Neural circuitry of motivational decision making in animal models: Implications for Drug Discovery.

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Effort-related Motivational Symptoms in Psychiatry

- Motivational symptoms such as fatigue, anergia and apathy are probably the most common psychiatric symptoms seen in general medicine (Demyttenaere et al. 2005).

- These symptoms are seen in schizophrenics with negative symptoms, people with depression, multiple sclerosis, chronic fatigue syndrome, Parkinson’s Disease, and inflammatory conditions associated with pro-inflammatory cytokines (Tylee et al. 1999; Stahl 2002; Demyttenaere et al. 2005; Danzer 2012).
Effort-related Motivational Symptoms in Psychiatry

• Motivational symptoms are highly resistant to treatment. SERT inhibitors such as fluoxetine and citalopram do not typically treat these motivational symptoms effectively, and in fact, can induce or exacerbate these symptoms (Padala et al. 2012; Stenman and Lilja 2013; Fava et al. 2013).

• Thus far, the more effective treatments for motivational symptoms of depression and other disorders seem to be catecholamine uptake inhibitors such as bupropion, or stimulants such as methylphenidate (Rampello et al. 1991; Dalery et al. 1997; Stahl 2002; Demyttenaere et al. 2005; Pae et al. 2007; Dunlop et al. 2007; Fava et al. 2007, 2012).
DA & Effort-Related Decision Making in Animal Models


- Animals given choice between high effort/high reward option vs. low effort/low reward option

- Interference with accumbens DA transmission shifts choice behavior, decreasing selection of the high effort/high reward option.

Forebrain Circuits: Effort-Related Decision Making in Animal Models

- Various drug and lesion manipulations can reduce selection of the high effort alternative; rats remain directed towards the acquisition and consumption of food, but they exert less effort and select lower cost alternatives in choice tasks.

  i.e., anergia, fatigue, psychomotor retardation

- Considerable evidence indicates that a distributed forebrain circuit that includes prefrontal/anterior cingulate cortex, nucleus accumbens, mesolimbic dopamine, basolateral amygdala, and ventral pallidum, mediates effort-related decision making (Salamone and Correa 2012).

Lesions or inactivation here alter effort-related decision making.

DAT Knockdown increases exertion of effort.

Adenosine $A_{2A}$ receptor antagonism reverses effects of DA antagonists.

Interference with DA transmission here alters effort-related decision making.

Schweimer and Hauber 2005
Floresco and Ghods-Sharifi 2007
Cagniard et al. 2006
Farrar et al. 2008

GABA $\alpha$ receptor stimulation in VP alters effort-related choice.
Effort-related Decision Making in Humans: Significance for Psychiatry

• Treadway et al. (2009) developed EEfRT task-a measure of effort-related decision making in humans based upon our animal tests.

• Schizophrenic patients with negative symptoms were less willing to expend effort for rewards than controls (Gold et al. 2013).

• Depressed patients were less willing to expend effort for rewards than controls (Treadway et al. 2012).
Current Goal: Develop Animal Models of Anergia/Fatigue Symptoms in Psychiatry

It has been suggested that tests of effort-related decision making can be useful as animal models of motivational symptoms in psychiatry (Salamone et al. 2006, 2007; Salamone and Correa 2012; Nunes et al. 2013a).

Conditions being investigated:

- muscarinic receptor stimulation (Nunes et al. 2013a)
- selectively bred rat lines
- stress
- proinflammatory cytokines (Nunes et al. 2014)
- Tetrabenazine (DA depleting agent)
Tetrabenazine (TBZ) in humans

- TBZ is commonly used to treat Huntington’s disease, with common side effects that include fatigue, anergia, and depression (Astin and Gumpert 1974; Kingston 1979; Jankovic and Beach 1997; Kenney et al. 2007; Frank 2009).

- TBZ has been used in rodent models of depression (Preskorn et al. 1984; Kent et al. 1986; Wang et al. 2010)

- TBZ reversibly and selectively inhibits the vesicular monoamine transporter-2 (VMAT-2), blocking vesicular storage and depleting catecholamines, especially DA (Meyer et al. 2011; Owesson-White et al. 2012; Guay 2010; Henry and Scherman, 1989)
Recent Studies: TBZ and Effort-related Choice Behavior

• What are the neurochemical effects of TBZ on nucleus accumbens DA?

• What are the effects of TBZ on effort-related decision making?

• Are these effects reversible with co-administration of drugs?
TBZ Decreases Extracellular DA in Nucleus Accumbens

Nunes et al. 2013
Palatable food / FR 5
Lab chow / Free access

CONTROL RAT

DA DEPLETED OR DA ANTAGONIST

To press or not to press… THAT is the question.
Concurrent FR5/chow feeding task: TBZ Reduces FR5 Lever Pressing and Increases Chow Intake

Nunes et al. 2013
In Feeding Tests TBZ Does not Reduce Consumption of Pellets or Chow & does not affect Preference

Nunes et al. 2013
In Sucrose Feeding Tests TBZ Does not Reduce Markers of Sucrose “Liking”

*Correa et al. in prep.*
Concurrent FR5/chow feeding task: Intra-accumbens TBZ Reduces FR5 Lever Pressing and Increases Chow Intake

Nunes et al. 2013
Eventually, the rats stop lever pressing and switch to chow intake.

Citius, Altius, Fortius... Why bother?
Concurrent Progressive Ratio/Chow Feeding
Task: Systemic Injection of TBZ

Dose Tetrabenazine (mg/kg IP)

Lever Presses (30 min)

Active Lever Time (sec)

Highest Ratio Achieved

Chow Consumption (g)
Hmmm… DO I CLIMB THE BARRIER TO GET 4 PELLETS… OR DO I ‘WIMP OUT’ AND WALK OVER THERE TO GET 2 PELLETS???
T maze: TBZ Decreases Selection of high effort/high Reinforcement Arm

Yohn et al. IN PREP

<table>
<thead>
<tr>
<th>Dose Tetrabenazine (mg/kg)</th>
<th>No Barrier</th>
<th>4-0 Barrier</th>
<th>4-2 Barrier</th>
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<tbody>
<tr>
<td>VEH</td>
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<td>0.25</td>
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<td>0.75</td>
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</table>
TBZ: Choice between Running Wheel or Sucrose

Time in RW (seconds)

- TBZ Dose (mg/kg)

Time Drinking Sucrose (seconds)

- TBZ Dose (mg/kg)

* * *

Cruz et al. IN PREP
Drug Reversal Studies

- MAO-B inhibitor deprenyl
- Naturally occurring nutritional supplement curcumin
- Adenosine A2A antagonist MSX-3
- Well known antidepressant bupropion (Wellbutrin); catecholamine uptake inhibitor
Concurrent FR5/chow feeding task: The Catecholamine Uptake Inhibitor Bupropion Reverses Effects of TBZ

Nunes et al. 2013
Concurrent FR5/chow feeding task: Adenosine A\textsubscript{2A} Antagonist MSX-3 Reverses Effects of TBZ

Nunes et al. in prep
PROG: Effect of TBZ is Reversed by Bupropion
MSX-3 Reverses the effects of TBZ on the PROG/Choice

**Lever Presses (30 min)**

- **TBZ**:
  - 0.75
  - 0.75
  - 0.75
  - 0.75
  - 0.75
- **MSX**:
  - 3
  - 0.5
  - 1.0
  - 2.0

**Chow Consumption (g)**

- **TBZ**:
  - 0.75
  - 0.75
  - 0.75
  - 0.75
  - 0.75
- **MSX**:
  - 3
  - 0.5
  - 1.0
  - 2.0

**Highest Ratio Achieved**

- **TBZ**:
  - 0.75
  - 0.75
  - 0.75
  - 0.75
  - 0.75
- **MSX**:
  - 3
  - 0.5
  - 1.0
  - 2.0

**Active Lever Time (s)**

- **TBZ**:
  - 0.75
  - 0.75
  - 0.75
  - 0.75
  - 0.75
- **MSX**:
  - 3
  - 0.5
  - 1.0
  - 2.0
T maze: Effect of TBZ is Reversed by Bupropion

![Graph showing the effect of TBZ on barrier crossings reversed by Bupropion.](image-url)

Dose Bupropion (mg/kg)

- veh/veh
- tbz/veh
- tbz/5
- tbz/10
- tbz/15

Barrier Crossings
T maze: Effect of TBZ is Reversed by Adenosine A_2A Antagonist MSX-3

Yohn et al. IN PREP
EFFORT-RELATED DECISION MAKING: THE IMPORTANCE OF INDIVIDUAL DIFFERENCES

• PROG/chow feeding task leads to tremendous individual differences in performance.

• Individual differences are related to DA signaling.

• Individual differences are related to drug responsiveness.

Randall et al. 2012; Randall et al. in preparation
Much Individual Variability

Workers vs. Slackers

PROG LEVER PRESS ---> BIOSERVE PELLETS

(preferred)

Workers: Mean Lever Pressing = 812.4
(range 205-2852 )

Slackers: Mean Lever Pressing = 116.3
(range 54-190)

Randall et al. 2012
DARRP-32 Expression in High Responders vs. Low Responders: High Responders (Workers) have higher DARPP-32 (Thr 34) Expression in Accumbens Core
Bupropion Enhances PROG/Choice Lever Pressing Output: Greater Effect in Low Performers (slackers)

*p < 0.05, high vs. low performers; treatment x work group interaction p < 0.05

Randall et al. in prep.
Summary

• The VMAT-2 inhibitor TBZ produces effort-related impairments on the T-maze tasks, PROG/chow, and FR5/chow procedures.

• These effects of TBZ are not related to changes in appetite, food preference, or discrimination of reward magnitude.

• TBZ produces behavioral effects similar to accumbens DA depletion and DA antagonism.
Summary & Conclusions

• The effects of TBZ are reversible with co-administration of the adenosine A$_{2A}$ antagonist MSX-3, the MAO-B inhibitor deprenyl, the naturally occurring nutritional supplement curcumin, and the catecholamine uptake inhibitor bupropion.

• Individual differences in effort exertion are related to DA signaling, and drug responsiveness.

• These studies indicate that tests of effort-related decision making can be used to assess novel compounds for their potential utility in treating psychiatric symptoms.
Summary & Conclusions

• Studies of effort-related decision making are translatable from rodents to humans.

• This line of research is consistent with the NIMH RDoC (Research Domain Criteria) approach for modeling symptoms and circuits related to psychopathology.
Significance for Clinical Trials

• How would you measure an effort-related motivational effect in a human clinical trial?

• Would you use the MADRS?

• Cusin et al. (2009) "Because this scale was never updated or modified, it does not target reversal of neurovegetative symptoms."
THANK YOU!