Food “Addiction”: Translational Studies of the Fine Line Between Food Reward and Addiction

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Outline of the talk

• Some factors contributing to the obesity epidemic
• Background on food-reward and some of its associated brain systems
• Defining an addiction and contrasting it with “normal” rewarding experiences
• Addiction-like behavioral and neurochemical changes seen in animal models of hedonic overeating
• Assessment of “food addiction” in clinical studies
• Conclusions and next steps
The BIG problem: Obesity in the US

- ~65% of adults in the U.S. are overweight, of which ~36% are obese.
- Being obese or overweight can lead to comorbid health concerns (e.g., heart disease, diabetes).
- Increased body weight may also be associated with psychological, economic, and social consequences.
Why are so many people overweight or obese?

- Portion size and portion creep

Twenty years ago
333 calories

Today’s Burger
590 calories

Original 8-ounce bottle
97 calories

12 ounce can
143 calories

20-ounce bottle
242 calories
Why are so many people overweight or obese?

- Food acquisition is easier than it used to be
Obesity is an endpoint, with multiple contributing factors:

- Genetic disorders (Prader-Willi syndrome)
- Sedentary lifestyle
- Genetic vulnerability
- Increase in portion size
- Ease of food procurement
- Social norms regarding food
- Stress and endocrine factors
- Food reward (addiction?)
Hedonic eating vs. caloric need

- People sometimes eat because they want to eat, not because they have to eat (people may eat because of boredom, stress, etc.)

- Foods that are rich in fats and sugars, and consequently calories, taste good.

- Palatable food is ubiquitous for most people in our society.

- Food is a part of our social lives.
What happens in the brain when we eat?

- There are overlaps in the brain pathways activated by palatable foods and drugs of abuse.
- Drugs that are abused act on brain systems that evolved to reinforce natural behaviors (e.g., sex, feeding).
Defining an addiction: DSM IV criteria

- **Tolerance**
  - Using more, and for longer, than intended

- **Withdrawal**
  - Intention to, or failed attempts to, limit or quit

- **Use regardless of consequences**
- **Social and work consequences due to use**
- **Excessive time dedicated to getting, using, and recovering from use**
- **Substance Dependence**

- Using more, and for longer, than intended
- Intention to, or failed attempts to, limit or quit
- Excessive time dedicated to getting, using, and recovering from use
- Social and work consequences due to use
- Use regardless of consequences
Could some people be “addicted” to eating highly-palatable foods rich in sweets and fats in ways that resemble drug addiction?

Could such out-of-control eating result in increased body weight and obesity in some individuals?
Comparing and contrasting normal feeding and drug addiction

<table>
<thead>
<tr>
<th>Normal Feeding</th>
<th>Drug Addiction</th>
</tr>
</thead>
<tbody>
<tr>
<td>- We need food to survive (but not hyperpalatable foods).</td>
<td>- We don’t need drugs of abuse to survive.</td>
</tr>
<tr>
<td>- Food is not regulated, eating is socially accepted and encouraged, and food is readily available.</td>
<td>- Drugs of abuse are illegal, discouraged by society, and hard to procure.</td>
</tr>
<tr>
<td>- <strong>Dopamine</strong>- Motivation to eat. With food, dopamine release normally wanes with repeated access.</td>
<td>- <strong>Dopamine</strong>- Reinforcement. Drugs increase extracellular dopamine each time they are administered.</td>
</tr>
<tr>
<td>- <strong>Opioids</strong>- Antagonists do not precipitate withdrawal signs.</td>
<td>- <strong>Opioids</strong>- Antagonists precipitate withdrawal signs.</td>
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</tbody>
</table>
**Animal models:**

Which conditions could promote an addictive-like response to palatable food?

1. Overeating (Bingeing on) Sugars and Fats
2. “Junk Food”
3. Obese vs lean
4. Variety of food choices
Assessing Addiction Using Animal Models

- **Craving**
- **Bingeing**
- **Withdrawal**

**Cross-sensitization**

- Enhanced locomotion
- Increased Consumption
Evidence for sugar addiction: Behavioral and neurochemical effects of intermittent, excessive sugar intake

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Table 1
Summary of findings in support of sugar addiction in rats using an animal model of sucrose or glucose binging.

<table>
<thead>
<tr>
<th>Substance dependence</th>
<th>Animal model of sugar dependence</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>A. DSM-IV-TR</strong></td>
<td></td>
</tr>
<tr>
<td>Tolerance</td>
<td>Escalation of daily sugar intake (Colantuoni et al., 2001)</td>
</tr>
<tr>
<td>Signs of withdrawal</td>
<td>Somatic signs (teeth-chattering, tremor), Anxiety measured by plus-maze,</td>
</tr>
<tr>
<td></td>
<td>Ultrasonic distress vocalizations (Colantuoni et al., 2002 and Avena et al., 2008)</td>
</tr>
<tr>
<td></td>
<td>Deprivation effect (Avena et al., 2005)</td>
</tr>
<tr>
<td><strong>B. Behavioral signs</strong></td>
<td></td>
</tr>
<tr>
<td>Locomotor cross-sensitization</td>
<td>Amphetamine (Avena and Hoebel, 2003)</td>
</tr>
<tr>
<td>Proclivity to consume other drugs of abuse</td>
<td>Alcohol (Avena et al., 2004)</td>
</tr>
<tr>
<td><strong>C. Neurochemical changes in the NAc</strong></td>
<td></td>
</tr>
<tr>
<td>Repeated release of DA</td>
<td>Rada et al. (2005) and Avena et al. (2006)</td>
</tr>
<tr>
<td>↑ D₁ receptor binding</td>
<td>Colantuoni et al. (2001)</td>
</tr>
<tr>
<td>↓ D₂ receptor binding</td>
<td>Colantuoni et al. (2001)</td>
</tr>
<tr>
<td>↑ D₃ receptor mRNA</td>
<td>Spangler et al. (2004)</td>
</tr>
<tr>
<td>↓ preproenkephalin mRNA</td>
<td>Spangler et al. (2004)</td>
</tr>
<tr>
<td>DA/ACH imbalance during withdrawal</td>
<td>Colantuoni et al. (2002) and Avena et al. (2008)</td>
</tr>
</tbody>
</table>

Bingeing/Tolerance

From Rada, Avena, and Hoebel (2005)
Alterations in Brain Dopamine Levels

Dopamine repeatedly increases in sugar bingeing rats, but not in control rats.

Also seen in response to fat (Liang, Hajnal, & Norgren, 2006).

Rats are not overweight.

From Rada, Avena and Hoebel (2005)
Rats fed a highly-palatable food (rich in sugar and fat, and variety) become obese and show downregulation of D2 receptors (Johnson & Kenny, 2010).

These rats also show compulsive food seeking behavior.

Decreased D2 receptors have also been noted in animals that overeat sugar (Colantuoni et al., 2001).

From Johnson & Kenny, 2010
Sugar bingeing rats show signs of anxiety when given an opioid antagonist (naloxone), or when fasted from all food for 36 h.

Opioid systems are perturbed by overeating, as revealed by increased mu-opioid receptor binding in these animals prior to withdrawal.

*From Avena, Bocarsly, et al., 2008*
Withdrawal of sugar is concurrent with decreases in dopamine and increases in acetylcholine levels in the nucleus accumbens, similar to the pattern seen during drug withdrawal.

From Avena, Bocarsly, et al., 2008
But fat bingeing does not result in opiate-like withdrawal...

We experimented with different types of fats (complete diet, vegetable fat, oil), forms (solid, liquid), schedules of feeding (short, long access) and were unable to elicit the signs of opiate-like withdrawal that emerge with naloxone or spontaneously in sugar-bingeing rats.

From Bocarsly et al., 2011
Fat may release or affect neurochemicals that counteract the opiate-like withdrawal

Galanin

- Chronic exposure to addictive drugs enhances CREB-regulated gene expression in the NAc, and it has been proposed that CREB mediates a form of tolerance and dependence, which contributes to a negative emotional state during early phases of withdrawal (Kivinummi et al., 2011).

- Galanin protects against behavioral and neurochemical correlates of opioid reward (Hawes et al., 2008).

- Fat-associated attenuation of CREB in the NAc, via hypothalamic galanin (Bocarsly, Avena, SfN abstract 2012).
Baclofen suppresses binge eating of pure fat but not a sugar-rich or sweet-fat diet
Laura A. Berner, Miriam E. Bocarsly, Bartley G. Hoebel and Nicole M. Avena

Data from Bocarsly et al., in prep
Craving

- Rats prone to overeat are more likely to cross a shock grid to get access to palatable food (Oswald, Murdaugh, King & Boggiano, 2011).

- Rats that overeat sugar daily show an increase in intake following a period of abstinence (Avena et al, 2005), and will work harder to get access to sugar-associated cues (Grimm et al., 2005).
Cross-sensitization to drugs of abuse

- Sugar-bingeing rats are hyperactive in response to a low dose of amphetamine.
- Sugar-bingeing rats consume more alcohol.

From Avena and Hoebel, 2003; Avena et al., 2004
Variety and hyperpalatability: are they promoting addictive overeating?

Nicole M Avena and Mark S Gold


- Food variety attenuates habituation to food in humans (Epstein et al., 2009).....when you have variety, you eat MORE.
- In addition to the changes in dopamine receptors discussed earlier, a cafeteria-style diet produces signs of opiate-like withdrawal in rats (Le Magnan et al., 1990).
From Geiger et al., 2009

Rats with access to a Cafeteria-style diet are hyper-responsive to amphetamine in terms of dopamine release.

However, they do not respond to a lab chow meal. These rats need “junk food” to release accumbens dopamine.
Decreased Dopamine D2 Receptors in Obese Human, Monkey and Rodent

**Human**

- **BMI = 23**
  - **PET**[^1^C]raclopride

**Bonnet macaques**

- **BMI = 23**
  - **PET**[^1^C]raclopride

**Zucker rat**

- **BMI = 42**
  - **Weight = 400 g**
  - **PET**[^3^H]spiperone

- **BMI = 50**
  - **Weight = 650 g**
  - **PET**[^1^C]raclopride

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ARG, autoradiography; PET, positron emission tomography

The Yale Food Addiction Scale has been created to study food addiction by applying the DSM-IV criteria for substance dependence to eating behaviors.

Sample items:

“I find myself continuing to consume certain foods even though I am no longer hungry”
“I eat to the point where I feel physically ill”
“I find that when I start eating certain foods, I end up eating much more than planned”

The items are answered using a Likert type scale (i.e., Never, Once a month, 2-4 times a month, 2-3 times a week, 4 or more times or daily).
Neural Correlates of Food Addiction

Ashley N. Gearhardt, MS, MPhil; Sonja Yokum, PhD; Patrick T. Orr, MS, MPhil; Eric Stice, PhD; William R. Corbin, PhD; Kelly D. Brownell, PhD

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“Food addiction” in obesity and eating disorders

REGULAR ARTICLE

An Examination of the Food Addiction Construct in Obese Patients with Binge Eating Disorder

Ashley N. Gearhardt, MS1*
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Robin M. Masheb, PhD2
Peter T. Morgan, MD, PhD2
Ross D. Crosby, PhD3,4
Carlos M. Grilo, PhD1,2

ABSTRACT
Objective: This study examined the psychometric properties of the Yale food addiction scale (YFAS) in obese patients with binge eating disorder (BED) and explored its association with measures of eating disorder and associated psychopathology.

Method: Eighty-one obese treatment-seeking BED patients were given the YFAS, structured interviews to assess psychiatric disorders and eating disorder psychopathology, and other pathology measures.

Results: Confirmatory factor analysis revealed a one-factor solution with an excellent fit. Classification of “food addiction” was met by 57% of BED patients. Patients classified as meeting YFAS “food addiction” criteria had significantly higher levels of depression, negative affect, emotion dysregulation, eating disorder psychopathology, and lower self-esteem. YFAS scores were also significant predictors of binge eating frequency above and beyond other measures.

Discussion: The subset of BED patients classified as having YFAS “food addiction” appear to represent a more disturbed variant characterized by greater eating disorder psychopathology and associated pathology. © 2011 by Wiley Periodicals, Inc.

Keywords: binge eating; food addiction; substance use; drug use; emotional eating; obesity

(Int J Eat Disord 2011; 00:000–000)

“...classification of food addiction was met by 57% of obese BED patients...”
“Food addiction” in obesity and eating disorders

Medical Hypotheses 79 (2012) 508–511

Food addiction and body-mass-index: A non-linear relationship

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ABSTRACT

Excessive food consumption has been recognized to show similarities with substance dependence. Subsequently, it has been proposed that food addiction might contribute to the obesity epidemic. Recent studies using questionnaires for the assessment of food addiction have found statistically significant, but negligible positive correlations with body-mass-index (BMI). Moreover, group comparisons between food-addicted and non-addicted individuals in normal-weight or obese samples did not show differences in BMI. However, the prevalence of food addiction diagnoses is remarkably increased in obese individuals. In the current article, it is suggested that there might be a cubic relationship between food addiction and BMI. Food addiction symptomatology may remain stable in the under- and normal-weight range, increase in the overweight- and obese range, and level off at severe obesity. Empirical data in support of this view are presented.

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While food addiction is more prevalent in obese vs. non-obese groups, the data don’t suggest a linear relationship between BMI and food addiction.

“...there may be a cubic relationship between food addiction and BMI....symptomology may remain stable in the under- and normal-weight range, but increase in the overweight and obese range.”
Important Questions

• Which models are best for assessing addictive-like responses to food? How can/should they be refined?

• What neural alterations are distinctly associated with overeating sugars vs. fats?

• Pharmacological treatments to attenuate hedonic overeating

• Terminology (e.g., addiction, or some other word)

• The fine line between being rewarding/reinforcing and "addictive"

• Which clinical groups are susceptible to addictive-like feeding behaviors?
Conclusion

- Most of the possible DSM IV criteria for substance dependence have been met in animal or human studies of overeating.

- Questions remain regarding the use of this construct in the treatment of obesity or other types of disordered eating.

- Food addiction is a young area of research, and we have much more to learn about how highly-palatable foods affect brain reward systems.

*From Allen et al., 2012*

<table>
<thead>
<tr>
<th>DSM IV criteria</th>
<th>Animal model</th>
<th>Humans</th>
<th>Evidence</th>
</tr>
</thead>
<tbody>
<tr>
<td>1 Tolerance</td>
<td>✓</td>
<td>✓</td>
<td>Food binging, hyperphagia, delayed satiety</td>
</tr>
<tr>
<td>2 Withdrawal</td>
<td>✓</td>
<td>✓</td>
<td>Hypofunctioning brain dopamine system, opiate withdrawal-like symptoms, psychological and physical dependence</td>
</tr>
<tr>
<td>3 Use more than intended in longer periods of time</td>
<td>✓</td>
<td>✓</td>
<td>Hyperphagia, change of eating patterns and meal frequency (snacking), negative experience triggers, cue-induced behaviors, larger portion size, proximity to food sources, lower cost of high-energy foods</td>
</tr>
<tr>
<td>4 Attempts to cut back</td>
<td></td>
<td>✓</td>
<td>Dietary restraint</td>
</tr>
<tr>
<td>5 Spend time in the pursuit/use/recovery of the substance</td>
<td>✓</td>
<td>✓</td>
<td>Participation in weight loss programs</td>
</tr>
<tr>
<td>6 Missed important activities</td>
<td>✓</td>
<td>✓</td>
<td>Anticipation and preoccupation, cravings, food thoughts, increased brain dopamine levels in response to anticipation and consumption, negative experience triggers, cue-induced behaviors, change of eating patterns and meal frequency, increase in habitual (vs. physical) hunger</td>
</tr>
<tr>
<td>7 Persistent behavior in spite of knowledge of consequences</td>
<td>✓</td>
<td>✓</td>
<td>Social &amp; occupational activities given up, social marginalization, psychological distress, discrimination Lack of diet compliance, failure to achieve long-term weight loss, hyperphagia resistant to aversive cues</td>
</tr>
</tbody>
</table>
Thank you!

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