bodies in Ventral Tegmental Nucleus
  - Project to:
    - Ventral striatum (Nucleus accumbens)
    - Pre-frontal cortex
- Result: Reinforcement of behaviors (affective and impulsive)

Dopamine dysregulation syndrome
Impaired reward function

- Dopamine deficient cell bodies in Ventral Tegmental Nucleus
  - Project to:
    - Ventral striatum (Nucleus accumbens)
    - Pre-frontal cortex
- Result: Impulsive behaviors (ADHD like?)

- NB: Loss of dopamine in VTA not as bad as SN

Post dopamine replacement therapy

- Increased motor system function
  - Relief of motor symptoms of PD
- Increased reward system function leading to decreased impulse control (ICD)
- Addictive behaviors with respect to the DRT

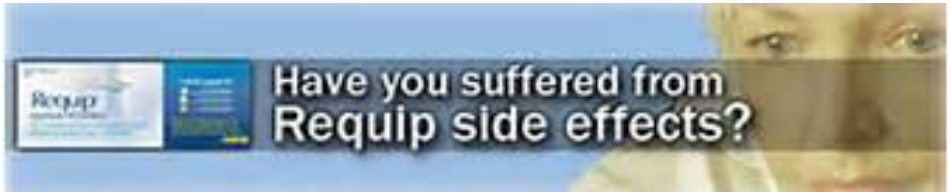
Parkinson's model

- Dopamine cell bodies
  - Substantia nigra
  - Dorsal caudate-putamen
    - Motor systems impaired
  - Ventral tegmental area (receive glutamate)
    - Nucleus accumbens (receive glutamate)
    - Pre-frontal cortex (send glutamate to VTA and NA)
    - Ventral caudate-putamen
      - Reward circuitry mildly impaired

Fenu et al., 2009

Anti-Parkinsonian Medications

- Dopamine replacement therapy—all D receptors
  - levodopa
- Monoamine oxidase inhibitors—inhibit metabolism
  - Selegiline
- Dopamine agonists—D2/D3
  - Bromocriptine
    - Parlodel ®
  - Amantadine*
    - Symmetrel ®
  - Ropinirole
    - Requip®
  - Pramipexole
    - Mirapex®



* Indirect: increases release and inhibits re-uptake of dopamine

Anti-Parkinsonian Medications

- Gambling
- Hypersexuality
- Spending
- Binge Eating
- Skin picking
- Pathological internet use
- Punding

Fenu et al., 2009

Treatment

- Cognitive Behavioral Therapy
- Motivational Interviewing
- 12 step
- Financial Planning
- Self restriction from casinos—video gaming, internet gaming
- Medication Assisted Treatment

Medication Assisted Treatment (Grant et al., 2010)

- Opioid antagonists
  - Nalmefene—Grant et al., 2006; Grant et al., 2010
  - Naltrexone—Kim et al., 2001; Grant et al., 2008; Grant et al., 2008
- Selective serotonin reuptake inhibitors
  - Paroxetine—Kim et al., 2002
  - Fluvoxamine—Hollander et al., 2000; Blanco et al., 2002
  - Sertraline—Saiz-Ruiz et al., 2005
  - Escitalopram—Grant & Potenza, 2006; Black et al., 2007
- N-Acetyl Cysteine—Grant et al., 2007
- Carbamazepine—Black et al., 2008
- Lithium—Hollander et al., 2005

Amantadine is a complex medication…or a drug looking for an indication

- Anti-viral (influenza)
- Dopaminergic (Parkinson's, cocaine withdrawal)
- NMDA receptor antagonist (Alzheimer's, gambling)

Hubsher et al., 2012

A suggested algorithim

- If urges or cravings to gamble are present
  - Trial of opioid antagonist
  - If co-occurring SUD trial of opioid antagonist
  - If depression/anxiety playing a major role trial of SSRI
  - If mania/hypomania playing a major role trial of Li

  - Always consider CBT

Grant and Kim, 2006

Other process addictions

- Hypersexuality
  - Opioid antagonists—naltrexone (Bostwick & Bucci, 2008)
- Kleptomania
  - Opioid antagonists—naltrexone (Grant & Kim, 2002)
- Shopping/spending
  - SSRIs—citalopram (Koran et al., 2002)
- Hoarding
  - SSRIs—paroxetine (Saxena et al., 2006)
- Binge eating
  - SSRIs—sertraline (McElroy et al., 2000); citalopram (McElroy et al., 2003)
- Internet gaming
  - SSRIs—escitalopram (Dell'Osso et al., 2008)
- Trichotillomania
  - Opioid antagonists—naltrexone (Carrion, 1995)

Summary and major themes

- Medication Assisted Treatment for chemical addictions was not initially evidence based but has been transformed.
- The neurobiology of chemical addiction is well understood and the knowledge base continues to grow.
- The neurobiology of process addictions is not as well understood but the knowledge base continues to grow.
- There is considerable overlap of treatment approaches between the chemical and process addictions.
- Gambling disorder is an excellent model to study process addictions.
- Opioid antagonists and SSRIs are major classes of medications that show promise in the treatment of process addictions.

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