Das Belohnungssystem bei Anorexia nervosa – ein Update zur Neurobiologie

Ursula Bailer

Medizinische Universität Wien
Universitätsklinik für Psychiatrie und Psychotherapie
Klinische Abteilung für Allgemeine Psychiatrie

University of California San Diego, Department of Psychiatry
Personality Traits in AN

- Anxiety ↑
- Harm avoidance ↑
- Perfectionism ↑
- Obsessionality ↑
- Behavioral inhibition
- Overconcern with consequences
- Fear of making mistakes
- Anhedonia
- Asceticism (self denial of food, as well as most comforts and pleasures in life)

Bulik et al., 2006 Arch Gen Psych
Elison & Fong 1998
Kaye et al., 2006 Ann Rev Eat Disord
Kaye et al., 2008 Physiol Behav
What is the balance in AN?

Immediate gratification

Long term gratification
• Ventral Circuit: here and now, immediate
  • OFC (orbital frontal), PreF (prefrontal), CG (anterior cingulate), amygdala, etc

• DA nuclei
  • VTA (ventral tegmental), SN (substantia nigra)
• Ventral Circuit: here and now, immediate
  • OFC (orbital frontal), PreF (prefrontal), CG (anterior cingulate), amygdala, etc

• DA nuclei
  • VTA (ventral tegmental), SN (substantia nigra)

Dorsal Circuit: planning and consequences, long-term
fMRI Study

How Do People with RAN Respond to Reward?

- ‘Guessing-game’ task to see how the brain responds to positive (WIN) and negative (LOSS) feedback
- Functional magnetic resonance brain imaging (fMRI) used to look at AVS and DCA
- Change in neuronal activity in response to a task thought to be reflected in change in blood flow.
- 13 recovered RAN vs 13 matched CW

The Guessing Game

• 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
• Outcomes are determined before each guess and are randomly distributed but equal count.
Left Ventral Striatum

CW: wins vs losses p < .001

AN: wins vs losses p ns

Wagner et al., Am J Psychiatry 2008
Left Caudate (future consequences)

CW vs. REC RAN p < .0001

% change from time 1

Time

Wagner et al., Am J Psychiatry 2008
Altered Response in AN to Positive and Negative Feedback

- RAN may have altered ability to discriminate pleasurable and aversive stimuli in Ventral (reward/affect) Circuit
  - May alter learning from experience
  - May explain why it is difficult to use reward to motivate people who are underweight and malnourished

- Increased response in Dorsal (planning, consequence) circuit – associated with anxiety, HA
  - Over concerns with future consequences
  - Over sensitivity to uncertainty
Neural Systems for Emotional Perception
Phillips et al., Biological Psychiatry 2003

<table>
<thead>
<tr>
<th>Ventral system</th>
<th>Dorsal system</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Limbic</strong></td>
<td><strong>Executive/Associative</strong></td>
</tr>
<tr>
<td>Emotional significance of environmental stimuli</td>
<td>Cognition integrated with emotion</td>
</tr>
<tr>
<td>Reward, affect</td>
<td>Plans, consequences, effortful function</td>
</tr>
<tr>
<td>Anterior ventral striatum</td>
<td>Dorsal striatum</td>
</tr>
<tr>
<td>Nucleus accumbens</td>
<td>caudate</td>
</tr>
<tr>
<td>Here and now</td>
<td>Future consequences</td>
</tr>
<tr>
<td><strong>AN do not distinguish emotional significance</strong></td>
<td><strong>AN ↑ neural activity</strong></td>
</tr>
</tbody>
</table>
What is the balance in AN?

LIMBIC
Immediate
Gratification

EXEC/
ASSOCIATIVE
Long term
consequences
PET Scan of Dopamine$_{D2/D3}$ Receptor Binding in Anteroventral Striatum

Harm Avoidance and Dopamine$_{D2/D3}$ Receptor Binding in the Dorsal Caudate in REC AN

Trait Anxiety and Mean % Signal Change in Healthy Controls and REC AN in the dorsal caudate

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\(^a\)

Women Recovered From Restricting-Type Anorexia Nervosa\(^b\)

\begin{align*}
\text{Percent of Signal Change} \\
\text{Trait Anxiety}
\end{align*}

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

\(^b\) Recovered women: losses, \(r=0.74\) (\(p=0.004\)), wins, \(r=0.68\) (\(p=0.010\)).
Do such correlations imply that PET Dopamine D2/D3 binding might be related to the BOLD response to monetary choice in the dorsal caudate of REC AN?

→ Insight from Multimodal Imaging
Correlation between %fMRI signal change and DA D2/D3 binding in the caudate

Bailer et al. 2017 Int J Eating Disorders
Conclusion

• REC AN with the most activity in the dorsal caudate, had the most elevated DA D2/D3 receptor binding, and the most anxiety.
• Increased middle caudate DA D2/D3 receptor binding was associated with enhanced cognitive response to feedback in REC AN, perhaps related to an anxious anticipation of consequences.
Discussion

• It is well known that AN have exaggerated inhibition and anxiety, and are insensitive to reward (Kaye, 2013).
• It may be that AN have an imbalance between ventral limbic and dorsal executive processes, with ventral limbic-striatal circuitry being inhibited by “hyperactive” inputs from dorsal executive processes.
• Dorsal caudate D2 receptor function plays a key role in risk avoidance and inhibition (Ghahremani, 2012) in healthy controls.
• Food-induced DA release in the dorsal caudate stimulates anxiety in AN (Bailer, 2012).
Increase in DA in “reward center” (antero-ventral striatum or nucleus accumbens) induced by food and by amphetamines in rodents. Volkow and Wise 2005.
Visual Analog Scale (VAS) self-report of anxiety (0 to 10) at baseline (0) before amphetamine administration, and then at 30 minutes after amphetamine

REC AN reported a significant increase in anxiety in response to amphetamine compared to controls

F(1,141)=6.51, p=0.01

Bailer et al., 2012
Relationships between change in $[^{11}\text{C}]$raclopride binding potential ($\Delta BP$) for CW in the VST and euphoria and between $\Delta BP$ for REC AN in the DCA

**Control women**

$$r = -.76; \ p = .03$$

**Recovered AN**

$$r = -.62; \ p = .05$$

*(Antero-) Ventral striatum (VST)*

Dorsal Caudate (DCA)

Bailer et al., 2012
Summary

• In response to amphetamine, REC AN were anxious not euphoric.

• In control women, the magnitude of DA release in the anterior ventral striatum was associated with euphoria (Laruelle et al., 1995; Martinez et al., 2003; Volkow et al., 1999; Drevets et al., 2001)

• REC AN did not have a hedonic response in the anterior ventral striatum. DA release in the dorsal caudate in REC AN was aversive (anxiety ↑↑).
Implications

- Identification of DA neural circuits that might explain the puzzling appetitive symptoms that are the core feature of this deadly illness.

- AN appear to have an imbalance between limbic and executive/associative circuits, which might explain why:
  - Eating makes individuals with AN anxious, whereas dietary restraint functions to reduce anxiety in AN.
  - AN resist eating and become emaciated, when most people struggle to lose a few pounds.

- Follow up imaging and genetic studies could be used to probe DA circuit dysfunction, as well as identify more specific targets for pharmacological interventions.