The neurobiology of Pathological Gambling

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Outline

• Probing Compulsive and Impulsive Behaviors, from Animal Models to Endophenotypes: A Narrative Review (Fineberg et al., 2010)

• Decision-making during gambling: an integration of cognitive and psychobiological approaches (Clark, 2010)

• Nucleus Accumbens D2/3 Receptors Predict Trait Impulsivity and Cocaine Reinforcement (Dalley et al. 2007)

• Dopaminergic Network Differences in Human Impulsivity (Buckholtz et al., 2010)
There exist certain mental disorders for which impulsive and compulsive behaviors seem, at least on phenotypic grounds, to be the core and most damaging ingredient. These often highly heritable disorders, currently classified across several DSM-IV-TR (APA) diagnostic categories, include:

- Obsessive-compulsive disorder (OCD),
- Body dysmorphic disorder (excessive concern about and preoccupation with a perceived defect of their physical features),
- Tourette’s syndrome (multiple physical (motor) tics and at least one vocal (phonic) tic),
- Trichotillomania (compulsive urge to pull out (and in some cases, eat) one's own hair leading to noticeable hair loss, distress, and social or functional impairment),
- Attention deficit hyperactivity disorder (ADHD),
- Pathological gambling, and
- Substance addictions (SAs).

Of interest, autism is characterized by both compulsive behavior (as one of the three core symptom domains) as well as impulsive behavior.

This group of disorders is characterized by considerable phenotypic heterogeneity and overlap. -> Translational approach: investigates from the perspective of underlying mechanisms, and may thus be capable of pinpointing neural contributions driving specific aspects of mental disorder.

Fineberg et al. (2010) Neuropsychopharmacology
Failures in cortical control of fronto-striatal neural circuits may underpin impulsive and compulsive acts. 
- projections from orbitofrontal cortex (OFC) to medial striatum (caudate nucleus), proposed to drive compulsive activity, and 
- projections from the anterior cingulate/ventromedial prefrontal cortex to the ventral striatum (nucleus accumbens shell), proposed to drive impulsive activity

Disordered regulation of impulsive or compulsive behavior may be associated with adverse consequences.

**Impulsivity**: a predisposition toward rapid, unplanned reactions to internal or external stimuli with diminished regard to the negative consequences of these reactions to the impulsive individual or to others.

**Compulsivity**: a tendency to perform unpleasantly repetitive acts in a habitual or stereotyped manner to prevent perceived negative consequences, leading to functional impairment.

Each potentially involves alteration within a wide range of neural processes, including attention, perception, and coordination of motor or cognitive responses.
- In the **compulsive circuit**, a striatal component (caudate nucleus) may drive compulsive behaviors and a prefrontal component (orbitofrontal cortex, OFC) may exert inhibitory control over them.
- Similarly, in the **impulsive circuit**, a striatal component (ventral striatum/nucleus accumbens shell) may drive impulsive behaviors and a prefrontal component (anterior cingulate/ventromedial prefrontal cortex, VMPFC) may exert inhibitory control.

Thus, in this model, there exist at least two striatal neural circuitries (one compulsive and one impulsive) that drive these behaviors, and two corresponding prefrontal circuitries that restrain these behaviors. Hyperactivity within the striatal components or abnormalities (presumably hypoactivity) in the prefrontal components may thus result in an increased automatic tendency for executing impulsive or compulsive behaviors, depending on the sub-component afflicted.

Fineberg et al. (2010) Neuropsychopharmacology
Compulsivity and impulsivity: candidate neural processes contributing to mental disorders.

<table>
<thead>
<tr>
<th>Disorder</th>
<th>OCD</th>
<th>Obsessive Compulsive Personality Disorder</th>
<th>Trichotillomania</th>
<th>Pathological Gambling</th>
</tr>
</thead>
<tbody>
<tr>
<td>DSM-IV classification</td>
<td>Anxiety Disorder</td>
<td>Axis II Cluster C</td>
<td>Impulse Control Disorder not elsewhere specified</td>
<td>Impulse Control Disorder not elsewhere specified</td>
</tr>
<tr>
<td>Observed Behavior</td>
<td>Obsessions, Compulsions, Rigid</td>
<td>Rigid</td>
<td>Repetitive body-focused acts</td>
<td>Repetitive reward-focused acts</td>
</tr>
<tr>
<td>Compulsivity and/or Impulsivity</td>
<td>Motor Impulsivity and Compulsivity</td>
<td>Compulsivity</td>
<td>Motor Impulsivity</td>
<td>Reward-Seeking Impulsivity and Specific Compulsivity</td>
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</table>

Candidate Fronto-striatal Circuitry

- OFC, plus VLPFC, RIFC, ACC
- VLPFC
- RIFC
- OFC plus VMPFC, ventral ACC

- Caudate / Putamen
- Caudate (?)
- Putamen
- Ventral Striatum/NA

Fineberg et al. (2010) Neuropsychopharmacology
Key questions:
(i) how much do compulsivity and impulsivity contribute to these disorders,
(ii) to what extent do they depend on shared or separate neural circuitry,
(iii) what are the mediating monoaminergic mechanisms,
(iv) do impulsive or compulsive behavioral components have any prognostic value related to clinical treatment, and
(v) Is there a unifying-dimensional model that fully accommodates these data?

TRANSLATIONAL MODELS OF IMPULSIVITY AND COMPULSIVITY

**Impulsivity** may derive from one or more distinct neurocognitive mechanisms:
- tendency to pre-potent **motor disinhibition**, measured by the stop signal reaction time (SSRT) task, mediated in human beings through activation of right inferior frontal (RIF) cortex and its subcortical connections and modulated by *norepinephrine*;
- **difficulty in delaying gratification** and choosing immediate small rewards despite negative long-term consequences, measured by decision making or gambling tasks such as the Cambridge Gambling Task (CANTAB), mediated through orbitofrontal and related cortical circuitry under probable serotonergic modulation, and subcortical circuitry under joint dopaminergic and serotonergic control,
- **insufficient information sampling** before making a choice, measured by information sampling tasks such as the Reflection Task.
Compulsivity is less well understood. Failures in (i) **reversal learning** (i.e. the ability to adapt behavior after negative feedback, measured by specific reversal learning tasks) and (ii) **attentional set shifting**, may each contribute toward its expression. Both deficits constitute measures of **cognitive inflexibility**, but each seems subserved by separate neural circuitry.

(i) **Reversal learning** is impaired by lesions to the **OFC**. Reducing brain **serotonin**, especially in specific regions such as the OFC, impairs reversal learning.

(ii) Lesions to the **lateral PFC** impair **attentional set shifting** in primates, and in human beings performance of the task is associated with selective activation of the bilateral ventrolateral prefrontal cortex (VLPFC).

<table>
<thead>
<tr>
<th>Neurocognitive domain</th>
<th>Definition</th>
<th>Task</th>
<th>Neural system</th>
<th>Neurochemistry</th>
</tr>
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<tbody>
<tr>
<td>Impulsivity</td>
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<tr>
<td>Motor impulsivity</td>
<td>Prepotent motor disinhibition</td>
<td>Stop signal reaction time task (SSRT)</td>
<td>Right inferior frontal cortex and subcortical connections</td>
<td>Norepinephrine</td>
</tr>
<tr>
<td>Decision-making impulsivity</td>
<td>Difficulty in delaying gratification and choosing immediate small rewards despite negative long-term consequences</td>
<td>Decision making or gambling tasks (eg Cambridge Gambling Task (CANTAB), Iowa gamble task)</td>
<td>Orbitofrontal cortex and subcortical connections</td>
<td>Cortex—serotonin Subcortical circuitry-serotonin/dopamine</td>
</tr>
<tr>
<td>Reflection impulsivity</td>
<td>Insufficient information sampling before making a choice</td>
<td>Reflection task, 5-CSRTT</td>
<td>Not known</td>
<td>Not known</td>
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<tr>
<td>Compulsivity</td>
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<tr>
<td>Cognitive inflexibility: reversal learning</td>
<td>Inability to adapt behavior after negative feedback</td>
<td>Reversal learning tasks</td>
<td>Orbitofrontal cortex and subcortical connections</td>
<td>Serotonin</td>
</tr>
<tr>
<td>Cognitive inflexibility: attentional set-shifting</td>
<td>Inability to switch attention between stimuli</td>
<td>Extra-dimensional attentional set-shifting (CANTAB)</td>
<td>Ventrolateral PFC—humans Lateral PFC—primates and subcortical connections</td>
<td>Dopamine</td>
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In animal models, an intriguing dissociation between the effects of 5-HT2A and 5-HT2C receptor antagonists on measures of impulsivity and compulsivity has been observed. These data pharmacologically dissociate impulsivity and compulsivity, suggesting that they cannot hinge on a common process of behavioral inhibition. The dissociation cannot easily be explained in terms of differences in species, drug, or dose of receptor antagonist used or the form of motivation used; they must be task-dependent – as both tasks require response inhibition for efficient performance. These results also imply that impulsivity and compulsivity are functionally separate and reciprocally yoked.
Hollander et al (2007a) compared groups of pathological gambling (predominantly impulsive) and OCD and autism (predominantly compulsive) disorders, using clinical, cognitive, and functional imaging tasks. During execution of response-inhibition tasks (go/no-go) that normally activate fronto-striatal circuitry, between-group analyses showed **decreased dorsal ACC activation in all three patient groups relative to healthy controls.** During response inhibition, both compulsive and impulsive disorders were characterized by diminished dorsal ACC activation -> failure to properly inhibit motoric behaviors across these disorders.

- Within the pathological gambling group, increased ventral ACC/ventral striatum activation correlated positively with clinical measures of increased impulsive reward-seeking behavior. Gamblers with increased activation in the ventral ACC showed lower compulsivity scores on tasks of cognitive set-shifting.
- In contrast, in the autistic (compulsive) group, increased ventral ACC/ventral striatum activity correlated with increased severity of compulsive habits, and increased activation within the same areas of the ventral ACC correlated with increased compulsivity on the attention shift task and decreased impulsivity on the Time Estimation task.

This ‘double-dissociation’ suggests that in pathological gambling and autism, prevailing differences in neuromodulation impact on ventral cortico-striatal pathways during behavioral inhibition, which in pathological gambling may primarily drive impulsivity and in autism drive compulsivity.
INTEGRATING MECHANISMS OF INHIBITORY CONTROL, REWARD, AND DA

- Models of compulsivity and impulsivity posit a balance between 5-HT (2A, 2C) receptor activity in VMPFC/OFC regions regulating aspects of response inhibition, and DA tone in the ventral loops linking ventral ACC with ventral striatum/nucleus accumbens regulating reward and reinforcement behavior. DA neurotransmission, particularly phasic release, in the nucleus accumbens has been associated with reward seeking and reinforcement. Pro-dopaminergic drugs have been associated with altering reversal learning to unexpected punishment and ICDs in patients with Parkinson’s disease.

- More research is needed to better understand the relationship between impulsivity, compulsivity, and DA function as they relate to specific psychiatric disorders such as pathological gambling. Impulsive or compulsive disorders may potentially derive from a mesolimbic DA deficiency. Probing both the ventral and dorsal striatal circuitry in human subjects with specific impulsive and compulsive disorders using receptor-specific serotonergic and dopaminergic ligands would be an important next step.
IMPULSIVITY AND ‘BEHAVIORAL’ ADDICTIONS

- Pathological gambling and SAs share many features. The disorders frequently co-occur and show similarities with respect to symptom profiles, gender differences, natural histories, and familial propensities. Pathological gambling and SA show high levels of impulsivity on reward-discounting tasks, which correlate with poor measures of functioning and poor treatment outcome for individuals with SAs and thus may have prognostic value for pathological gambling and other ICDs.

- Neurocognitive and fMRI data suggest pathological gambling and SAs share similar mediating neurocircuitry, in which relatively diminished activation of the ventral striatum and VMPFC has been observed in reward processing and other paradigms.

- Over time, impulsive habitual responding in pathological gambling and SA may shift toward a more compulsive pattern of behavior, and it has been hypothesized that progressive recruitment of neighboring parallel and increasingly dorsal, cortico-striatal loops occurs in a spiraling manner.

- Prospective, longitudinal studies after these changes within individuals over time will be informative and clinically relevant. Promising research from treating individuals with pathological gambling with opioid antagonists not only discriminate pathological gambling from OCD, in which opioid antagonists have been shown to make OCD worse, but also suggest a therapeutic function for opioid antagonists in other related ICDs.
Key questions and answers:

(i) how much do compulsivity and impulsivity contribute to these disorders?
   - Impulsivity, and compulsivity, each seem to be multidimensional and underpin at least some of the impulsive and compulsive disorders, although the disorders show overlapping, but also distinct profiles.

(ii) to what extent do they depend on shared or separate neural circuitry?
   - Pathological gambling has been associated with impulsivity linked to poor decision making and abnormal ventral cortico-striatal circuitry, particularly involving the VMPFC and ventral striatum, that identifies it more closely with SAs.

(iii) what are the mediating monoaminergic mechanisms?
   - Inter-relating serotonin, DA, and noradrenaline projections are likely to have important modulating functions, as well as other systems as yet incompletely characterized.

(iv) do impulsive or compulsive behavioral components have any prognostic value related to clinical treatment?
   - High levels of reward-related impulsivity correlate with poor treatment outcome for SAs and may have prognostic significance for pathological gambling and other ICDs. Compulsive behaviors occurring with autism are associated with similar abnormalities in ventral reward circuitry. OCD, on the other hand, shows motor impulsivity and compulsivity, presumably mediated through disruption of OFC-caudate circuitry, as well as VLPFC, RIF cortex, cingulate, and parietal connections.

(v) Is there a unifying-dimensional model that fully accommodates these data?
   - The ‘model’ probably involves a complicated interaction of multiple, orthogonally related diatheses, variably expressed across these circuits and disorders.
• Probing Compulsive and Impulsive Behaviors, from Animal Models to Endophenotypes: A Narrative Review (Fineberg et al., 2010)

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Decision-making during gambling: an integration of cognitive and psychobiological approaches

Two dominant approaches to gambling behaviour:

1) The cognitive approach has identified a number of erroneous beliefs held by gamblers, which cause them to over-estimate their chances of winning,

2) The psychobiological approach has examined case-control differences between groups of pathological gamblers and healthy controls, and has identified dysregulation of brain areas linked to reward and emotion, including the ventromedial prefrontal cortex (vmPFC) and striatum, as well as alterations in dopamine neurotransmission.

Anomalous recruitment of the brain reward system (including the vmPFC and ventral striatum) during two common cognitive distortions in gambling games: the near-miss effect and the effect of personal control. In games of chance, near-misses and the presence of control have no objective influence on the likelihood of winning. These manipulations appear to harness a reward system that evolved to learn skill-oriented behaviours, and by modulating activity in this system, these cognitive distortions may promote continued, and potentially excessive, gambling.
1) The cognitive approach

- The cognitive formulation of gambling argues that the problem gambler continues to play because they possess distorted beliefs about gambling that cause them to overestimate their chances of winning. Several kinds of erroneous beliefs have been identified, which ultimately give rise to an ‘illusion of control’ where the gambler confuses a game of chance with a game of skill.

- the ‘think aloud’ procedure: the gambler is asked to verbalize all thoughts during a brief period of gambling in a naturalistic setting. Speech output is recorded by the experimenter, and statements are categorized subsequently as accurate (e.g. ‘It’s a machine, we have no control over it, it’s all luck’) or erroneous (‘I’m getting good at this game. I think I’ve mastered it’).

- In regular gamblers, around 70–80% of strategic statements about the game were erroneous. (The house always wins). High rates of erroneous thoughts were even present in players who were clearly aware that the outcomes were determined by chance.

- At a psychological level, there appear to be at least two mechanisms at work: 1) humans are generally poor at processing probability and judging randomness, 2) various features of gambling games directly foster distorted beliefs.
- Subjects fail to appreciate the independence of turns, and expect small samples to be representative of the populations from which they are drawn.
- Impaired processing of randomness may give rise to the ‘Gambler’s Fallacy’, where the gambler believes that a win is ‘due’ after a series of losses. **Most people perceive a ‘streak’ on the third consecutive win or loss event.**

- Two structural characteristics that appear to manipulate the player’s perceptions of winning:
  1) **Personal control** refers to the gambler’s level of involvement in arranging their gamble. **Players have inflated confidence when they are given the opportunity to arrange the gamble themselves.** In a study by Langer (1975), subjects were invited to buy a lottery ticket, and the experimenter later asked to buy back their ticket. Subjects who were initially able to choose their ticket from a bag demanded more money ($9) to exchange compared with a group who were allocated a ticket at random ($2). In a follow-up experiment, subjects who had chosen their ticket were more likely to refuse a swap for a ticket in a second lottery with a higher chance of winning. Perceived control can actually cause subjects to reject a genuine opportunity to increase their chances of winning.
- Craps players, when it is a player’s turn to shoot the dice, they are more likely to place a bet, place higher bets, and place more risky bets compared with when other players are shooting.
2) The near-miss effect
Near-misses occur when an unsuccessful outcome is proximal to a win. Near-misses are salient events to the gambler. **Gamblers often interpret near-misses as evidence that they are mastering the game**, the gambler feels that he is ‘not constantly losing but constantly nearly winning’.

- Slot-machine simulation where the three reels stopped sequentially. The reels contained red and green stimuli, and wins were awarded for three reds.

<table>
<thead>
<tr>
<th>Red probability</th>
<th>.7</th>
<th>.5</th>
<th>.3</th>
<th>.3</th>
<th>.5</th>
<th>.7</th>
</tr>
</thead>
<tbody>
<tr>
<td>Group 1</td>
<td><img src="red.png" alt="Red" /> <img src="red.png" alt="Red" /> <img src="green.png" alt="Green" /></td>
<td><img src="green.png" alt="Green" /> <img src="red.png" alt="Red" /> <img src="red.png" alt="Red" /></td>
<td></td>
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<tr>
<td>Group 2</td>
<td><img src="green.png" alt="Green" /> <img src="red.png" alt="Red" /> <img src="red.png" alt="Red" /></td>
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</table>

The actual proportion of wins was matched across the two groups. **Subjects in group 1 played for significantly longer than subjects in group 2.**

However, the potency of near-misses is diminished if they are over-represented, rather like ‘crying wolf’ (at 15, 30 and 45 per cent frequencies of near-misses, an ‘inverted U’ effect was found with maximal persistence in the intermediate group).
2) The psychobiological approach

- Studies of neurotransmitter function in gamblers have focussed on the monoamines, **dopamine, serotonin and noradrenaline**, which are known to play key roles in arousal, motivation and higher cognitive functions.

- peripheral markers in urine, plasma or cerebrospinal fluid:
  - increases in markers of noradrenaline function,
  - reductions in markers of serotonin function and
  - alterations in dopamine function.

*Findings from peripheral markers must be treated with caution as their relationship with central activity is complex.*

- Another indirect approach has been to study genetic variants that are thought to affect neurotransmitter function.
  - dopamine D2 receptor gene displays a common polymorphism (TaqI A, occurring in A1 and A2 alleles) that influences D2 receptor density in the brain, and is linked to the prevalence of alcohol and stimulant addictions. Changes in DRD2 and DRD4 polymorphism frequencies were found in groups of pathological gamblers. The reported TaqI A association (increased prevalence of the A1 allele) is consistent with reduced D2 receptor binding in the striatum in pathological gamblers.

Genetic studies have also indicated effects on other genotypes affecting serotonin and noradrenaline function. However, *this field has been plagued by failures of replication.*
Neuropsychological studies

- Several studies have detected in PG impairments on traditional tests of frontal lobe function; namely, the *Wisconsin card sort test*, which requires the subject to **perform abstract rule shifts**, and the *Stroop test*, which requires the subject to **override the automatic tendency** to read colour words in order to name the colour of the ink that the word is printed in *(black)*.
- Deficits resemble the effects seen in patients with damage to the ventromedial prefrontal cortex (vmPFC), who often display real-life difficulties with financial decision-making. This syndrome was initially measured using the Iowa gambling, where subjects make a series of card choices from four decks (A, B, C, D) that win and lose sums of hypothetical money. Unbeknownst to the subject, decks A and B are ‘risky’, associated with large wins but larger losses that incur gradual debt. Decks C and D are safe decks that yield smaller wins but with negligible losses.
- While **healthy subjects develop a preference for the safe decks over 100 trials**, **patients with vmPFC damage maintain a preference for the risky decks**, accumulating considerable debt.
- **Similar performance has been reported in at least five studies of pathological gamblers.**
ANOMALOUS RECRUITMENT OF THE BRAIN REWARD SYSTEM DURING COGNITIVE DISTORTIONS

- Neurobiological findings indicate the existence of a specialized brain reward system that processes reinforcers and uses reinforcement to guide future decision-making (‘reinforcement learning’). At an anatomical level, fMRI studies demonstrate the central roles of the ventral striatum and the mPFC in this reward system; these regions are activated by monetary wins.

- At a neurochemical level, the mesolimbic dopamine projection from the midbrain to the striatum and PFC is also central to neurobiological accounts of reward processing. A dominant hypothesis is that dopamine cells code a reward prediction error: the difference between the obtained and the expected reward.

- Recent work indicates that activity within the brain reward system is modulated by some of the psychological manipulations that affect gambling behaviour.
The right-hand reel is spun so that the volunteer can either win £0.50p (if the two reels align) or not win anything.

**(a)** The contrast of monetary wins minus non-win outcomes, at $y = 4$ (ventral striatum) and $y = 34$ (medial prefrontal cortex).

**(b)** The contrast of near-miss outcomes minus full-miss outcomes, within regions sensitive to monetary wins, at $y = 4$ (ventral striatum).

**(c)** The interaction between near-miss outcomes (i.e. near-misses minus full-misses) and personal control (participant-chosen trials minus computer-chosen trials), within regions sensitive to monetary wins, at $y = 34$ (medial prefrontal cortex).
Gambling games harness a brain reward system that has evolved to learn about skill-oriented behaviours: situations where response feedback can be used either to improve the precision of the motor response itself, or to improve the prediction of future outcomes. This system often responds inappropriately under conditions of chance. Using the example of the near-miss, in many real-world situations such as target practice or getting to the railway station two minutes late, it is advantageous for the brain to assign value to near-miss outcomes, as they are a valid and useful signal of future success.

However, in gambling games, where winning outcomes are largely or purely determined by chance, near-misses provide no information on future success, and it is misleading for the brain to assign them value. Similarly, in the case of personal control, it is obviously adaptive for the brain to learn how to control its environment, and specialized and sophisticated processes have evolved to identify rewards that occur contingently upon behaviour. However, the random nature of gambling games means that the availability of personal control has no actual bearing on the likelihood of a win occurring.

Two of the better-established cognitive distortions in gambling behaviour, the near-miss effect and the effect of personal control, are associated with anomalous recruitment in components of the brain reward system. The term ‘anomalous’ is justified by the objective status of near-misses as loss events that do not signal future success, and the objective irrelevance of personal control to gambling success on games of chance.

Clark et al. (2009).
“I almost got it - next time I’ll succeed!"
• Probing Compulsive and Impulsive Behaviors, from Animal Models to Endophenotypes: A Narrative Review (Fineberg et al., 2010)

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Nucleus Accumbens D2/3 Receptors Predict Trait Impulsivity and Cocaine Reinforcement

- Accumulating evidence suggests that certain personality traits, including sensation (or novelty) seeking, impulsivity, and antisocial conduct disorder, may predispose humans to drug abuse and addiction.
- Current hypotheses: long-term drug use impairs inhibitory control functions mediated by the prefrontal cortex and the associated limbic brain circuitry, leading to a loss of inhibition or to impulsivity.
- Trait differences in impulsivity:
  - Rats that are selected for high novelty-induced locomotor activity more readily acquire intravenous amphetamine and cocaine self-administration at lower doses than do rats that show reduced levels of activity;
  - rats that are impulsive on a delay-of-reward task, choosing a small immediate reward over a large but delayed reward, show an increased propensity to self-administer cocaine, as compared to low-impulsive rats;
  - studies in nonhuman primates show that cocaine is more readily self-administered by subordinate, rather than dominant, monkeys.

- A key neural substrate underlying individual differences in drug vulnerability is thought to involve the mesolimbic and mesocortical DA pathways innervating the nucleus accumbens and prefrontal cortex.

Dalley et al. (2007) Science
Dalley et al. investigated the relevance of a spontaneously occurring form of impulsivity in rats to intravenous cocaine self-administration and to underlying changes in striatal DA function.

Impulsivity was defined as high levels of anticipatory responses made before the presentation of a food-predictive, brief light stimulus in a five-choice serial reaction time (5-CSRT) task of sustained visual attention. Typically, 5-CSRT task impulsivity occurs in ~7% of male rats and, once identified, is a stable trait that persists throughout adulthood.

![Graph showing behavioral attributes of trait impulsivity on the 5-CSRT task](Fig. 1).

(A) Impulsive rats exhibit high levels of premature responding on days when visual targets are presented either 5 s after trial initiation (days 1, 2, 4, and 5) or 7 s after trial initiation (day 3), as compared to non-impulsive rats. Two-way analysis of variance (ANOVA) of premature responses revealed a significant main effect of day \( F(4,40) = 144.9, P < 0.01 \) and a significant main effect of group \( F(1,10) = 26.1, P < 0.01 \). However, there were no significant effects on other measures of task performance, including (B) attentional accuracy \( F(1,10) = 1.17, P = 0.306 \), (C) latency to collect food reward \( F < 1, \text{not significant (ns)} \), (D) omissions \( F < 1, \text{ns} \), (E) latency to respond correctly \( F(1,10) = 3.0, P = 0.113 \), and (F) the time required to complete both standard and challenge (long-ITI) sessions \( F < 1, \text{ns} \). Black circles, high-impulsive rats; white circles, non-impulsive rats.
Reduced D2/3 receptor availability in the ventral striatum but not the dorsolateral striatum of high-impulsive rats as compared to non-impulsive rats (likely due to decrease in the number of D2/3 receptors).

Inverse correlation between D2/3 receptor availability in the ventral striatum and impulsivity

ventral striatum
$R = 0.58; \ p = 0.048$

primary reinforcing effects of drugs depend on DA afferents to this region

dorsolateral striatum mediates the compulsive forms of drug-seeking behavior

Fig. 2. Reduced binding potential (BP) of the selective D2/3 receptor antagonist $[^{18}F]$fluprydaze in the ventral striatum of drug-naive trait-impulsive rats ($n = 6$ rats) as compared to drug-naive non-impulsive rats ($n = 6$). (Top) ROIs are shown in the schematic coronal sections of the rat forebrain [adapted from (46)]. Dorsal and ventral striatal ROIs are depicted by the shaded and striped circles, respectively. Anterior-posterior coordinates (in millimeters) relative to bregma are shown on each coronal section. The ROIs have diameters of 2 mm in the transverse plane. BP values are averages of left and right striata. (A to D) Horizontal MR coregistered PET images of $[^{18}F]$fluprydaze binding in the dorsal (upper panels) and ventral (lower panels) striatum of a non-impulsive rat ([A] and [C]) and a high-impulsive rat ([B] and [D]). The images are 4.5 mm ([A] and [B]) and 7.0 mm ([C] and [D]) below the dorsal brain surface (BP threshold = 9).
Consequences of trait impulsivity for the acquisition and maintenance of intravenous cocaine self-administration

- Impulsive rats exhibited a clear increase in their rate of intravenous cocaine self-administration as compared to non-impulsive rats

- decreased D2 receptor availability in the striatum may be a predisposing neurobiological trait and not only a consequence of chronic cocaine exposure;
- trait impulsiveness is a drug-vulnerable phenotype;
- consistent with the hypothesis that dysfunctional DA neurotransmission at D2-like receptors in the nucleus accumbens confers susceptibility to increased cocaine self-administration in high-impulsive rats.
Prolonged exposure of trait-impulsive rats to **cocaine decreased levels of premature responding** on the 5-CSRT task when the animals were tested in withdrawal.

One clear consequence of long-access cocaine exposure and subsequent cocaine withdrawal in trait-impulsive rats was a selective normalization of premature responding on the 5-CSRT task.
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Dopaminergic Network Differences in Human Impulsivity

- Dopamine (DA) has been theorized to play a key role in impulsivity, but the precise systems-level mechanisms linking variation in DA signaling to trait differences in impulsivity remain unclear.
- A neurobiological model of individual differences in human impulsivity:
  - Highly impulsive individuals are characterized by diminished midbrain autoreceptor availability, which leads to enhanced DA cell firing and potentiated DA release in terminal fields following exposure to novel, salient, or rewarding stimuli.

- PET study to test the model:
  - 32 physically and psychiatrically healthy volunteers,
  - [18F]fallypride, aD2/D3-selective ligand that labels striatal and extrastriatal receptors,
  - at placebo and after oral administration of 0.43 mg/kg d-amphetamine (AMPH)
  - The Barratt Impulsiveness Scale (BIS-11) is one of the oldest and most widely used self-report measure of impulsive personality traits. The BIS-11 includes 30 items which may be scored to yield six first-order (attention, motor, self-control, cognitive complexity, perseverance, and cognitive instability impulsiveness) and three second-order factors (attentional, motor, and non-planning impulsiveness). (http://en.wikipedia.org/wiki/Barratt_Impulsiveness_Scale)
The first ten items of the **Barratt Impulsiveness Scale**

DIRECTIONS: People differ in the ways they act and think in different situations. This is a test to measure some of the ways in which you act and think. Read each statement and put an X on the appropriate circle on the right side of this page. Do not spend too much time on any statement. Answer quickly and honestly.

<table>
<thead>
<tr>
<th></th>
<th>Rarely/Neber</th>
<th>Occasionally</th>
<th>Often</th>
<th>Almost Always/Always</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>I plan tasks carefully.</td>
<td>1 2 3 4</td>
<td></td>
<td></td>
</tr>
<tr>
<td>2</td>
<td>I do things without thinking.</td>
<td>1 2 3 4</td>
<td></td>
<td></td>
</tr>
<tr>
<td>3</td>
<td>I make-up my mind quickly.</td>
<td>1 2 3 4</td>
<td></td>
<td></td>
</tr>
<tr>
<td>4</td>
<td>I am happy-go-lucky.</td>
<td>1 2 3 4</td>
<td></td>
<td></td>
</tr>
<tr>
<td>5</td>
<td>I don’t “pay attention.”</td>
<td>1 2 3 4</td>
<td></td>
<td></td>
</tr>
<tr>
<td>6</td>
<td>I have “racing” thoughts.</td>
<td>1 2 3 4</td>
<td></td>
<td></td>
</tr>
<tr>
<td>7</td>
<td>I plan trips well ahead of time.</td>
<td>1 2 3 4</td>
<td></td>
<td></td>
</tr>
<tr>
<td>8</td>
<td>I am self controlled.</td>
<td>1 2 3 4</td>
<td></td>
<td></td>
</tr>
<tr>
<td>9</td>
<td>I concentrate easily.</td>
<td>1 2 3 4</td>
<td></td>
<td></td>
</tr>
<tr>
<td>10</td>
<td>I save regularly.</td>
<td>1 2 3 4</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

[http://www.impulsivity.org/measurement/bis11](http://www.impulsivity.org/measurement/bis11)

- D2/D3 receptor availability (binding potential, $BP_{ND}$) and AMPH-induced DA release SPMs were calculated and correlated with participants’ BIS-11 total scores.

- (A) Trait impulsivity was inversely correlated with D2/D3 autoreceptor availability in the substantia nigra/ventral tegmental area, and positively correlated with the magnitude of AMPH-induced DA release in the striatum.

- Path modeling (mediation analysis) was used to test the mechanistic hypothesis that lower SN/VTA autoreceptor availability leads to impulsivity by enhancing stimulated DA release in the striatum.

- (B) The ability of SN/VTA D2/D3 $BP_{ND}$ to predict impulsiveness is at least in part mediated through the impact of SN/VTA autoreceptor availability on AMPH-induced striatal DA release.
- Given that heightened subjective “wanting” responses to initial stimulant exposure is a risk factor for future drug dependence and that
- BIS-11 scores predict drug craving in substance-dependent individuals,
- these data suggest a neurobiological link between human impulsiveness and drug abuse vulnerability.

- Individual differences in midbrain autoreceptor availability are associated with the expression of impulsivity in humans, an effect that appears to be mediated, in part, through diminished inhibitory autoreceptor control over stimulated striatal DA release,

- dysregulation within ascending dopaminergic projection pathways subserving reward and motivation may produce deficits in impulse control, a critical feature of the psychopathological architecture underpinning substance abuse.
Thank you