A Computational Approach to Understanding Motivational Symptoms in Depression

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Disclosures

• Consultant for Cambridge Cognition
• Consultant for Takeda
• Consultant for GE
Motivation is central to depression

- Anhedonia
  - Loss of interest or pleasure
  - Cardinal symptom of depression
- Fatigue
- Difficulty in decision-making
- “Interest-activity” cluster of symptoms predicts poor response to treatment
- Reports of lower effort exertion depression

**Review**

*Reward and Punishment Processing in Depression*

Neir Eshel and Jonathan P. Roiser

Motivation in the clinic

DSM-V

Major Depressive Disorder 296.xx (F32.x and F33.x)

A. Five (or more) of the following symptoms have been present during the same 2-week period and represent a change from previous functioning; at least one of the symptoms is either (1) depressed mood or (2) loss of interest or pleasure.

Note: Do not include symptoms that are clearly attributable to another medical condition.

1. Depressed mood most of the day, nearly every day, as indicated by either subjective report (e.g., feels sad, empty, hopeless) or observation made by others (e.g., appears tearful). (Note: In children and adolescents, can be irritable mood).

2. Markedly diminished interest or pleasure in all, or almost all, activities most of the day, nearly every day (as indicated by either subjective account or observation).

3. Significant weight loss when not dieting or weight gain (e.g., a change of more than 5% of body weight in a month), or decrease or increase in appetite nearly every day. (Note: In children, consider failure to make expected weight gain.)

HAM-D

7. WORK AND INTERESTS
0 = No difficulty
1 = Feelings of incapacity, listlessness, indecision and vacillation
2 = Loss of interest in hobbies, decreased social activities
3 = Productivity decreased
4 = Unable to work. Stopped working because of present illness only. (Abstinence from work after treatment or recovery may rate a lower score).

BDI

12.

0 I have not lost interest in other people.
1 I am less interested in other people than I used to be.
2 I have lost most of my interest in other people.
3 I have lost all of my interest in other people.

Snaith-Hamilton Pleasure Scale
Temporal Experience of Pleasure Scale
Chapman Physical Anhedonia Scale
Motivation in the lab

The willingness to engage in an effortful activity (cost) in order to attain an outcome (reward)

Depends on:
- Magnitude of the anticipated rewards
- Effort required (cost)
Motivation in the lab

The willingness to engage in an effortful activity (cost) in order to attain an outcome (reward) depends on:

- Magnitude of the anticipated rewards
- Effort required (cost)
The willingness to engage in an effortful activity (cost) in order to attain an outcome (reward) depends on:

- Magnitude of the anticipated rewards
- Effort required (cost)

Motivation in the lab

$10 for 20 push-ups (green check)

$10 for 1000 push-ups (red X)
The Apple Gathering Task

- Effort-based decision-making task

- 5 blocks, 16 trials (80 total)

- 4 reward levels
  - 3, 6, 9, 12 points

- 4 effort levels
  - 20%, 40%, 60%, 80% of maximum voluntary contraction (SVC: calibrated individually)

Decisions affected by reward and effort

- 102 healthy controls (12 excluded), N=90 analysed

- Probability of accepting an offer
  - Significant effect of effort
    \( F(1.813,161.34)=185.22, p<0.001 \)
  - Significant effect of reward
    \( F(1.812,161.23)=107.73, p<0.001 \)
  - Significant effort x reward interaction
    \( F(5.14,458.24)=20.08, p<0.001 \)
Theory-driven Computational Psychiatry

• Uses existing theory/knowledge to specify and test mathematically precise hypotheses

Model specification: Mathematical formulation about the processes generating the observed data (often not directly observable)

Model estimation: Adjustment of model parameters to best fit the data

Model parameters

Model structure

Model comparison: Trades explanatory power against complexity to identify the most parsimonious model

Model testing: how well Model recapitulates patterns in the data (surrogate data)

Model specification

\[ \text{eq.5} \quad (\theta_{\text{noise}} \ast \frac{1}{2}) + ((1 - \theta_{\text{noise}}) \ast \text{Bernoulli(eq.4)}) \]

\[ \text{eq.4} \quad \text{inv.logit}(\theta_{\text{bias}} + \text{eq.3}) \]

\[ \text{eq.3} \quad \text{(eq.1) + (eq.2)} \]

\[ \text{eq.2} \quad (\theta_R \ast \text{Reward}) \]

\[ \text{eq.1} \quad (\theta_E \ast \text{Effort}) + (\theta_{E2} \ast \text{Effort}^2) \]
Model specification

eq. 1 \quad (\theta_E \times \text{Effort}) + (\theta_{E^2} \times \text{Effort}^2)

-eq. 3 \quad \text{Subj. value Offer}

-eq. 4 \quad \text{Accept Probability}

-eq. 5 \quad \text{Observation}

Decision noise
Accept bias
Effort Sensitivity

(e.g. 12 points, 20% effort)

\(\theta_{\text{effort}} \times \text{effort}\)

\(\theta_{\text{effort}^2} \times \text{effort}^2\)
Model specification

Subjective reward

Subjective effort

Subjective offer

\[ \text{eq.3} = (\text{eq.1}) + (\text{eq.2}) \]
Model specification

- Decision noise
- Accept bias
- Effort Sensitivity
- Reward Sensitivity

Observation
(eq. 5)

Accept Probability
(eq. 4)

Subjective Value Offer
(eq. 3)

Effort
(eq. 1)

Reward
(eq. 2)

Offer
(e.g. 12 points, 20% effort)

\[
\text{eq. 4 } \quad \text{inv.logit}(\theta_{bias} + \text{eq. 3})
\]

Probability of accepting subjective Offer

Effort level

lower $\theta_{bias}$

higher $\theta_{bias}$
Model specification

Decision noise

Accept bias

Effort Sensitivity

Reward Sensitivity

Observation (eq. 5)

Accept Probability (eq. 4)

Subject value Offer (eq. 3)

Offer (e.g. 12 points, 20% effort)

\[
eq 1 \quad (\theta_E \ast \text{Effort}) + (\theta_{E2} \ast \text{Effort}^2)
\]

\[
eq 2 \quad (\theta_R \ast \text{Reward})
\]

\[
eq 3 \quad (\text{eq.1}) + (\text{eq.2})
\]

\[
eq 4 \quad \text{inv.logit}(\theta_{bias} + \text{eq.3})
\]

\[
eq 5 \quad (\theta_{noise} \ast \frac{1}{2}) + ((1 - \theta_{noise}) \ast \text{Bernoulli(eq.4)})
\]
Model estimation

Maximum likelihood works well for non-extreme (balanced) datasets
Parameter estimation is quick
Model estimation

Maximum likelihood works poorly for unbalanced datasets
Hierarchical parameter estimation using sampling (Stan: http://mc-stan.org)
Model estimation
Hierarchical parameter estimation improves estimation accuracy

Population level parameters

Subject specific parameters

- Decision noise
- Accept bias
- Effort Sensitivity
- Reward Sensitivity

\[ a \sim \beta(a, b) \]

\[ \sim \mathcal{N}(\mu, \sigma) \]

\[ \sim \mathcal{N}(\mu, \sigma) \]

\[ \sim \mathcal{N}(\mu, \sigma) \]
Model comparison
Model checking

Simulated behaviour from winning model over all subjects

Data

Model
Model checking

Parameter recovery and identifiability
### Sub-clinical depressive symptoms

Questionnaires submitted to factor analysis

- (F1) Low mood / anxiety
- (F2) Apathy
- (F3) Anhedonia
- (F4) Dysfunctional attitudes

<table>
<thead>
<tr>
<th>Questionnaire/Antidote</th>
<th>Factor 1</th>
<th>Factor 2</th>
<th>Factor 3</th>
<th>Factor 4</th>
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<tr>
<td>Neg. Urg.</td>
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<tr>
<td>Lack of Persev.</td>
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<td>0.6240</td>
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**BDI** = Beck Depression Inventory  
**AES** = Apathy Evaluation Scale  
**CPAS** = Chapman Physical Anhedonia Scale  
**DAS** = Dysfunctional Attitudes Scale  
**LOTR** = Life Orientation Test  
**SHAPS** = Snaith-Hamilton Pleasure Scale  
**STAI** = State/Trait Anxiety Inventory  
**TEPS** = Temporal Experience of Pleasure Scale  
**UPPS** = Urgency, Premeditation, Perseverance, Sensation seeking, and Positive urgency
Factor correlations

(F1) Low mood / anxiety
(F2) Apathy
(F3) Anhedonia
(F4) Dysfunctional attitudes

Factor correlations matrix:

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<tr>
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<td>0.6240</td>
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</table>

Graphs showing correlation between reward sensitivity and mood/anxiety factors.
Clinical study

- Case-control design

- Two sessions:
  - Session 1: MINI, Ham-D, FIGS, questionnaires
    - Healthy controls (CTR): No history of MH disorder, or 1st degree relatives
    - At Risk (RSK): No history of MH disorder, 1st degree relatives had/have MDD
    - Depressed (MDD): Currently depressed, Ham-D > 7, not currently taking psychotropic medication (past 4-8 weeks)
    - Remitted (REM): Past depressive episode(s), Ham-D currently <= 7, >6 months since last episode
  - Session 2: Testing (Apple Gathering Task + others)
### Demographic characteristics

<table>
<thead>
<tr>
<th></th>
<th>CTR (n=42)</th>
<th>RSK (n=30)</th>
<th>REM (n=42)</th>
<th>MDD (n=53)</th>
<th>Statistics</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Age</strong></td>
<td>29 (8.9)</td>
<td>26 (8.9)</td>
<td>28 (8.4)</td>
<td>28 (10.9)</td>
<td><strong>F(3,162)=.55, p&gt;.05</strong></td>
</tr>
<tr>
<td><strong>Gender (m/f)</strong></td>
<td>15/27</td>
<td>9/21</td>
<td>18/24</td>
<td>15/38</td>
<td><strong>X²(3,167)=2.5, p&gt;.05</strong></td>
</tr>
<tr>
<td><strong>IQ (WTAR)</strong></td>
<td>112 (6.9)</td>
<td>112 (7.9)</td>
<td>115 (6.9)</td>
<td>114 (9.8)</td>
<td><strong>F(3,160)=2.05, p&gt;.05</strong></td>
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<tr>
<td><strong>Ham-D</strong></td>
<td>0.6 (1.08)</td>
<td>0.9 (1.23)</td>
<td>1.31 (1.88)</td>
<td>16.56 (5.4)</td>
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<tr>
<td><strong>BDI</strong></td>
<td>2.14 (2.86)</td>
<td>2.33 (2.85)</td>
<td>4.47 (4.12)</td>
<td>28.5 (7.8)</td>
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<tr>
<td><strong>STAI trait</strong></td>
<td>26.9 (4.37)</td>
<td>29.9 (8.47)</td>
<td>32 (9.05)</td>
<td>55.7 (11)</td>
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<tr>
<td><strong>SHAPS</strong></td>
<td>0.73 (1.63)</td>
<td>0.66 (1.21)</td>
<td>0.97 (1.21)</td>
<td>7.92 (3.3)</td>
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<tr>
<td><strong>TEPS ant.</strong></td>
<td>45.4 (6.6)</td>
<td>46.9 (7.76)</td>
<td>43.8 (7.21)</td>
<td>30.5 (8.89)</td>
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<tr>
<td><strong>TEPS con.</strong></td>
<td>35.5 (5.4)</td>
<td>38 (6)</td>
<td>35.1 (6.22)</td>
<td>26.2 (7.22)</td>
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</tbody>
</table>
167 participants tested, 145 analysed

Excluded 22

N=20 calibration, N=2 missing data

25% of depressed sample excluded!

Significant effect of effort
\[ F(1.742,245.625)=292.017, p<0.001 \]

Significant effect of reward
\[ F(1.682,237.195)=233.266, p<0.001 \]

Significant effort x reward interaction
\[ F(4.959,699.263)=69.58, p<0.001 \]

Significant reward x group interaction
\[ F(5.047,237.195)=3.051, p<0.05 \]

Significant effect of group
\[ F(3,141)=4.96, p<0.005 \]
Behavioural results (groups)

CTR

RSK

MDD

REM
Symptom clustering

Factors:

- Low mood / anxiety
- Apathy
- Anhedonia
- Dysfunctional attitudes
Model comparison

Model 6: Bias + LinR + LinE

Model 9: Bias + LinR + LinE + E^2

Model 51: Bias + LinR + LinE + Guess

Model 54: Bias + LinR + LinE + E^2 + Guess
Parameter estimates

- **Bias**
  - CTR/RSK
  - >REM

- **Reward**

- **Effort**

- **Effort^2**
Parameter clustering

Parameters:

- Bias
- Reward
- Effort
- Effort^2
**MDD correlations**

(F1) Low mood / anxiety
(F2) Apathy
(F3) Anhedonia
(F4) Dysfunctional attitudes

<table>
<thead>
<tr>
<th>Factor</th>
<th>Factor 1</th>
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<td>HamD</td>
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Conclusions

- Computational approach provides a powerful means of dissecting reward-related behaviour

- Anhedonia is related to effort discounting, rather than reward sensitivity
  - Consistent in both clinical and non-clinical samples
  - Reward sensitivity associations inconsistent

- Patterns vary greatly within groups – is there a specific sub-group of depressed patients who show pronounced effort discounting?

- Unclear whether this is a state or trait feature of decision making in those who exhibit high effort discounting
Acknowledgments

External collaborators

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Barbara Sahakian
Ben Seymour
Carlos Zarate

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Karl Friston
Eileen Joyce
Glyn Lewis
Steve Pilling
Oliver Robinson
Nick Wood

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Caroline Charpentier
Danai Dima
Neir Eshel
Paul Faulkner
Alan Gray
Chamith Halahakoon
Rebecca Lawson
Níall Lally
Eleanor Loh
Anahit Mkrtchian
Camilla Nord
Madeline Payne
Ioannis Sarigiannidis
Vincent Valton
Acceptance rate vs. success rate: pilot study
Acceptance rate vs. success rate: clinical study