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New Theories of Addiction: Beyond Dopamine and the Reward Center

Jennifer Buckman, PhD
Fiona Conway, PhD

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Old Theory of Addiction

DRUGS OF ABUSE TARGET THE BRAIN'S PLEASURE CENTER

The diagram is divided into two main sections. On the left, a brain cross-section shows the 'Brain reward (dopamine) pathways' with labels for the 'Ventral Tegmental Area', 'Nucleus Accumbens', and 'Caudate Putamen'. Below this is a caption: 'These brain circuits are important for natural rewards such as food, music, and sex.' On the right, under the heading 'Drugs of abuse increase dopamine', there are two sub-diagrams. The first, labeled 'FOOD', shows a 'Dopamine Receptor' on a cell membrane with a moderate number of dopamine molecules (yellow dots) binding to it. The second, labeled 'COCAINE', shows a 'Dopamine Receptor' with a significantly higher density of dopamine molecules binding to it, indicating an exaggerated increase. A caption below states: 'Typically, dopamine increases in response to natural rewards such as food. When cocaine is taken, dopamine increases are exaggerated, and communication is altered.'

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Somatic-Marker Theory of Addiction

Bechara & Damasio, 2005
Verdejo-Garcia & Bechara, 2009

- Started as a theory of how emotions influence decision-making.
- Prior to this work, it was assumed that people were equipped with “*unlimited knowledge, time, and information-processing power*” when making a decision. No one considered emotion as an influence!

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Somatic-Marker Theory

- **EMOTION** – defined as “a collection of changes in body and brain states triggered by a dedicated brain system that responds to specific contents of one’s perceptions, actual or recalled, relative to a particular object or event.”
- Translation: conscious and unconscious reactions to our perceptions of specific objects or events.
- *Where Do These Perceptions Come From?*

Somatic-Marker Theory

- **DECISION** = a juncture at which a choice must be made.
- **CONFLICT** = competing cues/events/ideas
- When the decision involves a conflict, what happens to help a person resolve it (make a decision)?
- Bechara & Damasio proposed a role for emotion and “a systems-level neuroanatomical and cognitive framework for decision-making and its influence by emotion”

Somatic-Marker Theory of Addiction

- This “systems-level neuroanatomical and cognitive framework for decision-making and its influence by emotion” was then applied to **gambling**, then to **addiction**.
- *Decision-making in addiction is “characterized by marked obliviousness to the long-term consequences of their decisions, and the failure to learn from repeated mistakes.”*

Somatic-Marker Theory of Addiction

KEY POINT:

Addiction results from impaired decision-making that stems from an inability to properly weight **immediate** reward against **long-term** negative consequences.

Somatic-Marker Theory

How we make decisions

- Consider advantages (benefits) & disadvantages (costs). (Cost-benefit analysis)

- Option 1: Great vacation
- Option 2: Go to work

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Somatic-Marker Theory

How we make decisions

- Consider advantages (benefits) & disadvantages (costs). (Cost-benefit analysis)
- Option 1: Great vacation
- Option 2: Go to work

✓ *Great vacation*
... all else being equal...

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Somatic-Marker Theory

How we make decisions

- But costs and benefits aren't only those that occur immediately.
- There are immediate and delayed costs and benefits.
- Option 1: Great vacation
 - Totally stressed and overworked.
 - You've never been to Maui.
- Option 2: Go to work
 - Could save more for your retirement & retire earlier.
 - Did have vacation in May.

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Somatic-Marker Theory

More layers than an onion ...

- Option 1: Great vacation
 - Totally stressed and overworked.
 - But you kind of love it. EMOTIONAL TAG
 - You've never been to Maui.
 - Amazing Beach EMOTIONAL TAG
 - But cousin Joey is going and will drive you crazy. EMOTIONAL TAG
- Option 2: Go to work
 - Could save more for your retirement & retire earlier.
 - But that's so far away... EMOTIONAL TAG
 - Did have vacation in May.
 - But that's so far away.... EMOTIONAL TAG

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Somatic-Marker Theory

- **Decision-making is when all immediate and future prospects are weighted and considered, and then an overall positive or negative signal (go or no-go) is chosen.**
 - **VALENCE** – the 'positive' or 'negative' valuation of the decision.
 - Related to natural selection.
 - Stronger signals gain selective advantage over weaker ones until a winner takes all.
 - Once the dominant pattern emerges, neural systems that modulate feeling, cognition, and the behavioral decision as to whether to seek the drug or not can be acted upon.

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Somatic-Marker Theory

KEY POINT:

- Options mean different things to different people.
- Each have a different SALIENCE & VALENCE.
- Each trigger different EMOTIONAL RESPONSES.
- Decision-making is individualized and personal.
- Decision-making is also temporally-dependent (*just because you choose it today doesn't mean you'll choose it again next week*).


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Somatic-Marker Theory

DECISION-MAKING IS A PROCESS GUIDED BY EMOTIONS

Somatic markers: emotional signals (feelings generated from emotions) that have been connected by learning to anticipated future outcomes.

Negative Marker + Future outcome = **Alarm Bell**



Positive Marker + Future outcome = **Incentive**




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Somatic-Marker Theory

Somatic markers: emotional signals (feelings generated from emotions) that have been connected by learning to anticipated future outcomes.

SOMATIC (soma = body, Greek): Collection of body-related responses that are hallmarks of emotions.

- Includes internal milieu and viscera
- May or may not be observable
 - Hormone release
 - Heart rate*
 - Smooth muscle contraction
 - Posture
 - Facial expression*
 - Fight or flight/freezing



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Somatic-Marker Theory

KEY POINT:

A somatic reaction is a whole body response to an object or event based on a previous pairing of that object/event with an emotional context.

There's that learning piece again...

Somatic-Marker Theory of Addiction

- The inability to make advantageous decisions in real-life is related to a defect in an emotional mechanism that rapidly signals the prospective consequences of an action, and assists in the selection of an advantageous response.
- Deprived of this emotional signal, individuals rely on a reasoned cost-benefit analysis of numerous and often conflicting options involving both immediate and future consequences.

Somatic-Marker Theory of Addiction

- Emotional impairment degrades speed of deliberation/ decision-making because of an endless reasoned analysis of pros and cons of choices.
- Impairment degrades adequacy of choice (choosing less advantageous option)



Response rigidity

I CAN'T DECIDE IF I NEED A HUG, 6 SHOTS, OR 2 WEEKS OF SLEEP.

Linking Somatic Response to an Object/Event

The Induction Phase:

- When pondering a decision, somatic states are triggered by primary AND/OR secondary inducers.

Primary Inducers

- Innate or learned stimuli that induce pleasurable or aversive (somatic) states automatically and obligatorily.
- Concepts or knowledge that through learning can automatically and obligatorily elicit an emotional response.
 - Seeing a snake
 - Actual encounter with a drug by a drug user
 - Being told you won the lottery

Humans automatically, involuntarily, and obligatorily elicit a “pleasure” response when they uncover a solution to a problem.

Secondary Inducers

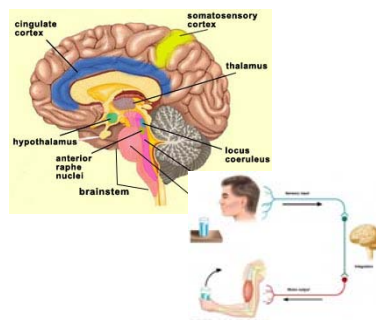
- Recollection of personal or hypothetical emotional events.
 - Memories of a primary inducer (seeing a snake)
 - Imagining winning the lottery
- Subsequent presentation of a stimulus evokes thoughts and memories that operate as a secondary inducer.
- Generate fainter activation of the somatic state than if it were triggered by the primary inducer.

Somatic-Marker Theory of Addiction

- In a normal brain, primary and secondary inducer processing can be elicited by the same stimulus at the same time.
- Looking at a picture of a baby with a tumor can quickly and automatically trigger an emotional response (serving as the primary inducer) and generate thoughts (picturing your own child in this situation) that operate as secondary inducers.



Top Down & Bottom Up



Somatic (bodily) state are triggered.

↓

Emotions are tied to it.

↓

This happens through learning/association.

↓

Objects become somatic markers.

↓


Somatic markers influence decisions.

↓

Decisions determine action/response.

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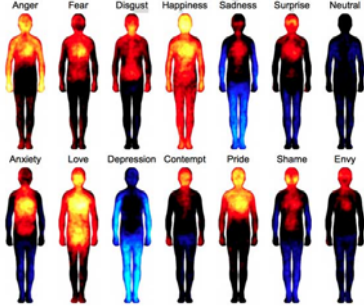
Triggering the somatic state



- **EFFECTOR STRUCTURES**
- Brain structures that produce changes in effector organs (heart, lungs, etc):
 - internal milieu (hypothalamus)
 - visceral reactions (brain stem)
 - facial expression (brain stem)
 - approach/avoid behaviors (ventral striatum/nucleus accumbens).
- Information from effector structures is integrated
 - Thalamus – subliminal processing of features of primary inducers
 - Early Sensory & Association Cortices – explicit processing of features of the primary inducers


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Feeling the Somatic State



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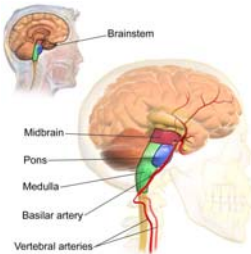
...from body to brain



- After, somatic states from primary and/or secondary inducers are induced in the body
- The vagus nerve and spinal cord convey body information to the brain.
- * **VAGUS IS PARTICULARLY IMPORTANT.**

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Up through the brain...



- The brain stem is filled with integration/relay centers.
 - Integrating various somatic cues.
 - Involved in communicating information to maintain body's steady state, initiate a reflexive bodily reaction, and promote an adaptive responding.
- Brain stem has multiple types of cell bodies (DA, 5-HT, NE, ACh).
- Terminal of these cells radiate throughout cortex

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... the limbic system

Hypothalamus – EFFECTOR structure.

- Control body temperature, hunger, important aspects of parenting and attachment behaviors, thirst, fatigue, sleep, and circadian rhythms.
- Metabolic processes, ANS, pituitary and hormones.

Thalamus – Relay center.

Hippocampus – memory (some aspects) and spatial coding.

Amygdala – EMOTION center.

- Formation & storage of memories with emotional content, fear condition, smell & pheromone processing, aggression, facial emotional processing, social skills/emotional intelligence, maternal behavior, sexual orientation, anxiety, OCD, PTSD, BPD.

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The amygdala

- Sends message to effector structures to trigger somatic states from primary inducers.
 - Embeds emotional signals within inducer.
- Detects or recognizes the environmental features that are potential sources of immediate pleasures, or satisfaction of homeostatic needs, such as an immediate stress or withdrawal relief from association cortices.
- Likely linked to addiction/reward through connect to **striatum**.

Experiment: Subliminal cues given in MRI.

- ✓ No conscious awareness, but triggered brain activation in amygdala and striatum.
- ✓ More activation correlated to conscious emotional evaluation of the same cues out of the scanner.

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Striatum – a cluster of nuclei

- Nucleus Accumbens (ventral) is recipient of **mesolimbic dopamine** projections.
- Strongly implicated in **motivation** & drive
- Associated with **seeking** drug rewards
- Caudate/Putamen (dorsal) are implicated in **habits & learning** of **implicit** actions
- Somatic states operate implicitly (correct response is learned without conscious awareness of whether response is correct). **“knowledge without awareness”**

Experiment: Don't tell people the rules, can they figure it out?

- ✓ Healthy participants can. They use feedback about right/wrong from repeated trials.
- ✓ Parkinsonian patients cannot.

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Limbic = Impulsive System

- ...amygdala is a trigger structure for emotional (somatic) states from primary inducers. It couples the features of primary inducers, which can be processed subliminally (e.g., via the thalamus) or explicitly (e.g., via primary sensory cortices), with effector structures that trigger the emotional/somatic response. However, the amygdala is also directly connected to the ventral striatum (V.S.) and its trigger can also activate classical motivational systems associated with approach of drug related cues.

We'll come back to this

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Wait... What does this have to do with decision-making?

- Neural circuits that underlie emotional processing (or somatic state activation) overlap considerably with those subserving decision-making.

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The cortex

- In mammals and humans.
- Folds ensure capacity for huge surface in the small volume of skull.
- 2/3 of cortex in human is buried in the grooves (sulci).
- Very well organized in layers and where it projects/receives input.
- Very well organized based on functional roles and cell/transmitter type.

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3 key areas of prefrontal cortex

- Ventromedial Prefrontal Cortex (VMPFC)**
 - Personal & social decision-making
 - Detecting irony, sarcasm, deception
 - Trigger structure for emotional (somatic) states from secondary inducers.
- Dorsolateral prefrontal cortex (DLPFC)**
 - Extremely prolonged period of maturation
 - Working memory, cognitive flexibility, planning, inhibition, and abstract reasoning.
 - Motor planning, organization and regulation
- Orbitofrontal cortex (OFC)**
 - Sensory integration
 - Emotional value of reinforcers
 - Decision-making and expectation
 - Signaling *expected* reward/punishment of an action given the particular details of a situation.

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Side note: Working Memory

Based on Mayer (2003); Moreno & Mayer (2007); Marois (2005); and Miyake, et al (1999)

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Side note: Working Memory

Three Types of Memory

The diagram shows a flow from 'World' to 'Sensory Memory' (under 'Sensing'), then to 'Working Memory' (under 'Thinking') via 'Attention/Selection', and finally to 'Long-Term Memory' (under 'Memory Bank') via 'Storing/Retrieving'. There is also an arrow from 'Long-Term Memory' back to 'Working Memory' labeled 'Involuntary Storing'.

Based on Mayer (2003); Moreno

explicit (or declarative) memory: ("knowing what") is memory of facts and events, and refers to those memories that can be consciously recalled (or "declared")

implicit (or procedural) memory: ("knowing how") is unconscious memory of skills and how to do things, particularly the use of objects or movements of the body, such as playing a guitar or riding a bike.

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Other important cortical structures

Posterior Cingulate Cortex

- Communicates with various networks simultaneously.
- Implicated as a neural substrate for human awareness
- Spatial memory, configural learning, and discriminative avoidance learning, attention
- Autobiographical memories (correct)
- Emotional salience (positive & negative, amygdala more for negative)
- Very quiet during meditation, very active during daydreaming/planning

Insula – more soon...

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Cortical structures = Reflective System

As you deliberate on several options and scenarios (which are held being held in your working memory), somatic states bias weightings to promote some options and reject others **before** any option are translated into action.

DLPFC - Recalled/imagined scenarios from working memory and executive processing (inhibition, planning, cognitive flexibility).

Posterior cingulate & insula - Representation of somatic states & emotional processing

VMPC/OFC - couples somatic states to secondary inducers

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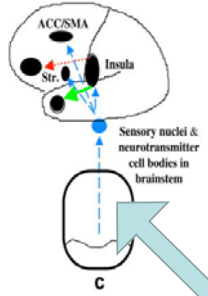
Cortical structures = Reflective System

- Functionally intact reflective system is critical for making decisions that are advantageous in the long run.
- Impairment in any of components of this system disrupts entire reflective system.

Impairments are well characterized in long-term substance users and adolescent substance users.

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Two system model of addiction



IMPULSIVE/REFLECTIVE
or TOP-DOWN/ BOTTOM-UP
or HOT/COOL
Or LIMBIC/CORTICAL

Potential Dysfunctions:

- Hyperactivity of impulsive system (exaggerates the rewarding impact of available incentives)
- Hypoactivity of reflective system (undervalues the long-term consequences of a given action)

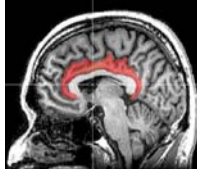
What mediates the 2 systems?
What is the role of the somatic marker?

AFFERENT (ASCENDING) INFORMATION STREAM!

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3rd part of the 2 system model...

The anterior cingulate cortex



Possible role in subjective feeling and craving.


- More likely a conflict monitoring center.
- Participates in motor response selection and generating plans for action.

Important because craving is a feeling connected to actions of seeking, obtaining, and consuming the drug. Maybe ACC isn't associated with craving, but with the tendency to act on the feeling.

- Biases response selection based on conscious/explicit information.
- "Action with awareness of what is right or wrong".
- The decisions are 'voluntary' or 'willful' and guided by knowledge, awareness, and premeditation.

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The insular cortex (insula)



- Consciousness, empathy
- Self-awareness (bodily, sense of agency)
- Emotional processing
- Motor control
- Cognitive function
- Interpersonal/social experience
- Disgust (even to imagined cues)
- Psychopathology

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The insular cortex (insula)



- **INTEROCEPTION AWARENESS** (ability to feel one's own heartbeat, or to empathize with the pain of others, gastric distension, full bladder, vertigo)
- Body homeostasis
 - Taste
 - visceral sensation (judges degree of pain)
 - Activated when imagining pain in body
 - autonomic control (control of BP)
 - immune)
- Links internal and external experiences

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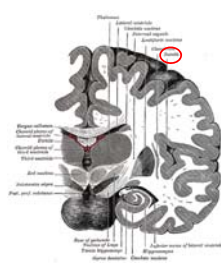
The insular cortex (insula)



- Somatic signals may remain unconscious or come to be subjectively experienced as a feeling of desire, anticipation, urge/craving.
- **INSULA** translates physiological information into what one subjectively experiences as a feeling.

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The insular cortex (insula)



- Well connected to both impulsive and reflective systems.
- Anterior insula is anatomically organized to receive signals from the entire viscera.
- **This theory sees homeostatic states as key in addiction. This process appears to depend on the insula.**

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The insular cortex (insula)



- Feedback loops arising from the body, reflecting the status of the viscera and homeostasis, and mediated through the insula, will adjust the strengths of activities within the impulsive and reflective systems.
- This can sensitize the impulsive system, and potentially over-ride the inhibitory control of the reflective system.

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The insular cortex (insula)



- Increased insula signaling may "hijack" the function of the reflective system, in such a way that it forces it to formulate plans for action to seek and procure drugs in order to satisfy urgent body needs, instead of forecasting the negative consequences of such actions, and controlling the impulsive system.

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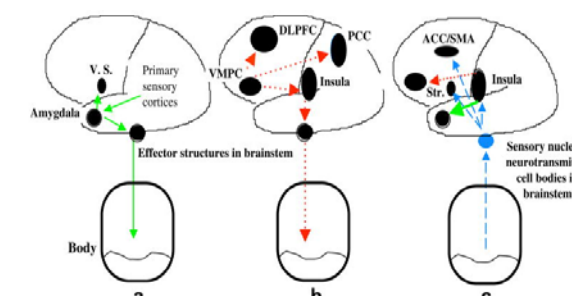
The insular cortex (insula)



- Feeling the somatic state ... **insula** translates physiological signals associated with an emotion into what becomes a 'feeling'.
- Perhaps what can be thought of as 'liking'.
- Subjective feeling association with the action of seeking, obtaining and consuming a drug (i.e., urge/desire) or WANTING.

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Somatic Marker Theory



Decisions are determined by impulsive vs. reflective inputs. Somatic markers stack the deck.

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Somatic markers Bias Behavioral Decisions

- For somatic signals to influence decisions, they must act on other neural systems that generate action.
 - Sensory comes into brain. (INSULA)
 - Motor goes out of brain. (IMPULSIVE/REFLECTIVE)
- **Addiction is viewed as a condition in which a person becomes unable to choose according to long-term consequences. This is important because if the pain signals triggered by thoughts of future negative consequences DO NOT dominate those triggered by the immediate rewarding consequences then consuming the drug continues.**
- Bottom-up somatic bias can modulate top-down cognitive mechanisms. It can interfere or hijack the top-down mechanisms that help orient decisions towards future outcomes.

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Proving the Theory Experimentally

- -Iowa gambling task
 - Simulation of real-life decision making
 - HUNDREDS of studies/papers have used this task

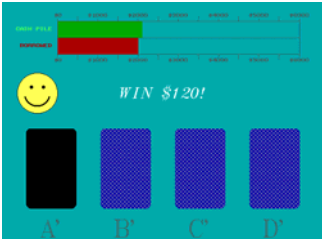


- 4 virtual decks of cards on a computer screen.
- Told that each time they choose a card they will win \$.
- Every so often, though, choosing causes them to lose \$.
- GOAL: Maximize winnings.
- Each deck has own win/loss
 - "bad decks" – LT losses
 - "good decks" – LT gains

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Proving the Theory Experimentally

- Healthy participants get really good at sticking to the 'good decks' after 40-50 trials.
- Healthy participants show **physiological** "stress" reaction [SOMATIC MARKER] after only 10 trials.
- Patients with VMPFC dysfunction chose high-yield immediate gains even though it led to higher future losses



WIN \$120!

A B C D

Newer evidence suggests 'subgroups' even among healthy controls! Surprised?

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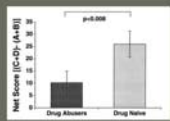
Proving the Theory Experimentally

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Proving the Theory Experimentally

Drug Abusers Can Not Use Conflict to Guide their Decision Making

- Young polysubstance abusers
- Iowa Gambling Task
- "Optimal" performance requires switching from selecting high gain/high loss decks to low gain/low loss (but more profitable) decks.



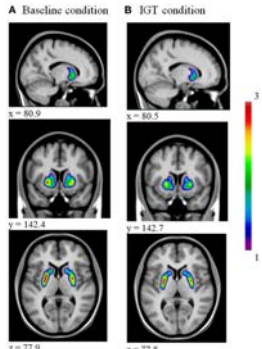
Grant, Contoreggi, London (2000) *Neuropsychologia* 38: 1160-1167

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IGT & Brain

PET = dopamine receptor labeling with a radioactive tracer

- VMPFC, ACC, insula, amygdala **in controls**.
- ↑ OFC, ↓ DLPFC **abstinent cocaine dependent patients**.
- This implies disruption in the reflective system*



General observation

- Typically the reflective system monitors impulsive system
- Monitoring is disrupted by dysfunction in any structure of reflective system
- Patients often demonstrate **rigidity** in responding compared to controls in many tasks with many conditions.
-

This is an ECONOMIC theory

- Economics?!?!?!?
- Yes, *behavioral economics*.
- BEHAVIORAL ECONOMICS = a method of economic analysis that applies psychological insights into human behavior to explain economic decision-making.
-

This is an ECONOMIC theory

- The field of behavioral economics focuses
 - “... on how people change established patterns of impulsive and harmful health behaviors, including alcohol misuse and related risk behaviors (e.g., sexual practices, other drug use).
 - “...integrates public health and clinical perspectives on behavior change strategies ...”


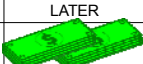

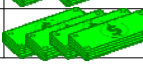
Delay discounting

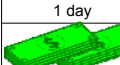
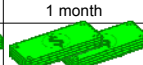
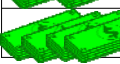
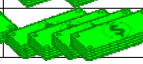
- “... refers to the reduction in the present value of a reward when its delivery is delayed.
- ... involve tradeoffs between costs and benefits occurring at different times.
- Such choices pervade our lives, from daily decisions to ones that can have life-long consequences, such as saving for retirement, education, and marriage.”

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Delay discounting tasks

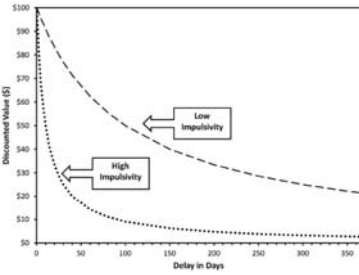
- Manipulate amount of reward.
- Manipulate delay until you'd receive it.
- Plot on a graph...

NOW	LATER
	
	

1 day	1 month
	
	

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Delay discounting tasks



Substance users *discount* the future.

- Impulsive
- Loss of self-control
- Decision-making
- 'gut' reaction

AND! Those with a SUD are often unaware of the problem, deny it, minimize it, or simply can't explain their behavior.

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Delay discounting – treatment?

- Strategies to
 - Promote consideration of future consequences.
 - Work to counteract shortsighted behavior
 - Teach self-control strategies that either shift some of the future costs to the present or reduce some of the immediate rewards (i.e., changing the values of the choices).
- How disulfiram (Antabuse) works?
 - Reduces value of immediate reward.
 - Induces aversive SOMATIC phenomena (nausea and vomiting) very rapidly after use.
 - Impact on learning

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SOMATIC MARKER & INCENTIVE SALIENCE

- The somatic-marker model is compatible with the incentive sensitization theory, in the sense that both models predict a strong salience attribution for drug related stimuli. However, the somatic-marker model proposes that this salience attribution is modulated by the development of strong somatic-markers of emotive nature, which are able to bias decision-making towards drug abuse.
- Internal factors associated with deprivation states (such as withdrawal) are viewed as "gates" that determine how effective the incentive input is in exciting the motivational circuits related to the *impulsive* system.