Neuroscience of Eating Disorders in Young Adults

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Learning Objectives

• Describe the neurobiology that contributes to abnormal eating behavior in young adults with anorexia nervosa and bulimia nervosa.

• Explain how the neurobiology of eating disorders can inform strategies to treat anorexia nervosa and bulimia nervosa.
Disclosures

Relevant Financial Relationship(s)
• None

Off-Label Usage
• None
ED stats: A public health crisis

- AN affects ~1% of women and BN affects ~1-3% of women
- Up to 24 million people in the U.S. suffer from an ED (AN, BN, BED)
- AN and BN have substantial and costly medical morbidity\textsuperscript{1,2}
- AN has the highest mortality rate of any psychiatric disorder\textsuperscript{3-5}
  - For females 15-24 years old with AN, mortality rate is 12x higher than death rate of all causes of death.
  - 5.1 deaths per 1000 people with AN per year; 1.7 deaths per 1000 with BN
- Alcohol and other substance abuse disorders 4x more common in ED than in general population
- AN and BN have high rates of disability and tend to be a significant burden to carers, and healthcare funders\textsuperscript{2,6-10}
- ED receives inadequate research funding. Research dollars spent per affected ED individual was $0.93 (NIH, 2011) compared to $88/Alzheimer’s disease patient, $81/Schizophrenia patient, and $44/Autism patient

\begin{footnotesize}
\begin{itemize}
\item\textsuperscript{1}McKenzie, 1992; \textsuperscript{2}Wonderlich, 1997; \textsuperscript{3}Birmingham, 2005; \textsuperscript{4}Papadopoulos, 2009; \textsuperscript{5}Sullivan, 1995; \textsuperscript{6}Strober, 2004; \textsuperscript{7}Touyz, 2013; \textsuperscript{8}Treasure, 2001; \textsuperscript{9}Striegel-Moore, 2008; \textsuperscript{10}Mathers, 2000
\end{itemize}
\end{footnotesize}
Overview

• Review eating disorder diagnostic classification updates
• Does temperament matter?
• The neurobiology underlying pathological eating (aka, the neuroscience of ED)
• Treatment implications
What do eating disorders look like?
DSM-V diagnostic classification

EDNOS

AN

BN

BED

ARFID
**ANOREXIA NERVOSA**

<table>
<thead>
<tr>
<th>DSM-IV-TR</th>
<th>DSM-V</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>A.</strong> Refusal to maintain body weight at or above a minimally normal weight for age and height (e.g., weight loss leading to maintenance of body weight less than 85% of that expected; or failure to make expected weight gain during period of growth, leading to body weight less than 85% of that expected.)</td>
<td><strong>A.</strong> Restriction of energy intake relative to requirements leading to a significantly low body weight in the context of age, sex, developmental trajectory, and physical health. Significantly low is defined as less than minimally normal, or, for children and adolescents, less than that minimally expected for age and height.</td>
</tr>
<tr>
<td><strong>B.</strong> Intense fear of gaining weight or becoming fat, even though underweight.</td>
<td><strong>B.</strong> Intense fear of gaining weight or becoming fat, OR persistent behaviors that prevent weight gain, even though at a significantly low weight.</td>
</tr>
<tr>
<td><strong>C.</strong> Disturbance in the way in which one’s body weight or shape is experienced, undue influence of body weight or shape on self-evaluation, or denial of the seriousness of the current low body weight.</td>
<td><strong>C.</strong> Disturbance in the way in which one’s body weight or shape is experienced, undue influence of body weight or shape on self-evaluation, or persistent lack of recognition of the seriousness of the current low body weight.</td>
</tr>
<tr>
<td><strong>D.</strong> In postmenarcheal females, amenorrhea, i.e., the absence of at least three consecutive menstrual cycles. (A woman is considered to have amenorrhea if her periods occur only following hormone, e.g., estrogen, administration.)</td>
<td>No amenorrhea criterion.</td>
</tr>
</tbody>
</table>
### BULIMIA NERVOSA

<table>
<thead>
<tr>
<th>DSM-IV-TR</th>
<th>DSM-V</th>
</tr>
</thead>
</table>
| A. Recurrent episodes of binge eating characterized by: 1) eating, in a discrete period of time (e.g., within any 2-hour period), an amount of food that is definitely larger than most people would eat in a similar period of time and similar circumstances 2) a sense of lack of control over eating during the episode (e.g., a feeling that one cannot stop eating or control what or how much one is eating). | A. Same  
B. Same  
C. **Frequency:** Binge eating and inappropriate behaviors both occur, on average, at least *once/week* for 3 months.  
D. Same |
| B. Recurrent inappropriate compensatory behavior in order to prevent weight gain, such as self-induced vomiting; misuse of laxatives, or diuretics. |  |
| C. **Frequency:** Binge eating and inappropriate behaviors both occur, on average, at least *twice/week* for 3 months. |  |
| D. Self-evaluation unduly influenced by body shape and weight.             |  |
### ED NOS/Other Specified Feeding or Eating Disorder

<table>
<thead>
<tr>
<th>DSM-IV-TR</th>
<th>DSM-V</th>
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</thead>
<tbody>
<tr>
<td>Eating Disorder Not Otherwise Specified</td>
<td>Other Specified Feeding or Eating Disorder</td>
</tr>
<tr>
<td>1) Atypical AN: all AN criteria but weight still within or above normal range despite sig. weight loss</td>
<td></td>
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<tr>
<td>2) BN of low frequency &amp;/or limited duration</td>
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<tr>
<td>3) BED of low frequency &amp;/or limited duration</td>
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<tr>
<td>4) Purging disorder</td>
<td></td>
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<tr>
<td>5) Night eating syndrome</td>
<td></td>
</tr>
</tbody>
</table>

Unspecified Feeding or Eating Disorder
DSM-IV adult AN weight criteria: BMI (kg/m²)

- 18.5 lower limit normal body weight
- > 17.5 mild
- 16 - 16.99 moderate
- 15 - 15.99 severe
- < 15 extreme
- Children/Adolescents: BMI for age
  - CDC BMI percentile calculator
  - < 5% percentile as guideline
Weight loss

Short-Term Obesity Therapy Does Not Result in Long-term Weight Loss

- Combined Therapy
- Behavior Therapy
- Diet Alone

Weight Loss in Anorexia Nervosa

76 obese women, average weight of 106 kg
Wadden et al Int J Obesity 1989

UCSD Eating Disorders Center
New understandings of ED

- **Family studies**
  - Increased rate of AN, BN, ED NOS in first degree relatives\(^1\text{-}^4\)

- **Twin studies**
  - Approximately 50 to 80% heritable risk\(^1,^5\text{-}^8\)
  - Genes more powerful than culture

- **Genes cause childhood (pre-morbid) behaviors**
  - Anxiety, harm avoidance, perfectionism, inhibition, drive for thinness, altered interoceptive awareness, obsessive personality\(^9\text{-}^11\)

- **Suggests powerful neurobiology**

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\(^1\) Kendler, 1991; \(^2\) Walters 1995; \(^3\) Lilenfeld, 1998; \(^4\) Strober, 2000; \(^5\) Treasure 1994; \(^6\) Berrettini, 2000; \(^7\) Bulik, 2006; \(^8\) Steinglass, 2004; \(^9\) Anderluch 2003; \(^10\) Stice 2002; \(^11\) Lilenfeld 2006
New constructs of ED: A shared temperament

- Impaired cognitive flexibility and set-shifting (Roberts 2007)
- AN have weak central coherence (Lopez 2008)
- Anxiety/inhibition vs. Reward/motivation
  - Harm avoidant (Kaye 2004)
  - Over concerned with consequences, exaggerated inhibition (Kaye 2009)
  - Intolerance of uncertainty (Frank 2011)
  - AN, BN: High punishment sensitivity
    - AN low, BN high: reward reactivity (Harrison 2011)
    - Elevated anticipatory anxiety
    - Interoceptive awareness deficits (Strigo 2013; Khalsa in press; Kerr in press)
- More likely to be encoded in brain circuitry
When good traits go bad: Temperament, personality and course of AN

Stice, 2002; Anderluh 2003; Connan, 203; Lilienfeld, 2006; Kaye, 2009
Neurobiology of ED

• Individuals with ED exhibit temperament and personality traits, which are related to neural circuit function, and are important in the development and maintenance of the disorder.

• This neurobiologically-based temperament is characterized by:
  • 1) elevated anxiety/harm avoidance
  • 2) altered reward sensitivity
  • 3) altered cognitive flexibility/inhibition
  • 4) altered interoceptive awareness
Individuals with ED exhibit temperament and personality traits, which are related to neural circuit function, and are important in the development and maintenance of the disorder.
Neurobiology overview

Ventral-limbic circuit (Valuation)  Salience circuitry

Dorsal-cognitive circuitry

Phillips 2003; Haber & Knutson, 2010; Kurth et al 2010; Medford & Critchley, 2010
Similar to fronto-striatal circuitry alterations in addiction

Tomasi & Volkow 2013
Is pathological eating related to an altered balance between reward and inhibition?

**Ventral Limbic Circuit**
- Reward valuation
- Salience processing
- Generate affective responses

**Dorsal Cognitive Circuit**
- Cognitive control
- Selective attention
- Conflict monitoring
- Decision-making
- Inhibition

Phillips et al 2003 *Biol Psych*
Is pathological eating related to an altered balance between reward and inhibition?
Is pathological eating related to an altered balance between reward and inhibition?
Is substance abuse related to an altered balance between reward and inhibition?

**Limbic**
- Emotion, reward
  - Learn: Seek pleasure

**Executive**
- Plans, consequence
  - Learn: Minimize risk

Reward
- Approach

Aversive
- Avoid

2.5 Years Later

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Reward processing in AN and BN

• Individuals with clinical and subclinical EDs have high punishment sensitivity in the ill and REC states.
• BN tend to have increased sensitivity to reward, but findings are mixed in AN
• Ill AN have enhanced ability to delay reward
• Clinical expression: lack of motivation

(Steinglass 2012)

Altered limbic and cognitive reward processing for wins and losses in AN & BN

REC AN showed elevated but abnormal AVS (limbic) response that failed to differentiate wins and losses, and exaggerated DC (cognitive) response (Wagner 2007)

REC BN showed decreased AVS (limbic) and DC (cognitive) response that failed to differentiate wins and losses (Wagner 2010)
Dopamine and reward

Fronto-Striatal circuitry

Monkey: DA neuron midbrain response to receipt and cues of reward (cue>receipt)

Schultz 2001
AN and BN have elevated DA binding, which is related to increased anxiety and harm avoidance.
Amphetamine-induced dopamine release increases anxiety in REC AN

Bailer, 2012
Do hunger and satiety affect eating differently in ED?
Hunger influences behavioral choice by making rewards more appetitive

In animals, hunger enhances sensitivity to drugs of abuse (Carr 2001 Physiol Behav) and increases drug intake (Carroll et al 1979 Science)
Hunger influences behavioral choice by making rewards more appetitive.

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Hunger increases rates of delay discounting (Wang et al 2010 *Psychol Sci*).
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Hunger reduces risk aversion (Levy et al 2013 *PLoS ONE*).
Hunger influences behavioral choice by making rewards more appetitive

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Hunger increases rates of delay discounting (Wang et al 2010 *Psychol Sci*)

Hunger reduces risk aversion (Levy et al 2013 *PLoS ONE*).

Hunger leads shoppers to overvalue higher-calorie foods (Tal & Wansink 2013 *JAMA Intern Med*, Goldstone et al 2009 *EJN*).
Hunger activates reward systems more for high-calorie foods
Hunger Does Not Motivate Reward in Women Remitted from Anorexia Nervosa

Christina E. Wierenga, Amanda Bischoff-Grethe, A. James Melrose, Zoe Irvine, Laura Torres, Ursula F. Bailer, Alan Simmons, Julie L. Fudge, Samuel M. McClure, Alice Ely, and Walter H. Kaye

Brains of Those With Anorexia React Differently to Hunger Signals

By Richard Ansaroff, HealthDay Reporter

THURSDAY, March 26, 2015 (HealthDay News) -- People with anorexia nervosa have an abnormal brain response to hunger signals, a new study finds.

"When normal people are hungry, they are motivated to eat," study first author Christina Wierenga, an associate professor of psychiatry at the University of California, San Diego School of Medicine, said in a university news release.

"Yet individuals with anorexia are the most hungry but still restrain their food intake. We wanted to identify brain mechanisms that may contribute to their ability to ignore hunger, like food," she explained.

The finding offers new insight into eating disorders and could lead to new treatments that target specific brain pathways, according to the researchers.

The findings were published recently in the journal Biological Psychiatry.

For the study, the researchers analyzed brain function in 23 women who had recovered from anorexia and 17 healthy people who never had the eating disorder.

The worse recovered from anorexia "showed decreased response to refeed, even when hungry. This is opposite of healthy women who refeed eating disorders, who showed greater activity in refeed when hungry," Wierenga said.

"Our study suggests that brain-stimuli differences in anorexia make them less sensitive to reward and the motivational drive of hunger. Put another way, hunger does not motivate them to eat," study senior author Dr. Walter Kaye, director of the Eating Disorders Treatment and Research Program at the university, said in the news release.
fMRI delay discounting task: Monetary reward

- Participants performed a DD task during fMRI on 2 visits 24 hours apart.
  - **Hungry visit:** fasted for 16 hours prior to scan session
  - **Satiated visit:** participants consumed standardized breakfast (~450kcal) 2 hours prior to scan visit

Choose between early reward {today, 2 weeks, 4 weeks} and delayed reward {2 weeks, 4 weeks} that differed by 3%, 5%, 10%, 15%, 25%, or 35%.
Decreased reward and increased cognitive processing during delay discounting in REC AN

**REWARD**

Right Ventral Striatum

Mean Percent Signal Change

Condition

<table>
<thead>
<tr>
<th>Condition</th>
<th>Hungry</th>
<th>Satiated</th>
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<tbody>
<tr>
<td>CW</td>
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<tr>
<td>RAN</td>
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**COGNITIVE**

Right Middle Frontal Gyrus

Mean Percent Signal Change

Group

<table>
<thead>
<tr>
<th>Group</th>
<th>CW</th>
<th>RAN</th>
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Z=+44

Wierenga 2015
Is pathological eating related to an altered balance between reward and inhibition?

**CW Hunger Condition**

**Ventral Limbic Circuit**
- Reward valuation
- Salience processing
- Generate affective responses

**Dorsal Cognitive Circuit**
- Cognitive control
- Selective attention
- Conflict monitoring
- Incentive valuation
- Decision-making
- Inhibition

**Limbic**
- Emotion, reward

**Executive**
- Plans, consequence
Is pathological eating related to an altered balance between reward and inhibition?

**CW Satiated Condition**

**Ventral Limbic Circuit**
- Reward valuation
- Salience processing
- Generate affective responses

**Dorsal Cognitive Circuit**
- Cognitive control
- Selective attention
- Conflict monitoring
- Incentive valuation
- Decision-making
- Inhibition

**LIMBIC**
- Emotion, reward

**EXECUTIVE**
- Plans, consequence
Is pathological eating related to an altered balance between reward and inhibition?

RAN Hunger and Satiated Condition

Ventral Limbic Circuit
- Reward valuation
- Salience processing
- Generate affective responses

Dorsal Cognitive Circuit
- Cognitive control
- Selective attention
- Conflict monitoring
- Incentive valuation
- Decision-making
- Inhibition

LIMBIC Emotion, reward

EXECUTIVE Plans, consequence
Anxiety may compromise reward sensitivity in AN & BN

Reward Circuitry: Right Ventral Striatum

Kaye et al in prep
AN have increased anticipatory and decreased receipt response to food; BN have increased receipt response to food
Interoceptive awareness in AN

- Endorse poor interoceptive awareness on self-reports
- Have difficulty detecting heartbeat
- Clinical expression: alexithymic, difficulty learning from experience, prediction errors, anticipatory anxiety

Pollatos, 2008; Lilenfeld 2006
Altered dorsal mid-insula activity during stomach interoception in WR-AN

Kerr, in press
AN have increased anticipatory and decreased receipt response to pain in the insula.
Altered inhibitory control in AN

Cognitive Set-Shifting

Motor Inhibition

Cognitive Inhibition

Zastro, 2009

Lock, 2011

Wierenga, 2014; Oberndorfer 2011
Altered inhibitory control in BN

Marsh, 2011
Does treatment of eating disorders work?

- Course in adults with **Anorexia Nervosa**: 
  - ~10% recover in less than 5 years 
  - ~50+% recover over 5 to 10 years 
  - ~30% chronically ill 
  - ~10%+ die (from heart failure, organ failure, malnutrition, suicide)

- Course in adults with **Bulimia Nervosa**: 
  - symptom abstinence in only 30-50% of treatment completers\(^1,2\) 
  - 10yr: 50%-70% rec, 30% some improvement, 20% chronic

- Course in adolescents more promising\(^3\)

- There is no proven treatment for AN or BN that reverses symptoms\(^4-11\)

- There is no FDA approved medication for AN or BN (and only one for BED)\(^6,12,13\)

- Only 1 in 10 women and men with ED receive treatment; only 35% of people that receive treatment for an ED get treatment at a specialized facility for ED

- Treatment failure is likely due to a poor understanding of the etiology of ED, hindering the ability of treatments to target mechanisms underlying disordered eating.

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\(^1\)Mitchell 2007; \(^2\)Wilson 2007; \(^3\)Lock 2015; \(^4\)Hay 2012; \(^5\)Rigaud 2007; \(^6\)Bulik 2007; \(^7\)Watson 2012; \(^8\)Brown 2012; \(^9\)Galsworthy-Francis 2014; \(^10\)Touyz 2013; \(^11\)NICE 2004; \(^12\)Attia 2005; \(^13\)Jimerson 1996
RCTs of psychosocial treatments of AN

- Limited number of randomized controlled trials for AN (<25 published reports)
- Drop out rates are high (~22%-73%)
- Ambivalence and reluctance to engage in treatment is common
- Treatment effects are minimal
  - “good” outcome reported in 0-50%
  - full recovery may take years
  - majority of treatments do not increase BMI to healthy range (>18.5)
  - no first-line gold standard treatment (treatment comparisons often equivocal; severity of illness makes it unethical to delay treatment in wait-list or placebo control studies)
- Treatment effects are more promising in adolescence
  - “good” outcome reported in 50-60%, with gains maintained¹⁻³

¹Lock et al 2010; ²Le Grange 2014; ³Marzola, 2014
Treatments for adolescents with AN are more promising

12 month outcome for Adolescent-Focused Individual Therapy (AFT) vs Family Based Treatment
Results: FBT superior to AFT for full remission (~50%); treatment response stable over 2 years

30 month outcome of Intensive Family Based Therapy
Results: ~60% good outcome

Lock et al 2010; Le Grange 2014

Marzola et al 2014
Treatment of BN

- Outpatient, partial programs often successful
- Proven treatments (in controlled trials)
  - Medication “Antidepressants”
  - Psychotherapy
    - CBT - “gold” standard
    - Interpersonal, dialectical behavior therapies
      - Reduce binge/purge, improve function and mood
- CBT + Medication – interactions not clear
- Cluster “B” PD respond poorly
New treatments for AN at UCSD

BRIEF REPORT

An Innovative Short-term, Intensive, Family-based Treatment for Adolescent Anorexia Nervosa: Case Series
Roxanne E. Rockwell¹, Kerri Boutelle¹², Mary Ellen Trunko¹, M. Joy Jacobs¹³ & Walter H. Kaye¹*

RESEARCH ARTICLE

Short-Term Intensive Family Therapy for Adolescent Eating Disorders: 30-Month Outcome†
Enrica Marzola¹, Stephanie Knatz², Stuart B. Murray², Roxanne Rockwell², Kerri Boutelle², Ivan Eisler³ & Walter H. Kaye²*
¹Department of Neuroscience, University of Turin, Turin, Italy
²Department of Psychiatry, University of California San Diego, San Diego, CA, USA
³Department of Pediatrics, University of California San Diego, La Jolla, CA, USA

REVIEW

Temperament-based Treatment for Anorexia Nervosa
Walter H. Kaye¹*, Christina E. Wierenga¹, Stephanie Knatz¹, June Liang¹, Kerri Boutelle¹², Laura Hill³ & Ivan Eisler⁴
¹Department of Psychiatry, University of California San Diego, San Diego, CA, USA
²Department of Pediatrics, University of California San Diego, La Jolla, CA, USA
³Department of Psychiatry, Ohio State University, Columbus, OH, USA
⁴Institute of Psychology, Kings College London, London, UK
Intensive Temperament Based Therapy (iTBT)

• Designed to teach AN and CA to recognize temperament patterns and develop adaptive coping/management strategies
• Adapts FBT to be developmentally appropriate for adult AN and their carers
• Two-pronged approach:
  – Teach AN constructive skills to cope with temperament
  – Teach CA skills to manage AN temperament
• Targets: anticipatory anxiety, reward/cognitive control, AN-CA meal behavior
• Outcome: weight, clinical symptoms

Kaye, Wierenga, 2014
Why an intensive format?

• iTBT is administered in a 5-day multi-family format

• To increase efficacy:
  – Adapts tenets of neuroplasticity:
    • increased tx frequency & intensity are critical components to elicit behavior change
  – Adapts tx models of anxiety:
    • intense, repeated, focused in vivo practice is key to altering biologically-driven avoidance behaviors by maximizing learning through massed practice
  – Initial efficacy is increased in intensive tx

• To increase feasibility, compliance, and dissemination:
  – Option to travel to specialty clinic
  – Reduce burden of time commitment
  – Can expand accessibility by disseminating to other centers

(Hebb, 1949; Kolb, 1995; Abramowitz, 2003; Deacon, 2006; Gallo, 2012; Ollendick, 2009; Santucci, 2009; Schmidt, 1992; Storch, 2007; Whiteside, 2010; Fernandez, 2006; Storch, 2008)
## iTBT: General format

<table>
<thead>
<tr>
<th>Clinical Approach</th>
<th>AN</th>
<th>CA</th>
</tr>
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<tbody>
<tr>
<td>1) Neurobiology Psychoeducation</td>
<td>Goal: increase insight of symptoms and relation to behavior</td>
<td></td>
</tr>
<tr>
<td>2) Experiential learning</td>
<td>Goal: gain insight by participating in exercises designed to experience how neurobiology can influence behavior</td>
<td></td>
</tr>
<tr>
<td>3a) Strategies: Create external structure</td>
<td>Diversion, routine, rules</td>
<td>External structure</td>
</tr>
<tr>
<td>3b) Strategies: Learn strategies to cope with temperament</td>
<td>Constructive use of temperament</td>
<td>Provide alternative perspective</td>
</tr>
<tr>
<td>4) Build competency</td>
<td>In vivo practice</td>
<td>In vivo practice</td>
</tr>
<tr>
<td>5) Apply to real world</td>
<td></td>
<td>Family meal</td>
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</tbody>
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Kaye, Wierenga, 2014
## Target: Anticipatory meal-related anxiety

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<td>Goal: neurobiology of appetite dysregulation and restricted eating due to anxiety; exaggerated anticipatory response to food that is anxious and aversive</td>
<td></td>
</tr>
<tr>
<td>2) Experiential learning</td>
<td>Goal: gain insight into discrepancy between anticipated vs actual responses</td>
<td></td>
</tr>
<tr>
<td>3a) Strategies: Create external structure</td>
<td>Reduce uncertainty by constructing plan and implementing structure on meals</td>
<td></td>
</tr>
<tr>
<td>3b) Strategies: Learn strategies to cope with temperament</td>
<td>Pre-meal routine to distract</td>
<td>Provide meal coaching to distract/direct pt and support pt complete pre-meal routine</td>
</tr>
<tr>
<td></td>
<td>(Marek, 2013)</td>
<td></td>
</tr>
<tr>
<td>4) Build competency</td>
<td>In vivo practice</td>
<td>In vivo practice</td>
</tr>
<tr>
<td>5) Apply to real world</td>
<td>Modify meal plan for different occasions</td>
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Kaye, Wierenga, 2014
## Target: Reward insensitivity, motivation

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<tr>
<td>1) Neurobiology Psychoeducation</td>
<td>Goal: understand that brain basis supporting anxiety/HA is associated with altered sensitivity to reward/punishment, behavior driven by avoidance of negative consequences</td>
<td></td>
</tr>
<tr>
<td>2) Experiential learning</td>
<td>Goal: reframe idea of motivation – from being about striving for reward to the avoidance of future negative consequences</td>
<td></td>
</tr>
<tr>
<td>3a) Strategies: Create external structure</td>
<td>Contingency management through <strong>behavioral contracting</strong></td>
<td></td>
</tr>
<tr>
<td>3b) Strategies: Learn strategies to cope with temperament</td>
<td>Identify positive and negative motivating factors</td>
<td>Learn basic behavior management principles</td>
</tr>
<tr>
<td>4) Build competency</td>
<td>In vivo practice</td>
<td>In vivo practice</td>
</tr>
<tr>
<td>5) Apply to real world</td>
<td>Implement contract outside of treatment</td>
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Kaye, Wierenga, 2014
Considerations for future treatment development

• Target change vs compensation?
• “Brain-Directed” vs “Neurobiologically-Informed”?
  – Neuromodulation
  – Surgical
  – Gastric
  – New psychosocial/behavioral targets
  – New pharmacological targets
• Challenge of identifying appropriate targets and outcome
• What does recovery look like?
NEW FED TR-treatment
Neurobiologically Enhanced With Family Eating Disorder Trait Response

One Week Family PHP Treatment Program
For Eating Disorders

A unique opportunity for clients and support persons to learn and heal together

February 15-21, 2015
June 14-20, 2015
August 2-8, 2015
May 9-16, 2015
July 11-18, 2015
September 12-19, 2015

The Center for Balanced Living
8801 Ravines Edge Court, Suite 201
Columbus, OH 43235

UCSD Eating Disorder Center
4510 Executive Drive, Suite 315
San Diego, CA 92121

✓ 5 CLIENTS WILL BE ACCEPTED per week
✓ Ages 18+
✓ One week, 40 hours, 8 am-4 pm, M-F
✓ (Mandatory pre/post testing on family reflected in dates above.)
✓ Current or previous Anorexia Nervosa diagnosis
✓ At least one support person required to attend all 5 days with client
✓ Sliding fee scale
✓ Treatment scholarships for those without insurance thanks to NEDA Feeding Hope Research Grant

New brain-based treatment tools and Dialectical Behavior Therapy (DBT) integrated with a new dietary approach and medication management. Client and family support every step of the way.

For more information call 614.896.8222

www.TheCenterForBalancedLiving.org or http://eatingdisorders.ucsd.edu/patient/adult-trt.html

Research funding for this program made possible through the National Eating Disorder Association’s 2014 “Feeding Hope Grant,” awarded to The Center for Balanced Living and University of California San Diego Eating Disorders Center.
UCSD Eating Disorders Treatment and Research Program is conducting imaging research studies with adolescents and adults ill or recovered from Anorexia and/or Bulimia Nervosa. This research will help us examine the neurobiology of eating disorders.

Participants may receive compensation up to $1250.00 for completion of the studies. We may also be able to provide travel compensation to San Diego.

For more information, contact edresearch@ucsd.edu or our website http://eatingdisorders.ucsd.edu/research/
Acknowledgements

Collaborators:

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• Stephanie Knatz, Ph.D.
• June Liang, Ph.D.
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• Laura Hill, Ph.D.

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• Ivan Eisler

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### Intensive format effective in adolescent AN

**Table 1**: Intake and outcome clinical information for each individual

<table>
<thead>
<tr>
<th>ID</th>
<th>Diagnosis</th>
<th>Age at onset (years)</th>
<th>Number of months inpatient/residential treatment</th>
<th>Age at admission (years)</th>
<th>Admission IBW (%)</th>
<th>Discharge medication</th>
<th>Days post-follow-up</th>
<th>Follow-up IBW (%)</th>
<th>Change in IBW</th>
<th>Hospitalization since IPT</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>AN</td>
<td>12</td>
<td>0</td>
<td>15</td>
<td>69.3</td>
<td>Escitalopram 10 mg/day</td>
<td>297</td>
<td>84.4</td>
<td>15.2</td>
<td>No</td>
</tr>
<tr>
<td>2</td>
<td>AN</td>
<td>12</td>
<td>0.5</td>
<td>13</td>
<td>72.0</td>
<td>Olanzapine 3.75 mg/day, citalopram 10 mg/day</td>
<td>285</td>
<td>112.1</td>
<td>40.1</td>
<td>No</td>
</tr>
<tr>
<td>3</td>
<td>AN</td>
<td>13</td>
<td>8</td>
<td>17</td>
<td>74.2</td>
<td>Citalopram 40 mg/day, olanzapine 5 mg/day</td>
<td>255</td>
<td>91.4</td>
<td>17.3</td>
<td>No</td>
</tr>
<tr>
<td>4</td>
<td>AN</td>
<td>12</td>
<td>0</td>
<td>17</td>
<td>77.2</td>
<td>None</td>
<td>393</td>
<td>107.1</td>
<td>29.9</td>
<td>No</td>
</tr>
<tr>
<td>5</td>
<td>AN</td>
<td>12</td>
<td>2.5</td>
<td>13</td>
<td>77.4</td>
<td>Risperidone 0.25 mg b.i.d.</td>
<td>182</td>
<td>107.6</td>
<td>30.2</td>
<td>No</td>
</tr>
<tr>
<td>6</td>
<td>AN/BN</td>
<td>12</td>
<td>4</td>
<td>15</td>
<td>80.2</td>
<td>Sertaline 100 mg/day, olanzapine 5 mg/day, transdermal 25 mg q.h.s., p.r.n.</td>
<td>66</td>
<td>89.1</td>
<td>8.9</td>
<td>No</td>
</tr>
<tr>
<td>7</td>
<td>AN</td>
<td>14</td>
<td>0</td>
<td>16</td>
<td>80.9</td>
<td>None</td>
<td>190</td>
<td>89.6</td>
<td>8.7</td>
<td>No</td>
</tr>
<tr>
<td>8</td>
<td>AN</td>
<td>11</td>
<td>1</td>
<td>15</td>
<td>82.3</td>
<td>Olanzapine 2.5 mg/day</td>
<td>451</td>
<td>90.2</td>
<td>7.9</td>
<td>No</td>
</tr>
<tr>
<td>9</td>
<td>AN</td>
<td>14</td>
<td>0</td>
<td>16</td>
<td>82.6</td>
<td>Aripiprazole 2.5 mg/day</td>
<td>738</td>
<td>134.6</td>
<td>52.0</td>
<td>No</td>
</tr>
<tr>
<td>10</td>
<td>NOS</td>
<td>9</td>
<td>0</td>
<td>10</td>
<td>83.5</td>
<td>Olanzapine 1.25 mg/day</td>
<td>87</td>
<td>98.2</td>
<td>14.7</td>
<td>No</td>
</tr>
<tr>
<td>11</td>
<td>AN</td>
<td>11</td>
<td>0</td>
<td>12</td>
<td>86.7</td>
<td>None</td>
<td>52</td>
<td>99.5</td>
<td>12.8</td>
<td>No</td>
</tr>
<tr>
<td>12</td>
<td>AN</td>
<td>11</td>
<td>2.5</td>
<td>16</td>
<td>87.9</td>
<td>None</td>
<td>157</td>
<td>92.6</td>
<td>4.7</td>
<td>No</td>
</tr>
<tr>
<td>13</td>
<td>AN</td>
<td>11</td>
<td>0</td>
<td>12</td>
<td>88.9</td>
<td>Fluoxetine 30 mg/day</td>
<td>129</td>
<td>100.2</td>
<td>11.3</td>
<td>Yes</td>
</tr>
<tr>
<td>14</td>
<td>AN/BN</td>
<td>13</td>
<td>0.75</td>
<td>15</td>
<td>89.0</td>
<td>None</td>
<td>591</td>
<td>102.6</td>
<td>13.6</td>
<td>No</td>
</tr>
<tr>
<td>15</td>
<td>AN</td>
<td>9</td>
<td>0.2</td>
<td>17</td>
<td>93.2</td>
<td>None</td>
<td>241</td>
<td>86.6</td>
<td>-6.6</td>
<td>No</td>
</tr>
<tr>
<td>16</td>
<td>AN</td>
<td>15</td>
<td>0</td>
<td>16</td>
<td>94.9</td>
<td>None</td>
<td>353</td>
<td>97.2</td>
<td>2.2</td>
<td>No</td>
</tr>
<tr>
<td>17</td>
<td>NOS</td>
<td>17</td>
<td>0</td>
<td>18</td>
<td>98.0</td>
<td>Fluoxetine 10 mg/day</td>
<td>58</td>
<td>101.0</td>
<td>3.0</td>
<td>No</td>
</tr>
<tr>
<td>18</td>
<td>NOS</td>
<td>13</td>
<td>0</td>
<td>16</td>
<td>99.1</td>
<td>Fluoxetine 40 mg/day</td>
<td>486</td>
<td>103.8</td>
<td>4.7</td>
<td>No</td>
</tr>
</tbody>
</table>

Mean: 123, 1.1, 15.0, 84.3, 27.8, 99.3, 15.0

SD: 20, 2.1, 2.1, 8.7, 193.8, 99.3, 14.5

IBW, ideal body weight; IPT, intensive family therapy; AN, anorexia nervosa; BN, bulimia nervosa; NOS, not otherwise specified; SD, standard deviation.
Intensive format effective in adolescent AN

Table 2. Participant characteristics at follow-up and by treatment structure in those who completed the follow-up study.

<table>
<thead>
<tr>
<th></th>
<th>Total sample participating in follow-up study (N=74)</th>
<th>S-IFT (N=20, 27%)</th>
<th>M-IFT (N=54, 73%)</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Length of follow-up, months, Mean(SD)</td>
<td>30.85 (20.2)</td>
<td>53.4 (16.07)</td>
<td>22.5 (14.37)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Age at follow-up, years, Mean(SD)</td>
<td>17.18 (3.4)</td>
<td>19.2 (3.03)</td>
<td>16.44 (3.25)</td>
<td>0.002</td>
</tr>
<tr>
<td>%EBW, Mean(SD)</td>
<td>99 (12.57)</td>
<td>102.17 (17.47)</td>
<td>97.83 (10.14)</td>
<td>0.57</td>
</tr>
<tr>
<td>AN</td>
<td>96.89 (14.42)</td>
<td>104.16 (21.92)</td>
<td>94.17 (9.47)</td>
<td>0.27</td>
</tr>
<tr>
<td>EDNOS</td>
<td>102.11 (8.52)</td>
<td>99.18 (7.52)</td>
<td>103.17 (8.78)</td>
<td>0.26</td>
</tr>
<tr>
<td>Outcome, N(%)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Full remission</td>
<td>45 (60.8)</td>
<td>13 (65)</td>
<td>32 (59.3)</td>
<td></td>
</tr>
<tr>
<td>Partial remission</td>
<td>20 (27)</td>
<td>5 (25)</td>
<td>15 (27.7)</td>
<td></td>
</tr>
<tr>
<td>No remission</td>
<td>9 (12.2)</td>
<td>2 (10)</td>
<td>7 (13)</td>
<td></td>
</tr>
<tr>
<td>Undergoing treatment, N(%)</td>
<td>36 (50.7)</td>
<td>6 (31.6)</td>
<td>30 (57.7)</td>
<td>0.06</td>
</tr>
<tr>
<td>On medications, N(%)</td>
<td>34 (45.9)</td>
<td>8 (40)</td>
<td>26 (48.1)</td>
<td>0.61</td>
</tr>
<tr>
<td>How long on medications, N(%)</td>
<td></td>
<td></td>
<td></td>
<td>0.9</td>
</tr>
<tr>
<td>&lt;6 months</td>
<td>9 (26.5)</td>
<td>3 (37.5)</td>
<td>6 (23.1)</td>
<td></td>
</tr>
<tr>
<td>6-12 months</td>
<td>8 (23.5)</td>
<td>1 (12.5)</td>
<td>7 (26.9)</td>
<td></td>
</tr>
<tr>
<td>&gt;12 months</td>
<td>12 (35.3)</td>
<td>3 (37.5)</td>
<td>9 (34.6)</td>
<td></td>
</tr>
<tr>
<td>n.a.</td>
<td>5 (14.7)</td>
<td>1 (12.5)</td>
<td>4 (15.4)</td>
<td></td>
</tr>
<tr>
<td>Hospitalization since IFT, individuals, N(%)</td>
<td>6 (8.1)</td>
<td>2 (10)</td>
<td>4 (7.4)</td>
<td>0.66</td>
</tr>
<tr>
<td>Residential treatments since IFT, individuals, N(%)</td>
<td>11 (14.9)</td>
<td>2 (10)</td>
<td>9 (16.7)</td>
<td>0.72</td>
</tr>
</tbody>
</table>

Fisher's Exact test and Mann-Whitney-Wilcoxon test were used to assess statistical significance for categorical and continuous variables, respectively.

Legend: S-IFT: single-family Intensive Family Therapy; M-IFT: multi-family Intensive Family Therapy; AN: anorexia nervosa; EDNOS: eating disorder not otherwise specified, restricting type; %EBW: % expected body weight

Marzola under review
## iTBT sample schedule

### UCSD MULTI FAMILY DAY TREATMENT

<table>
<thead>
<tr>
<th>Time</th>
<th>Monday</th>
<th>Tuesday</th>
<th>Wed</th>
<th>Thursday</th>
<th>Friday</th>
</tr>
</thead>
<tbody>
<tr>
<td>8:00-9:00</td>
<td>BREAK</td>
<td>BREAK</td>
<td>BREAK</td>
<td>BREAK</td>
<td>BREAK</td>
</tr>
<tr>
<td>9:00-9:30</td>
<td>Orientation</td>
<td>Neurobiology Psychoeducation</td>
<td>Neurobiology Psychoeducation</td>
<td>Neurobiology Psychoeducation</td>
<td>Patient-Carers Group: Brainstorming/problem-solving for transition home</td>
</tr>
<tr>
<td>9:30-10:00</td>
<td>Neurobiology Psychoeducation</td>
<td>Progress and symptom report/daily goal setting</td>
<td>Progress and symptom report/daily goal setting</td>
<td>Progress and symptom report/daily goal setting</td>
<td>SNACK/ In vivo meal Coaching</td>
</tr>
<tr>
<td>10:00-10:15</td>
<td>SNACK/ In vivo meal Coaching</td>
<td>SNACK/ In vivo meal Coaching</td>
<td>SNACK/ In vivo meal Coaching</td>
<td>SNACK/ In vivo meal Coaching</td>
<td>SNACK/ In vivo meal Coaching</td>
</tr>
<tr>
<td>10:15-10:30</td>
<td>1:00-1:30</td>
<td>10:00-11:00</td>
<td>Recovery Plan: Verbal team agreements</td>
<td>Recovery Plan: Written plan construction</td>
<td>Recovery Plan: Wrap-up and presentation</td>
</tr>
<tr>
<td>1:00-1:30</td>
<td>Lunch/In vivo meal coaching</td>
<td>Lunch/In vivo meal coaching</td>
<td>Lunch/In vivo meal coaching</td>
<td>Lunch/In vivo meal coaching</td>
<td>Lunch/In vivo meal coaching</td>
</tr>
<tr>
<td>1:30-2:00</td>
<td>BREAK</td>
<td>BREAK</td>
<td>BREAK</td>
<td>BREAK</td>
<td>BREAK</td>
</tr>
<tr>
<td>2:00-2:30</td>
<td>Carers group: Identifying and enlisting support</td>
<td>Carers group: Didactic supportskills training</td>
<td>Carers group: Feedback and Coaching</td>
<td>Carers group: Constructing support plan</td>
<td>Exit Strategies: Review and Closing</td>
</tr>
<tr>
<td>3:00-3:30</td>
<td>NB Skills practice</td>
<td>NB Skills practice</td>
<td>NB Skills practice</td>
<td>NB Skills practice</td>
<td>NB Skills practice</td>
</tr>
<tr>
<td>3:30-4:00</td>
<td>SNACK/ In vivo meal Coaching</td>
<td>SNACK/ In vivo meal Coaching</td>
<td>SNACK/ In vivo meal Coaching</td>
<td>SNACK/ In vivo meal Coaching</td>
<td>SNACK/ In vivo meal Coaching</td>
</tr>
</tbody>
</table>
Attrition:
- 1 of 9 patients dropped out

Acceptability:
- 78% of AN, 100% of CA would recommend iTBT to others
- 89% of AN, 100% of CA felt CA were better equipped to provide support
- 89% of AN, 100% of CA planned for continued CA involvement in treatment
- 100% of AN, 100% of CA enjoyed learning about the neurobiology of AN
- 100% of AN; 100% of CA felt the exercises on neurobiology improved their understanding of AN
- 89% of AN; 100% of CA felt more confident about CA’s ability to support patient through recovery.
- 100% of AN enjoyed interacting with others in the group.
- 78% of AN thought iTBT will be helpful in decreasing their ED behaviors (e.g., restricting, over-exercising).
Efficacy

- AN showed reduced anxiety
  - STAI trait: pre=59.3, post=56.5; $t(7)=2.3$, $p=.06$, Cohen’s $d=.81$
  - STAI state: pre=53.9, post=49.8; $p>.05$, Cohen’s $d=.38$
- AN experienced improved communication
  - FAD Communication subscale; $t(7)=2.2$, $p=.06$, Cohen’s $d=.78$
- CA experienced improvement in having clear rules and expectations between family members
  - FAD Behavioral Control subscale; $t(8)=2.0$, $p=.08$, Cohen’s $d=.67$
- CA reported significantly increased efficacy in family-based therapy for AN
  - Parents vs. Anorexia Scale: pre=2.6, post=3.9; $t(8)=-5.6$, $p<.001$
Future directions: Mechanisms of action of iTBT

<table>
<thead>
<tr>
<th>Target</th>
<th>Instrument</th>
</tr>
</thead>
<tbody>
<tr>
<td>Diagnostic Assessment</td>
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</tr>
<tr>
<td>Clinical Symptoms</td>
<td>- MINI</td>
</tr>
<tr>
<td></td>
<td>- SCID Modified Module 8</td>
</tr>
<tr>
<td></td>
<td>- Y-BOCS</td>
</tr>
<tr>
<td></td>
<td>- EDE</td>
</tr>
<tr>
<td>Treatment Development Measures</td>
<td></td>
</tr>
<tr>
<td>Acceptability &amp; Feasibility</td>
<td>- Developed by team</td>
</tr>
<tr>
<td>Mechanisms of Action</td>
<td></td>
</tr>
<tr>
<td>Anticipatory Anxiety</td>
<td>- Food Cue Physiological Reactivity</td>
</tr>
<tr>
<td></td>
<td>- Fear of Food Measure</td>
</tr>
<tr>
<td></td>
<td>- STAI</td>
</tr>
<tr>
<td></td>
<td>- TCI HA</td>
</tr>
<tr>
<td></td>
<td>- Intolerance of Uncertainty</td>
</tr>
<tr>
<td>AN-CA Alliance</td>
<td>- Family Meal</td>
</tr>
<tr>
<td>Weight</td>
<td>- BMI</td>
</tr>
<tr>
<td>Clinical Effects</td>
<td></td>
</tr>
<tr>
<td>AN Symptoms</td>
<td>- EDE</td>
</tr>
<tr>
<td>Possible Moderators</td>
<td></td>
</tr>
<tr>
<td>Family Function</td>
<td>- FAD</td>
</tr>
<tr>
<td></td>
<td>- Parents vs Anorexia (modified)</td>
</tr>
</tbody>
</table>
Neurobiology overview

Ventral-limbic/Dorsal-cognitive circuitry

Salience circuitry

Haber & Knutson, 2010

Medford & Critchley, 2010

Phillips 2003

Kurth et al 2010
Anxiety in AN

• AN experience elevated anxiety:
  – ↑ co-morbid anxiety disorders
  – ↑ intolerance of uncertainty
  – ↑ harm avoidance
  – ↑ pre-meal anxiety associated with decreased caloric intake
  – dietary restraint reduces anxiety
• Clinical expression: avoidance
• Anxiety associated with poorer outcome; treatments designed to reduce/manage anxiety may improve outcome.

Pharmacotherapy of AN: RCTs are few and inconclusive

• SSRI
  – No evidence effective when underweight\textsuperscript{1,2}
  – Fluoxetine may reduce relapse in restrictors, but not BP AN\textsuperscript{3,4}

• Atypicals
  – Open trials Olanzapine, aripiprazole, risperidone, quetiapine
  – Olanzapine:
    • 34 AN, increase weight gain, reduce obsessions\textsuperscript{5}
    • Effect on weight gain in outpatient setting; reduced OCD & depression\textsuperscript{6}

\textsuperscript{1}Attia, 1998, \textsuperscript{2}Ferguson, 1999 \textsuperscript{3}Kaye, 2001, \textsuperscript{4}Walsh, 2006; \textsuperscript{5}Bissada, 2008; \textsuperscript{6}Brewerton
Pharmacotherapy of BN: RCTs more promising

Double-Blind, Placebo-Controlled Trials of Antidepressants
% Reduction of Binges, Purges
22 reports, 1562 subjects
Pharmacotherapy of BN: RCTs more promising

- **SSRI (large scale trials)**
  - Fluoxetine 60mg reduced BP\(^1\)
  - Fluvoxamine not effective\(^2\)
  - Sertraline\(^3\)
    - 100 mg better than placebo in reducing BP

- **Bupropion\(^4\) (anti-depressant)**
  - Drug better than placebo in reducing BP
  - 4 of 69 patients had seizures (never replicated)
  - Contraindicated in BN

- **Ondansetron (anti-emetic, 5HT3 receptor effects)\(^5\)**
  - 4 week controlled trial, better than placebo in reducing BP

- **Topiramate (Anticonvulsant)**
  - 10 week studies\(^1-3\) doses 250 to 400 mg/day
  - Better than placebo in reducing BP but some weight loss
  - Long-term efficacy unknown

- **Lamotrigine (Anticonvulsant)**
  - Reduction in ED symptoms, improved mood, decreased impulsive drives in case study
Brain Imaging Response (fMRI) to Positive and Negative Feedback

• Participants guess whether the value of a hidden card is greater or less than ‘5’.
• Participants are given $5.00 at the start.
  – Correct guess: WIN $2.00
  – Incorrect guess: LOSE $1.00
  – No response: lose $0.50
Trait anxiety is associated with increased caudate response to wins and losses in restricting-type anorexia nervosa.

Figure 3. Correlation between trait anxiety and mean percentage signal change in the left caudate for losses and wins in healthy comparison women and women recovered from restricting-type anorexia nervosa.

Comparison women: losses, $r = -0.29$ (p = 0.340), wins, $r = -0.050$ (p = 0.078).

Recovered women: losses, $r = 0.74$ (p = 0.004), wins, $r = 0.68$ (p = 0.010).

Wagner 2007
12 month outcome comparing adolescent-focused individual therapy (AFT) vs family-based treatment

FBT superior to AFT for full remission
At 12 month follow-up

Lock et al 2010
Archival Report

Hunger Does Not Motivate Reward in Women Remitted from Anorexia Nervosa

Christina E. Wierenga, Amanda Bischoff-Grethe, A. James Melrose, Zoe Irvine, Laura Torres, Ursula F. Baill, Alan Simmons, Julie L. Fudge, Samuel M. McClure, Alice Ely, and Walter H. Kaye

Brains of Those With Anorexia React Differently to Hunger Signals

This is how anorexic women resist temptation to eat cake

Submitted by Mohit Jaiswal on Tue, 02/24/2015 - 08:10

Washington

Washington, March 24 • people suffering from anorexia (AN) are able to ignore the tempting allure of chocolate cake.

The research by Dr. Chri and colleagues sheds light on how hunger does not motivate reward in women recovering from anorexia.

"Hunger is a motivating drive and makes rewards more enticing," said Christina Wierenga, associate professor of psychiatry at University of California, San Diego.

"We have long been puzzled by the fact that individuals with anorexia nervosa (AN) can resist the appeal of food, even when hungry," Wierenga noted.

The researchers examined reward responsiveness in similar to metabolic state (hungry or satiated) in 23 women recovered from AN and 17 healthy women without eating disorder histories (e.g., the comparison group).

The healthy women, when in a state of hunger, showed increased activity in the part of the brains that motivate the seeking of reward, but the women recovered from AN did not.

Women who have recovered from anorexia nervosa showed similar patterns of changes in brain activity that may contribute to their capacity to maintain their abstinence from food.

First, hunger does not increase the engagement of reward and motivation circuits in the brain. This may protect people with anorexia from hunger-related urges.

Second, they showed increased activation of executive 'self-control' circuits in the brain, perhaps making them more effective in resisting temptations.

"This study supports the idea that anorexia nervosa is a neurobiologically-based disorder," Wierenga noted.

The researchers concluded that unlike others, hunger does not motivate anorexic women to eat.
Anticipatory anxiety & inhibitory control
AN have increased anticipatory and decreased receipt response to pain in the insula

FIGURE 1. Experimental pain anticipation paradigm. Subjects are presented with the blue cross and are cued to anticipate “high pain” (i.e., brief thermal heat temperature that produces high pain sensation) if the color of the cross changes to RED, “low pain” (i.e., brief thermal heat that produces low pain sensation) if the color of the cross changes to GREEN, or “unknown” (i.e., brief thermal heat of either high or low intensity) if the color of the cross changes to YELLOW (50% probability). Each temperature is delivered for 6 sec. [Color figure can be viewed in the online issue, which is available at wileyonlinelibrary.com.]

Strigo, 2013
Khalsa in press
Developmental pathophysiological model of BN

FIGURE 5 | Developmental pathophysiological model of BN. The dysregulation of frontostriatal circuits likely contributes to an impaired capacity for self-regulatory control that interacts with hunger to release eating behavior from regulatory control. Attempts to compensate for weight gain contribute to purging behaviors. Interactions with reward-based learning systems, including striatal and mesolimbic regions, may then allow the binge-eating and purging behaviors to solidify into “habit-like” behaviors, ultimately contributing to BN development.
Interoceptive awareness in AN

- Endorse poor interoceptive awareness on self-reports
- Have difficulty detecting heartbeat
- Clinical expression: alexithymic, difficulty learning from experience, prediction errors, anticipatory anxiety

Pollatos, 2008; Lilenfeld 2006
Eating Disorder Statistics: Public Health Crisis

- AN affects ~1% of women and BN affects ~1-3% of women
- Up to 24 million people in the U.S. suffer from an ED (AN, BN, BED)
- AN and BN have substantial and costly medical morbidity¹,²
- AN has the highest mortality rate of any psychiatric disorder³-⁵
  - For females 15-14 years old with AN, mortality rate is 12x higher than death rate of all causes of death.
  - 5.1 deaths per 1000 people with AN per year; 1.7 deaths per 1000 with BN
- Alcohol and other substance abuse disorders 4x more common in ED than in general population
- AN and BN have high rates of disability and tend to be a significant burden to carers, and healthcare funders²,⁶-⁹
- AN ranks among the ten leading causes of disability in young women¹⁰
- ED receives inadequate research funding (research dollars spent per affected ED individual was $0.93 (NIH, 2011) compared to $88/Alzheimer’s disease patient, $81/Schizophrenia patient, and $44/Autism patient

Pharmacotherapy of BN: Adverse Effects

- Tricyclics
  - Autonomic side effects
- MAOI’s
  - Indiscriminate binge eating
  - Drug abuse, diet pills, etc.
- Bupropion
  - seizures
- Lithium
  - fluid balance
<table>
<thead>
<tr>
<th></th>
<th>Outpatient</th>
<th>Higher Level</th>
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<tbody>
<tr>
<td>Weight</td>
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<td>&lt; 75%</td>
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<tr>
<td>Medical complications</td>
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<td>↓ HR, BP, K etc</td>
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<tr>
<td>Suicidal, comorbid psych disorders</td>
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<td>severe</td>
</tr>
<tr>
<td>Motivation, insight, cooperation</td>
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</tr>
<tr>
<td>Exercise, purge, etc</td>
<td>minimal</td>
<td>severe</td>
</tr>
<tr>
<td>Stress, family dynamics</td>
<td>minimal</td>
<td>severe</td>
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<tr>
<td>Local ED treatment resources</td>
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</table>
Treatment of ED

- **Course in adults with AN:**
  - ~10% recover in less than 5 years
  - ~50+% recover over 5 to 10 years
  - ~30% chronically ill
  - ~10%+ die

- **Course in adults with BN:**
  - symptom abstinence in only 30-50% of treatment completers (Mitchell 2007; Wilson 2007)

- **Course in adolescents more promising** (Lock 2015)

- **There is no proven treatment for AN or BN that reverses symptoms** (Hay 2012; Rigaud 2007; Bulik 2007; Watson 2012; Hay 2012; Watson 2012; Brown 2012; Galsworthy-Francis 2014; Touyz 2013; NICE 2004)

- **This is no FDA approved medication for AN or BN (and only one for BED)** (Attia 2005; Bulik 2007; Jimerson 1996)

- **Treatment failure is likely due to a poor understanding of the etiology of ED, hindering the ability of treatments to target mechanisms underlying disordered eating. Most treatments target symptoms without acknowledging the core neurobiology underlying symptoms.**
Family Based (Maudsley) Treatment for Adolescent AN

- Studies suggest that Family Based Treatment (FBT) which focuses on parental re-feeding is effective for adolescents
  - Russell et al (1987) – 90% improvement in subgroup of with short-duration AN
  - Le Grange et al (1992) – 70% improvement
  - Robin et al (1999) – 90% improvement with family treatment compared to 65% with individual therapy
  - Eisler et al (2000) – 65% improvement in cohort
  - Lock et al (2010) – FBT superior to individual therapy at 1 year follow-up
  - Agras et al (2014) – FBT and family systems therapy equivalent
The problem

- Several psychosocial and behavioral interventions have been investigated in adult AN, including cognitive-behavioral therapy (CBT), behavioral therapy (BT), interpersonal psychotherapy (IPT), specialist supportive clinical management (SSCM), family therapy, dialectical behavioral therapy (DBT), focal psychodynamic psychotherapy, cognitive remediation therapy (CRT), exposure response prevention (ERP), Maudsley Model for Treatment of Adults with AN (MANTRA), and nutritional/dietary treatment.

- No approach has demonstrated clear primacy, and treatment effects, when found, are generally small. (McIntosh, 2005 #3850; Carter, 2011 #5690; Ball, 2004 #4340; Channon, 1989 #4324; Watson, 2012 #5685; Dahlgren, 2013 #5700; Zuchova, 2013 #5701; Tchanturia, 2013 #5726)

- There are few empirical treatment studies of AN, (Touyz, 2013 #5702; Hay, 2012 #5703) and a PubMed search for “randomized controlled trial (RCT) + anorexia” conducted in April 2015 revealed less than 50 studies, many of which were in adolescents, and less than 40 studies for bulimia, versus 181 RCTs for schizophrenia and 410 RCTs for depression
  - Note: only 11 for heroin addiction; 8 for methamphetamine addiction; 3 for marijuana; 26 for substance use.

- Low treatment efficacy is likely because recruitment is difficult, drop-out rates are high, AN prevalence is low, ambivalence and reluctance to engage in treatment are common, and randomization of participants to wait-list or placebo control groups is ethically precluded by the severity of the physical and psychiatric aspects of the illness.
Psychosocial Treatment of AN: RCTs

**Pike (NY; 03), 33 adult AN**
- CBT vs nutritional counseling, OP, 1 year
- Drop out/relapse: CBT (22%) < nutrit coun (73%)
- Good outcome: CBT (44%) > nutrit coun (7%)

**Halmi (NY, CA, MN; 05), 122 adult AN**
- CBT vs fluoxetine vs combination, 1 year
- Dropout rate overall: 46%
- No difference between groups in survival in treatment

**McIntosh (New Zealand; 05), 56 adult AN**
- CBT vs IPT vs nonspecific clinical management, 20 weeks
- Dropout rate: 70% did not complete or made small/no gains
- Nonspecific better than CBT or IPT

**Gowers (England; 07), 167 adolescent AN**
- IP ED vs OP ED vs general adolescent services, 2 yr
- No differences between groups
- Full recovery in only 33% at 2 years
What does recovery look like?
Many psychosocial treatments of AN do not increase BMI to healthy range

<table>
<thead>
<tr>
<th>Treatment</th>
<th>Change in BMI</th>
<th>Post-Treatment BMI</th>
<th>Reference</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cognitive Remediation Therapy/Cognitive Remediation Emotion Skills Training (CRT/CREST)</td>
<td>1.3</td>
<td>16.1</td>
<td>(Davies, 2012)</td>
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<td>Cognitive Behavioral Therapy Extended (CBT-E)</td>
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<td>17.9</td>
<td>(Fairburn, 2013)</td>
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<tr>
<td></td>
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<td>16.9</td>
<td>(Byrne, 2011)</td>
</tr>
<tr>
<td></td>
<td>0.8</td>
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<td>(McIntosh, 2005)</td>
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<td>Cognitive Behavioral Therapy AN (CBT-AN)</td>
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<td>(Touyz, 2013)</td>
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<tr>
<td>Maudsley Model for Treatment of Adults with AN (MANTRA)</td>
<td>1.7</td>
<td>18.0</td>
<td>(Wade, 2011)</td>
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<td>Specialist Supportive Clinical Management (SCCM)</td>
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<td>16.8</td>
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<tr>
<td></td>
<td>1.5</td>
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<td>(McIntosh, 2005)</td>
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<tr>
<td>Interpersonal Psychotherapy (IPT)</td>
<td>0.8</td>
<td>18.1</td>
<td>(McIntosh, 2005)</td>
</tr>
</tbody>
</table>
Does treatment of eating disorders work?

- Course in adults with AN:
  - ~10% recover in less than 5 years
  - ~50+% recover over 5 to 10 years
  - ~30% chronically ill
  - ~10%+ die (from heart failure, organ failure, malnutrition, suicide)

- Course in adults with BN:
  - symptom abstinence in only 30-50% of treatment completers

- Course in adolescents more promising

- There is no proven treatment for AN or BN that reverses symptoms

- There is no FDA approved medication for AN or BN (and only one for BED)

- Only 1 in 10 women and men with ED receive treatment; only 35% of people that receive treatment for an ED get treatment at a specialized facility for ED

- Treatment failure is likely due to a poor understanding of the etiology of ED, hindering the ability of treatments to target mechanisms underlying disordered eating.

- Most treatments target symptoms without acknowledging the core neurobiology underlying symptoms.

Dopamine and reward

Delgado 2007

Fronto-Striatal circuitry

Human: fMRI study of striatum response to reward (win) vs punish (loss) of money (Positive > Negative)
Altered limbic and cognitive reward processing during delay discounting in AN

Wierenga 2015