IS ANOREXIA NERVOSA AN EATING DISORDER?
NEW INSIGHTS INTO PUZZLING SYMPTOMS

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MH046001, MH042984, MH066122; MH001894;
Price Foundation, Davis/Wismer Foundation; Peterson Foundation
Overview

- Puzzling AN symptoms
- Neurocircuitry of behavior
- Appetite regulation
- Reward and consequences
- Anxiety
- Energy metabolism
- Treatment implications
Mrs. Duke’s daughter, in the eighteenth year of her age, fell into a total suppression of her monthly courses from a multitude of cares and passions of her mind...from which time her appetite began to abate. She thus neglected herself for two full years. Never did I see one conversant with the living, so much wasted, yet there was no fever, no distemper of the lungs, or signs of preternatural expence of the nutritious juices. Only her appetite was diminished.
Anorexia Nervosa

- 95% female
- Onset teens (puberty)
- Homogenous presentation, course
- Body image distortion: fear of being fat
- Restricted eating
- Emaciation
- >10% mortality
- Subtypes
  - Pure restricting, Binge – purge
Overview

• Psychiatric disorders are syndromes
• How are behaviors coded in neuronal circuits?
• How can we use neurobiology to improve treatment?
Puzzling AN Symptoms

- Reduced food intake, weight loss
- Body image distortions
- Anxious, obsessive, perfectionistic temperament
  - Over concern with consequences
- Increased exercise
  - Stereotypic, fidgety, relentless
- Resistance to treatment
  - Ego syntonic symptoms
- Lack of response to normally rewarding stimuli

**HOW ARE THESE BEHAVIORS ENCODED IN NEURAL CIRCUITS?**
Anorexia Nervosa

- Many women diet in our culture
- Relatively few develop anorexia nervosa
- Are there susceptibility factors that make some women vulnerable to dieting, weight loss?
- Eating disorders are familial and highly heritability in Twin Studies (50 to 80%)
- Genetics contribute to temperament and personality traits which make people vulnerable to develop AN
Childhood Symptoms of Obsessive-Compulsive Personality Traits: Percentage of Individuals With Traits

# Anxiety Disorders (AD) Lifetime and Premorbid Rates

<table>
<thead>
<tr>
<th>Study</th>
<th>ED</th>
<th>n</th>
<th>Lifetime AD</th>
<th>AD before ED</th>
</tr>
</thead>
<tbody>
<tr>
<td>Deep 95</td>
<td>AN</td>
<td>24</td>
<td>68%</td>
<td>58%</td>
</tr>
<tr>
<td>Bulik 97</td>
<td>AN</td>
<td>68</td>
<td>60%</td>
<td>54%</td>
</tr>
<tr>
<td>Bulik 97</td>
<td>BN</td>
<td>116</td>
<td>57%</td>
<td>54%</td>
</tr>
<tr>
<td>Godart 00</td>
<td>AN</td>
<td>29</td>
<td>83%</td>
<td>62%</td>
</tr>
<tr>
<td>Godart 00</td>
<td>BN</td>
<td>34</td>
<td>71%</td>
<td>62%</td>
</tr>
<tr>
<td>Kaye 04</td>
<td>AN,BN</td>
<td>672</td>
<td>64%</td>
<td>61%</td>
</tr>
</tbody>
</table>

23% OCD
13% social phobia
Temperament, Personality, and Course of AN

Stice 2002
Anderluh 2003
Connan 2003
Lilenfeld 2006
Kaye, Fudge, Paulus 2009

Traits
Negative emotion
Perfectionism
Drive to thinness
Increased interoceptive awareness
Obsessive personality

Puberty
Brain development
Hormones
Stress
Cultural factors

Dieting
Weight loss

Denial, rigidity, anxiety, depression, obsessionality

Neurobiological changes

Chronic illness (30–50%) Recovery (50–70%)
Background

Neural Circuitry 101
Subjects Studied
Emotions guide behaviors needed for preservation
Maternal care, communication, play
Some ability to learn, reason, error correct
Cortical-Striatal Networks
Fundamental motifs of cerebral organization
Yin and Knowlton 2005

emotional significance
consequences
motor output
### Neural Systems for Emotional Perception

**Phillips, Drevets, Rauch, Lane Biological Psychiatry 2003**

<table>
<thead>
<tr>
<th>Ventral system</th>
<th>Dorsal system</th>
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<tr>
<td>Limbic</td>
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</tr>
<tr>
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<tr>
<td>OFC, amygdala, anterior ACC</td>
<td></td>
</tr>
<tr>
<td>Emotional significance of environmental stimuli, produce affective states</td>
<td>Effortful regulation of resulting affective states</td>
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<td>Reward, emotion</td>
<td>Plans, consequences, selective attention</td>
</tr>
<tr>
<td>Here and now</td>
<td>Future consequences</td>
</tr>
</tbody>
</table>
How can we avoid confounding effects of malnutrition?

- **Subjects**: Women recovered from “restricting-type” AN > 1 y

<table>
<thead>
<tr>
<th>Group</th>
<th>n</th>
<th>Age</th>
<th>BMI</th>
<th>Harm Avoidance</th>
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<tbody>
<tr>
<td>Rec AN</td>
<td>16</td>
<td>26 ± 5</td>
<td>21 ± 3</td>
<td>18 ± 7</td>
</tr>
<tr>
<td>CW</td>
<td>16</td>
<td>27 ± 6</td>
<td>23 ± 2</td>
<td>10 ± 6</td>
</tr>
</tbody>
</table>
Appetite and Weight Regulation
Short-Term Obesity Therapy Does Not Result in Long-term Weight Loss

Weight Loss in Anorexia Nervosa

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

Comparison of obesity and anorexia nervosa
We do not understand Eating Behaviors in AN

• Typical symptoms
  – Self-restriction to few hundred calories per day
  – Vegan – like; avoids fats, red meats, desserts
  – Unusual combinations of food
  – Obsessed with food, counts calories, cooks for others
  – Not sure if hungry, fear can’t stop eating
  – AN: Anxiety reducing character to dietary restraint
    (Strober, 1995; Vitousek, 1994; Kaye 2003)

• Cause?
  – Secondary to body image disturbances?
  – Secondary to obsessionality or anxiety?
  – Primary disturbance of appetite regulation?
Systems Determining Food and Weight Regulation

**CNS Factors**
- Limbic, cognitive circuits
- Hypothalamic-brain stem System

**Peripheral Factors**
- Blood-Brain Barrier
- Metabolic Signals
  - Adipose tissue
  - Pancreas
  - GI Tract

**Cognitive Control**

**Pleasure & Motivation**

**Energy Balance**

**Appetite & Food Intake**
Top Down Regulation of Feeding
Alterations of Central Limbic and Dorsal Cognitive Circuits
Persists After Recovery
Rolls 2005; Berthoud 2006

- Humans can override hypothalamic energy balance signals
  - Obese overeat despite sufficient energy stores
  - AN restrict eating although emaciated
- Hunger
  - Food becomes more pleasurable
  - Increased motivation to eat
- Satiety
  - ‘Habituate’ to same foods
- Food can be aversive
- REC AN fMRI and pictures of food (Uher 2003):
  Altered response in limbic circuits
Testing Top Down Influences Using A Taste of Sucrose

Kaye, Fudge, Paulus
Nat Rev Neurosci 2009

Wagner et al 2007

Ventral limbic ROI

Dorsal Cognitive ROI
Understanding Appetite
Incentive Motivational Drive to Seek and Consume Food


Energy balance, metabolism

Sensory, hedonic, motivation

Ability to favor alternatives to eating

Food consumption

Hypothalamus

Ventral limbic

Dorsal Cog/Assoc

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Evidence that Hunger, Satiety Associated With Ventral Limbic Function

Hunger Activates (↑) the Insula and OFC Regions When Compared to Satiety

<table>
<thead>
<tr>
<th>Author</th>
<th>Year</th>
<th>Image</th>
<th>Insula</th>
<th>OFC</th>
</tr>
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<tbody>
<tr>
<td>Small</td>
<td>2001</td>
<td>PET</td>
<td>↑</td>
<td>↑</td>
</tr>
<tr>
<td>Tataranni</td>
<td>1999</td>
<td>PET</td>
<td>↑</td>
<td>↑</td>
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<tr>
<td>Moris</td>
<td>2001</td>
<td>PET</td>
<td>↑</td>
<td>↑</td>
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<tr>
<td>Kringelbach</td>
<td>2003</td>
<td>fMRI</td>
<td>↑</td>
<td>↑</td>
</tr>
<tr>
<td>Uher</td>
<td>2006</td>
<td>fMRI</td>
<td>↑</td>
<td></td>
</tr>
</tbody>
</table>
Blood Oxygen Level Dependent signal

- ↑ neural activity → ↑ blood flow → ↑ oxyhemoglobin → ↑ T2* → ↑ MR signal

fMRI

Functional images

Time

Condition 1

Condition 2

Region of interest (ROI)

~ 5 min

Source: Jody Culham’s fMRI for Dummies web site
• 10% Sucrose solution
• Water (Non-caloric contrast condition)
• 20 stimuli total per block (10 Sucrose + 10 Splenda)
• 2 blocks, pseudorandomly ordered
• Voxel-wise whole-brain analysis (AFNI)
• Restricted to a priori regions of interest, drawn according to Talairach atlas, 3T GE scanner
• 3dTtest comparisons: Main effect, p<0.005, Group, p<0.05

1 mL/sec Sucrose or water delivered by fMRI-triggered pump
“Swish once and swallow”

- 20 stimuli total per block (10 Sucrose + 10 Splenda)
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Left Insula/OFC Response to Sucrose

Wagner 2008 Neuropsychopharm

$CW$ vs. $AN$ $p = .003$
Left ventral putamen
Response to Sucrose

*Wagner 2008 Neuropsychopharmac.  CW vs. AN p = .002*

Similar differences throughout dorsal and medial caudate
Diminished Anterior Insula (AI), Striatal Response in REC AN

Sensory-Hedonic-Motivational Pathway

• **AI decreased signal**
  – Primary (sensory) gustatory cortex (Rolls 2005)
  – Food blindness?

• **Striatum decreased signal**
  – Reduced reward, motivation to approach food

• **AI projections to ventral putamen** (Fudge et al, 2005)
  – Pathway mediates hedonic, aversive aspects of taste (Small 2003), particularly highly palatable, high energy foods. (Kelley et al, 2002)

• **Is there a reduced drive (sensory-interoceptive-hedonic-motivation) in response to hunger**
  – Does this contribute to pursuit of emaciation to the point of death?
Insula (and connected regions) Play a Role in Interoceptive Information – The Sense of the Physiological Condition of the Entire Body

Craig, 2002; Paulus and Stein 2006

• Self-awareness of body states: temperature, touch, muscular and visceral sensations, vasomotor flush, air hunger, hunger and satiety, etc.
• Signal – change in body state. Link between cognitive and affective processes and the current body state
• Is only taste involved, or is there an alteration of all interoceptive stimuli?
  – Role in distorted body image?
  – Lack of recognition of the symptoms of malnutrition?
  – Altered insight and motivation to change?
Understanding Appetite in AN
Incentive Motivational Drive to Seek and Consume Food


Energy balance, metabolism

Sensory, hedonic, motivation

Ability to favor alternatives to eating

Hypothalamus

Ventral limbic

Dorsal Cog/Assoc

Food consumption
Reward and Anorexia Nervosa
Which Would You Rather Have?

But what if the Consequence was:
How does the brain compute this balance?

Immediate gratification

Long term consequences
What is the balance in AN?

Immediate gratification

Long term consequences
Brain Dopamine (DA) Optimal Response to Stimuli
Schultz 1997; Horvitz 2000; Berridge 1996; Kelly 2004

- DA mediates learning and reinforcement mechanisms associated with positive rewards (food in hungry animal)
- Role not selective for food but rather for signaling salience of a variety of potential rewards, or cues that predict rewards
- DA encodes motivation and appropriate choices (goal directed)
- ? Contribute to altered reward, motivation, motor activity in AN (Barry & Klawans 1976)
Evidence for altered striatal Dopamine (DA) in AN

- Reduced DA in brain (metabolite homovanillic acid (HVA) in cerebrospinal fluid)
  - Ill AN (Kaye 1988)
  - REC AN (Kaye 1999)
- Altered DA gene for D2 receptor (Bergen 2005)
- REC AN Increased DA D2/D3 receptor binding (Frank 2005)
## Neural Systems for Emotional Perception

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Eating Disorders Research and Treatment

How to AN respond to reward? fMRI - guessing game task

• How do subjects respond to winning and losing
• 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
• 13 recovered restricting AN and 13 CW
Left Ventral Striatum
CW: wins vs losses p < .001
AN: wins vs losses p ns
Wagner in press, Am J Psych
Left Caudate (future consequences)
CW vs. REC RAN p < .0001
Wagner in press Am J Psych

![Graph showing % change from time 1 over time]

- CW Win
- CW Loss
- AN Win
- AN Loss
Relationship between trait anxiety and % fMRI signal change in dorsal striatum

Wagner 2007 Am J Psych

Recovered RAN .73, .004

Recovered RAN .56, .05

Anxiety (Speilberger Trait)

% fMRI signal change dorsal striatum (loss)

% fMRI signal change dorsal striatum (win)
Altered Response in AN to Positive and Negative Feedback

- **Ventral (reward/affect):** May alter ability to discriminate pleasurable and aversive stimuli
  - May alter learning from experience
  - May explain why it is difficult to use reward to motivate people who are underweight and malnourished
- **Dorsal (planning, consequence):** Increased response in circuit, which is associated with anxiety
  - Over concerns with future consequences
  - Over sensitivity to uncertainty
- **Similar findings in malnourished AN** (Zastrow AJP 2009)
Altered balance in AN?

Limbic
Immediate Gratification

Difficulty in distinguishing positive and negative aspects of stimuli
? Altered code, scale, response to reward?

Exec/Associative
Long term consequences

Overconcern with future consequences
Both positive and negative consequences associated with anxiety
Understanding Appetite in AN
Incentive Motivational Drive to Seek and Consume Food


- Energy balance, metabolism
- Sensory, hedonic, motivation
- Ability to favor alternatives to eating
- Food consumption

When malnourished

Hypothalamus
Ventral limbic
Dorsal Cog/Assoc
Eating, or anticipation of food, is associated with anxiety

Not just diminished motivation
Dorsal Striatum Dopamine D2/D3 receptor binding and harm avoidance

(Frank 2005, submitted)

Control Women

\[ r = -0.6 \ p = 0.03 \]

Recovered AN Women

\[ r = 0.5 \ p = 0.006 \]

Circles indicates REC RAN, triangles indicates REC BAN
Y-axis values reflect DA-D2/D3 binding potential (BP)
AMPHEMATINE INDUCED DA RELEASE
PET C11 raclopride

For CW, DA release in AVS associated with an increase in euphoria (similar to Drevets 2001)

For REC AN, DA release in caudate associated with an increase in anxiety

Paradoxical effect of palatable foods in AN: anxiety, not pleasure?
Increase in DA in AVS (nucleus accumbens) induced by food and by amphetamines in rodents  
Volkow and Wise 2005

- Palatable food induced DA release is aversive (anxiety), not pleasurable for AN?
- What type of anxiety?
  - Uncertainty, anticipation
Energy Metabolism in AN

Increased caloric needs to gain weight
% Average Body Weight and Calories/kg per Day

DATE

January February March April May June July August

% Average Body Weight
65 70 75 80 85 90 95

Calories/kg per day
20 30 40 50 60 70 80

% Average Body Weight

DATE

January February March April May June July August

Cal/kg/day

% Average Body Weight

Cal/kg/day
Comparison of Daily Caloric Requirements


Graph showing the comparison of daily caloric requirements in kcal/kg/day after treatment, long-term recovered, and CW.
<table>
<thead>
<tr>
<th></th>
<th>Patient A</th>
<th>Patient B</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ill</td>
<td>42±2</td>
<td>49±1</td>
</tr>
<tr>
<td>Recovered</td>
<td>34±3</td>
<td>35±3</td>
</tr>
<tr>
<td>Months recovered</td>
<td>15</td>
<td>19</td>
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</table>
Understanding Appetite in AN
Drive, Anxiety, and Caloric Needs
Confusing Signals (when underweight)

1. Energy balance, metabolism
2. Sensory, hedonic, motivation
3. Ability to favor alternatives to eating

- Hypothalamus
- Ventral limbic
- Dorsal Cog/Assoc

- + + - -
- +

- Anxiet (not pleasure)
- Exaggerated caloric needs

- When malnourished
Vulnerabilities
Positive Aspects

• Many traits are positive
  – Precise, attention to detail, achievement oriented
  – Advantage in engineering, medicine, academics, etc
  – Beneficial and protective for ancestors

• Perhaps illness caused by
  – Excessive load of traits (overwhelms compensatory mechanisms)
  – Puberty (hormones) or brain changes during development
  – Environment influences: stress, culture, dieting, independence, abundant palatable food choices
How Can Understanding of Neurobiology Improve Treatment?

- UCSD treatment “laboratory”
- Inherent temperament and personality
  - Predates AN
  - Persists after recovery
- Improved nutrition and weight gain can be live saving
  - Reduces, but does not reverse T and P
- Anxiety: Uncertainly, anticipation
  - IP/residential likely to exacerbate such anxiety
- Maudsley “first step” providing parents with tools needed to deal effectively with AN
  - Learn how to manage anxiety, obsessions, etc
UCSD AN Comprehensive Evaluation and Intensive Multi-Family Treatment

- **Problem**: Expert advice, intervention for AN difficult to find
- **Goal**: Family understanding and management of AN, reduce relapse
- **One week (Mon-Fri) La Jolla (San Diego) ED offices**
- **Families live at Marriott Residential**
  - Next door to ED office
- **$5000 per week rate per family**
Components UCSD MFT

• Maudsley with a multi-family twist
  – Based on Ivan Eisler latest “update” and training
  – Up to 5 families

• Other components
  – Comprehensive medical, psychological evaluation
  – Psychoeducation “facts” about AN, caloric needs
  – Expert medication evaluation
  – Consultation with home therapist/physician,

Follow up therapy after discharge

Contracting
Family Therapy for Adolescent AN
General principles
Ivan Eisler

- Challenging disabling family beliefs, perceptions and meanings (e.g. beliefs about guilt and blame)

- Blocking the central role of the symptom in the family organization

- Reinforcing of the family adaptation processes that enable developmentally appropriate family life-cycle changes
MFG treatment
Basic principles

• Creating solidarity
  – “We are all in the same boat together”

• Overcoming stigmatisation & social isolation
  – “We are not the only ones with these problems”

• Stimulating new perspectives and reflectivity
  – “I can see clearly those things in them but not, when it comes to us”

• Learning from each other
  – “I like the way others manage this”
MFG treatment
Basic principles

• Being mirrored in others
  – “We do this just like you“

• Positive use of group pressure:
  – “We can’t cop out“

• Mutual support and feedback
  – “Terrific how you do this – and how do you think we are doing?!“

• Discovering and building on competencies
  – “I can do more than I thought, I am not all helpless“
MFG treatment
Basic principles

• Intensifying interactions and experiences
  – “It’s like a hot house, things happen here“

• Practicing new behaviours in a safe space
  – “We can experiment here, even if things go wrong at times“

• Encouraging open communication
  – “I am willing to listen, even if what you tell me is painful”

• Raising hopes
  – “Light at the end of the tunnel – even for us“
**Follow up on first 19 patients**

14 AN, 2 AN-BN, 3 NOS

<table>
<thead>
<tr>
<th></th>
<th>Mean ± SD</th>
<th>Range</th>
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<tbody>
<tr>
<td>Age</td>
<td>14 ± 2</td>
<td>10 to 17</td>
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<tr>
<td>Admit BMI</td>
<td>17.0 ± 2.0</td>
<td>12.4 to 20.8</td>
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<tr>
<td>Days follow up</td>
<td>278 ± 194</td>
<td>58 to 451</td>
</tr>
<tr>
<td>BMI at follow up</td>
<td>20.0 ± 2.7</td>
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<tr>
<td>Post treatment hospitalization</td>
<td>1 of 19</td>
<td></td>
</tr>
</tbody>
</table>
UCSD Eating Disorders Program
Evidence-based, Best-practice Treatments
Development of Next Generation of Therapy

www.eatingdisorders.ucsd.edu

Carmen Fang
(858)5348019
carmen.fang@ucsd.edu

Or contact W Kaye
Imaging Research
Volunteer Opportunities

• NIMH funded studies of appetite, reward, etc using fMRI
• Women recovered from AN, BN
• Women ill with AN, BN
• Studies support travel to UCSD, housing, and participant payment
• (858) 534-8062 or edresearch@ucsd.edu.