Negative symptoms: Clinical assessments, biomarkers and the role of reward processing

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Negative Symptoms as central features of SZ

• Kraepelin: “On the one hand, we observe a weakening of those emotional activities which permanently form the mainsprings of volition… The result is emotional dullness, .. Loss of mastery over volition, of endeavor, and ability for independent action. The essence of the personality is thereby destroyed”

Bleuler “ The patients appear lazy and negligent because they no longer have the urge to do anything either of their own initiative or at the bidding of another…. In mild cases, where wishes and desires still exist, they will nevertheless do nothing toward the realization of these wishes”

• Observations made long before introduction of APDs
Progress in understanding origins of negative symptoms has implications for assessment and for developing new targets/treatments
Anhedonia, Avolition, Reward Anticipation and Consumption.

• We generate action on basis of representations of expected reward, not reward experience.

• Laboratory research shows that PSZ have intact “in the moment” consummatory pleasure. They are NOT anhedonic in the sense that the term is used clinically.

• PSZ do not appear to want what they like.
Neural systems involved in goal-directed behavior.

- Appears to be largely normal
- Abnormal
- Maybe normal in PSZ
- Abnormal
- EMA, Rating scales

Many paths to similar behavioral deficit within/across S’s and disorders.

Components of Reward to Outcome Translation
Note: After Wallis (2007), From D. Barch
Overview

1: Clinical Assessment Tools

2: Behavioral Biomarkers

3: Neuroimaging tools.
• NIMH MATRICS Conference on Negative Symptoms (2005):
  – Concluded that there is evidence for 5 domains (blunted affect, alogia, asociality, anhedonia, and avolition) which may have different neurobiological substrates and serve as treatment targets
  – Development of new instruments was needed that assesses these domains, and which explicitly assess role of anticipatory and consummatory pleasure.

• 2 Instruments were developed in response to the MATRICS meeting-
  – Brief Negative Symptom Scale (BNSS) (Kirkpatrick et al., 2010)
  – Clinical Assessment Interview for Negative Symptoms (CAINS) (Forbes et al., 2010)
Both Scales show:

- Good test-retest reliability
- Good Inter-rater reliability
- Similar 2 factor structure: 1) Expressiveness (voice, gesture, face) 2) Motivation and Pleasure (anhedonia, avolition, asociality)
- Similar, high correlations with existing Neg Symptom scales

BNSS: Kirkpatrick 2011 SZ Bull, Strauss 2012a,b SZ Res, Strauss 2016 SZ Bull
Both scales show good convergent and divergent validity

### Table 4. Convergent Validity

<table>
<thead>
<tr>
<th></th>
<th>BNSS Total</th>
<th>BNSS EXP</th>
<th>BNSS MAP</th>
<th>CAINS Total</th>
<th>CAINS EXP</th>
<th>CAINS MAP</th>
</tr>
</thead>
<tbody>
<tr>
<td>SANS Total</td>
<td>0.88***</td>
<td>0.82***</td>
<td>0.81***</td>
<td>0.79***</td>
<td>0.77***</td>
<td>0.70***</td>
</tr>
<tr>
<td>SANS EXP</td>
<td>0.89***</td>
<td>0.94***</td>
<td>0.71***</td>
<td>0.70***</td>
<td>0.77***</td>
<td>0.56***</td>
</tr>
<tr>
<td>SANS MAP</td>
<td>0.72***</td>
<td>0.56***</td>
<td>0.76***</td>
<td>0.73***</td>
<td>0.63***</td>
<td>0.70***</td>
</tr>
<tr>
<td>BPRS Negative</td>
<td>0.82***</td>
<td>0.85***</td>
<td>0.66***</td>
<td>0.63***</td>
<td>0.67***</td>
<td>0.52***</td>
</tr>
<tr>
<td>LOF Total</td>
<td>-0.68***</td>
<td>-0.56***</td>
<td>-0.72***</td>
<td>-0.67***</td>
<td>-0.59***</td>
<td>-0.63***</td>
</tr>
<tr>
<td>LOF Social</td>
<td>-0.65***</td>
<td>-0.56***</td>
<td>-0.67***</td>
<td>-0.66***</td>
<td>-0.59***</td>
<td>-0.62***</td>
</tr>
<tr>
<td>LOF Work</td>
<td>-0.47***</td>
<td>-0.37**</td>
<td>-0.52***</td>
<td>-0.46***</td>
<td>-0.37**</td>
<td>-0.46***</td>
</tr>
<tr>
<td>MCCB Total</td>
<td>-0.29*</td>
<td>-0.39**</td>
<td>-0.15</td>
<td>-0.11</td>
<td>-0.20</td>
<td>-0.03</td>
</tr>
<tr>
<td>DPB</td>
<td>0.38**</td>
<td>0.38**</td>
<td>0.35**</td>
<td>0.32*</td>
<td>0.35**</td>
<td>0.26*</td>
</tr>
<tr>
<td>Chapman PA</td>
<td>0.19</td>
<td>0.16</td>
<td>0.21</td>
<td>0.11</td>
<td>0.13</td>
<td>0.08</td>
</tr>
<tr>
<td>Chapman SA</td>
<td>0.32*</td>
<td>0.25</td>
<td>0.35**</td>
<td>0.20</td>
<td>0.21</td>
<td>0.16</td>
</tr>
</tbody>
</table>

*Note*: EXP, emotional expressivity; LOF, Level of Function Scale; SANS, Scale for the Assessment of Negative Symptoms; MCCB, MATRICS Consensus Cognitive Battery; DPB, defeatist performance Beliefs Scale; Chapman PA, Chapman Scale Physical Anhedonia; Chapman SA, Chapman Scale Social Anhedonia. MCCB, n = 62; DPB, n = 60; Chapman PA and SA, n = 57. *P < .05, **P < .01, ***P < .001.

### Table 5. Discriminant Validity

<table>
<thead>
<tr>
<th></th>
<th>BNSS Total</th>
<th>BNSS EXP</th>
<th>BNSS MAP</th>
<th>CAINS Total</th>
<th>CAINS EXP</th>
<th>CAINS MAP</th>
</tr>
</thead>
<tbody>
<tr>
<td>BPRS Positive</td>
<td>0.15</td>
<td>0.05</td>
<td>0.25*</td>
<td>0.21</td>
<td>0.13</td>
<td>0.23</td>
</tr>
<tr>
<td>BPRS Disorganization</td>
<td>0.35*</td>
<td>0.18</td>
<td>0.42***</td>
<td>0.43***</td>
<td>0.32**</td>
<td>0.44***</td>
</tr>
<tr>
<td>BPRS Depression</td>
<td>-0.10</td>
<td>-0.10</td>
<td>-0.03</td>
<td>-0.02</td>
<td>-0.10</td>
<td>0.04</td>
</tr>
<tr>
<td>BPRS Total</td>
<td>0.59***</td>
<td>0.51***</td>
<td>0.62***</td>
<td>0.55***</td>
<td>0.47***</td>
<td>0.53***</td>
</tr>
</tbody>
</table>

*Note*: *P < .05, **P < .01, ***P < .001.
Both scales represent advances in assessment

• Both are based on a more explicit conceptualization of avolition implicating anticipatory as well as consummatory processes.

• Both are based on factor analytic models of structure of negative symptoms.

• Both have good psychometrics.

• No evidence to date that the new scales show an enhanced sensitivity to treatment effects because this has not been possible to test.
And both suffer from validity challenges.

- The limitations of self-report: Memory failures, memory biases which are known to be problematic in SZ. (See Strauss and Gold AJP 2012)

- Can PSZ introspect carefully enough to distinguish anticipatory from consummatory pleasure?

- Rater differences
Alternative Approaches:

Ecological Momentary Assessment
Why EMA?

- Ecological validity
  - Measure in lab based on report of past week vs. Repeated sampling of daily life

- Study phenomena in real-time, 5-10 x a day, for a week using phones or other devices.

- Facilitates detailed quantification of target behaviors of interest. Where are you, Who are you with, What are you doing, How are you feeling?
EMA Questionnaire

What are you doing at this moment?

- Inactive (TV, music, resting)
- Eating, dressing, hygiene care
- Shopping, chores, cooking
- Work, school or active leisure
- Other

Since the last questionnaire, about how many times did you talk or communicate with someone else?

- 0 (you had no interactions)
- 1 interaction
- 2 or 3 interactions
- 4 or more interactions
Well tolerated, easily trained to use device.

72% of questionnaires completed

87% completed >two-thirds of questionnaires

Noncompliant had greater cog impair than compliant

Missing data unrelated to age, sex, PANSS total, PANSS Pos or Neg

Assessment duration: M=4min,7sec (SD=3.75)

We have only lost 8 of >350 PDAs distributed
Frequency of functioning behaviors: EMA offers a much more nuanced view than interview based scales. This should increase sensitivity to treatment effects.

<table>
<thead>
<tr>
<th>Variable</th>
<th>M</th>
<th>SD</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Environment</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>At home</td>
<td>70.30%</td>
<td>20.00</td>
</tr>
<tr>
<td>At home of friend/fam</td>
<td>8.49%</td>
<td>12.04</td>
</tr>
<tr>
<td>At work or school</td>
<td>4.31%</td>
<td>5.91</td>
</tr>
<tr>
<td>Other location (inside)</td>
<td>8.36%</td>
<td>8.73</td>
</tr>
<tr>
<td>Other location (outside)</td>
<td>8.54%</td>
<td>10.92</td>
</tr>
<tr>
<td><strong>Social context</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Alone</td>
<td>48.36%</td>
<td>20.06</td>
</tr>
<tr>
<td>Family or friends</td>
<td>35.59%</td>
<td>21.17</td>
</tr>
<tr>
<td>Coworker, colleagues</td>
<td>5.38%</td>
<td>6.98</td>
</tr>
<tr>
<td>Stranger</td>
<td>4.00%</td>
<td>6.80</td>
</tr>
<tr>
<td>Other person</td>
<td>8.08%</td>
<td>11.80</td>
</tr>
<tr>
<td><strong>Functioning Activity</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Inactivity</td>
<td>52.48%</td>
<td>26.65</td>
</tr>
<tr>
<td>Self-care</td>
<td>10.55%</td>
<td>10.34</td>
</tr>
<tr>
<td>Shopping, chores</td>
<td>6.70%</td>
<td>8.67</td>
</tr>
<tr>
<td>Work/school, leisure</td>
<td>10.42%</td>
<td>9.63</td>
</tr>
<tr>
<td>Other activity</td>
<td>21.48%</td>
<td>24.12</td>
</tr>
</tbody>
</table>

% of completed questionnaires
EMA Limitations

New Method, without any kind of cross-lab standardization of probes, # probes per day, length of study period.

Enormous of amount of data, with no “industry standard” analytic approach.

Expense of providing devices to participants.

Even with these limitations, it seems very likely that some version of EMA will emerge as a standard outcome measure for intervention trials.
II. Behavioral Biomarkers

Most likely candidates related to Neg Symptoms:

1: Alterations in Effort-Cost Computations. The cost of effort looms larger than the anticipated value/benefit of reward receipt/goal achievement.

2: Deficits in reinforcement learning, particularly learning from rewarding outcomes.
On this trial you will only have a 50% chance of receiving your reward.
HNS patients are less influenced by certain differences in reward.
D2 Antagonism and Effort

Figure 1. Proportion of high-effort choices as a function of antipsychotic type. (A) Patients on first-generation drugs show marked indifference to increasing reward levels. (B) Haloperidol-equivalent dose across the patient groups. (C) Patients on first-generation drugs had much higher negative symptom ratings. BNSS, Brief Negative Symptom Scale; 1st Gen, first-generation drug; HC, healthy control.
Other Effort Studies

- **Neg symptom effect:**
- Barch 2014 J Abnormal
- Frevaha 2013 Psy Res (only when controls included).
- Treadway 2015 Scz Res.
- Hartman 2015 Sz Bull
- Wolf 2014 Sz Bull
- Moran 2017 J Abnormal
- Culbreth 2016 J Abnormal
- Horan 2015 Sz Bull
- Strauss 2016 Sz Res.
- **Contradictory**
- Docx 2015 Cogn Neuropsychiatry
- McCarthy 2016 Sz Res
- Fervaha 2015 Sz Res (impaired in Deficit Syndrome but not Neg sym)
Reinforcement Learning Methods

• Rich set of paradigms with potential translational applications.

• Can examine the effects of rewards vs. punishments, reward magnitude, probability.

• Ability to update in the face of reversal.

• Computational models can isolate the contribution of WM, learning rate, decision noise etc.
Adapted from Pessiglione, 2006.

S’s learn 4 pairs 2 & 90 vs 10, 80 vs. 20

In 2 pairs, you can win.

In the other two pairs,

Best you can do is avoid losing.

Winning and successful loss avoidance are both + PE
Learning over 4-40 item blocks.

HNS show most impairment with most rewarding stimulus

90% gain

80% gain

90% loss avoid

80% loss avoid
A perfect recipe for avolition:

Learn well from negative feedback what not to do.....

Don’t learn very well from positive feedback...

You learn better what NOT to do than what to do.

So you don’t initiate a lot of goal-directed behavior.
Table 4

Relationships Between Ecological Momentary Assessment—Motivation and Pleasure and Clinical Assessments and Task Behavior

<table>
<thead>
<tr>
<th>Variable</th>
<th>b</th>
<th>t</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>BPRS Psychosis</td>
<td>-.04</td>
<td>-1.25</td>
<td>.21</td>
</tr>
<tr>
<td>Negative Symptom Interview</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>CAINS MAP</td>
<td>.21</td>
<td>7.94</td>
<td>.001</td>
</tr>
<tr>
<td>MAP-SR</td>
<td>-.31</td>
<td>-2.73</td>
<td>.006</td>
</tr>
<tr>
<td>Task behavior</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>PILT reward 90%</td>
<td>-.28</td>
<td>-2.88</td>
<td>.001</td>
</tr>
<tr>
<td>PILT reward 80%</td>
<td>-.31</td>
<td>-2.95</td>
<td>.006</td>
</tr>
<tr>
<td>PILT loss 90%</td>
<td>-.12</td>
<td>-1.06</td>
<td>.30</td>
</tr>
<tr>
<td>PILT loss 80%</td>
<td>-.10</td>
<td>-0.79</td>
<td>.44</td>
</tr>
<tr>
<td>EElRT 50% hard choice</td>
<td>-7.88</td>
<td>-2.44</td>
<td>.02</td>
</tr>
<tr>
<td>EElRT 88% hard choice</td>
<td>-11.58</td>
<td>-3.99</td>
<td>.0005</td>
</tr>
</tbody>
</table>

Note. BPRS Psychosis = Psychosis Subscale of the Brief Psychiatric Rating Scale; CAINS MAP = Motivation and Pleasure Subscale of the Clinical Assessment Interview for Negative Symptoms; MAP-SR = Motivation and Pleasure—Self Report rating scale; PILT = Picture Incentive Learning Task; EElRT = Effort Expenditure for Rewards Task.
RL studies looking at neg symptoms or learning from gains vs. loss avoidance

Supportive, partially supportive:
Cheng 2012 Sz Res
Reinen 2016 Sz Res
Somla 2011 Sz Res
Barch 2017 J Abnormal
Hartman-Reimer 2017 Nature.com Scientific Reports

Contradictory:
Frevaha 2013 Sz Research
Behavioral Biomarkers

Effort and RL measures have strong evidence for clinical validity vis a vis negative symptoms.

Not difficult to implement.

**Limitations:**
Methods are not well standardized across labs.

Psychometrics/reliability of many measures is not well documented.

Some patients just “don’t get” RL tasks.
III. Imaging Biomarkers

Monetary Incentive Delay

Reinforcement Learning
Monetary Incentive Delay task

Fig. 3. Monetary Incentive Delay (MID) task trial structure (Knutson et al., 2003a).
Anticipation effects maximal in VS

Outcome signal maximal in MedPFC
Negative Symptom Severity Predicts Gain Anticipation Responses in L VS

Gain vs. Loss-avoidance (GLA) Task

**Trial Structure**

- **Frequent (70%)**
  - Winner (A)
  - Infrequent (30%)
  - Winner (B)
- **Frequent (70%)**
  - Correct (C)
  - Incorrect (D)
- **Frequent (70%)**
  - Loss-avoider (E)
  - Loser (F)

**Reward Contingencies**

- Frequent (70%)
  - Winner (A)
  - Infrequent (30%)
  - Winner (B)
- Frequent (70%)
  - Correct (C)
  - Incorrect (D)
- Frequent (70%)
  - Loss-avoider (E)
  - Loser (F)

- Not a winner
- Keep your money!
SZ and controls show similar responses to PEs, in striatum, insula, and dmPFC.

In PSZ, gains = loss avoidance, reduced gain-loss avoidance relates to neg. svm.

(A) HVs show differential neural responses to gains and instances of loss-avoidance, but (B) SZ patients do not; (C) Experience valued [Gain - Loss-avoidance] contrasts in VS correlate with ratings for avolition/anhedonia in SZs, as do (D) expected value [Expected Gain - Expected Neutral] contrasts.

Waltz et al. (In Press).
RL Imaging Tools

Rich set of paradigms and computational models to isolate different aspects of RL that may be related to negative symptoms.

Limitations: Retest reliability of fMRI with these paradigms not established.
The Biomarker Glass: Half Full or Half Empty?

• Some methods closer to Phase 3 prime time than others. Some best suited for Phase 2, proof of concept.

• Investment needed in method standardization and psychometrics to facilitate use.

• Potential payoff: Robust translational tools that span phases of drug development.
Thanks to....

Matthew Albrecht
Michael Frank
Greg Strauss
James Waltz
Leeka Hubzin
Sharon August
Deanna Barch

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