Pragmatic Aspects of including Reward Processing Tasks in drug development trials

Stephane Pollentier, ISCTM February 2020
Conflicts of interest / Disclosure

• Full-time employee of Boehringer Ingelheim
Outline

- Task selection
- Examples of industry-sponsored studies
- Experience in a larger phase 2 study
- Reward Task Optimization Consortium & study
- Practical considerations
Reward Processing Tasks in drug development

- Indication
  - Clinical diagnosis
    - Symptoms
      - State - Trait
    - Brain circuit malfunction
- Endpoints
  - Clinical scales
    - (self- or rater-report)
  - Behavioural tasks
    - (Performance measures)
  - Brain function measures
    - fMRI, EEG, MEG,...
- Late Stage
  - • Subgroup identification & response prediction
  - • Supportive evidence
  - • Functional capacity
- Early Stage
  - • Target engagement
  - • Pharmacodynamic effect
  - • Proof of concept Go/NoGo
Reward Processing Task selection - considerations

• Intended context of use
• Targeting one or more sub-domains of reward processing – single task or battery
• Stand-alone or combined with brain activity measure
• Data on validity and reliability
• Compliance with data integrity requirements
• Standardization, operational aspects (time/platform) and training
• Accessibility (copyright & license; language;...)
• ...
# Reward Task Selection

<table>
<thead>
<tr>
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</thead>
<tbody>
<tr>
<td>1.1. Initial Response to Reward</td>
<td>Simple Guessing Task</td>
<td>3.1. Reward (probability)</td>
</tr>
<tr>
<td>1.2. Reward Anticipation</td>
<td>Monetary Incentive Delay Task</td>
<td>3.1. Delay</td>
</tr>
<tr>
<td>1.3. Reward Satiation</td>
<td>Fixed-ratio Satiation Schedule</td>
<td>3.3. Effort</td>
</tr>
</tbody>
</table>

Currently favoured in industry-sponsored trials:

- Monetary Incentive Delay (MID)
- Reinforcement Learning tasks
- Effort-based tasks

National Advisory Mental Health Council Workgroup on Tasks and Measures for RDoC, April 5-6, 2016:
Nalmefene Reduces Reward Anticipation in Alcohol Dependence: An Experimental Functional Magnetic Resonance Imaging Study


Biological Psychiatry June 1, 2017; 81:941–948

- Nalmefene (µ and d opioid antagonist, k opioid partial agonist), registered in EU for alcohol-dependence with „high-drinking levels“
- Single dose 18mg vs placebo cross-over. fMRI under alcohol clamp (IV alcohol administration); N=22 alcohol-dependent males
- Striatal BOLD signal change during anticipation of reward in MID
Using imaging and behavioral methods probing reward functions as tools for decision making in a proof-of-mechanism study of the PDE10 inhibitor RG7203 in patients with schizophrenia and negative symptoms

D. Umbricht, MD,
Roche Innovation Center Basel
F. Hoffmann-La Roche Ltd, Switzerland

- Patients with chronic SZ (PANNS Neg Symptoms ≥18) and on D2 antagonists
- Three-way cross-over of two doses & pb; N=24 completers
- MID: increased activation reward vs non-reward in context of overall blunted activation in drug conditions; behavioral tasks: decreased willingness to work

ASCP, 2018
BI425809, GlyT1 inhibitor for cognitive impairment in schizophrenia

The trial aims to:
Randomize 1:1:1:1:2 to oral BI 425809 (2, 5, 10, and 25 mg) or placebo, once daily, for 12 weeks

504 patients

12 weeks

Phase II

Double blind Placebo controlled Parallel group

BI 425809: 2 mg once daily n=64
BI 425809: 5 mg once daily n=64
BI 425809: 10 mg once daily n=64
BI 425809: 25 mg once daily n=64
Placebo once daily n=108

Efficacy, safety, and pharmacokinetics of BI 425809 once daily in patients with schizophrenia: methodology of a randomized trial.
Podhorna J et al, Poster 27 – SIRS 2019

Novel endpoints of motivation and reinforcement learning in a large interventional trial of BI 425809 in patients with schizophrenia.
Podhorna J et al, P244 – ECNP 2019

Actual randomized N=509
Reward task substudy (US only) N=215

ISCTM Feb 2020
Balloon Effort Task (BET)\textsuperscript{1}

- A computerized, objective task that assesses reward-based decision-making and addresses how much effort a participant is willing to put forth to receive a monetary reward of variable certainty

- Abbreviated version (dropping 4$ and 6$ reward levels)

- Motivation to exert effort for reward is quantified according to the proportion of hard choices made in relation to the potential reward value ($3, $5, or $7) and reward probability (50% or 100%)

Balloon Effort task - baseline results (N= 214)

Compared to published studies:

<table>
<thead>
<tr>
<th></th>
<th>100% Reward: Patients</th>
<th>50% Reward: Patients</th>
<th>100% Reward: HC</th>
<th>50% Reward: HC</th>
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</thead>
<tbody>
<tr>
<td><strong>Gold et al, 2013</strong></td>
<td>$3 = 35</td>
<td>$3 = 21</td>
<td>$3 = 40</td>
<td>$3 = 12</td>
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<tr>
<td>N = 44</td>
<td>$5 = 53</td>
<td>$5 = 31</td>
<td>$5 = 71</td>
<td>$5 = 29</td>
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<tr>
<td></td>
<td>$7 = 68</td>
<td>$7 = 40</td>
<td>$7 = 89</td>
<td>$7 = 39</td>
</tr>
<tr>
<td><strong>Reddy et al, 2015</strong></td>
<td>$3 = 50</td>
<td>N.A.</td>
<td>$3 = 61</td>
<td>N.A.</td>
</tr>
<tr>
<td>N = 94</td>
<td>$5 = 65</td>
<td>$5 = 79</td>
<td>$5 = 79</td>
<td>N.A.</td>
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<tr>
<td></td>
<td>$7 = 75</td>
<td>$7 = 89</td>
<td>$7 = 89</td>
<td>N.A.</td>
</tr>
</tbody>
</table>

*No 50% probability
$4 & $6 values not shown

Probabilistic Reversal Learning Task (PRLT)

Computerized task that assesses the patient’s ability to learn shifting rules and adapt to them

- **Discrimination Phase**
  - 3 blocks stimulus pairs
  - 3 phases of 50 trials per block
  - Phase achieved when 9/10 correct
  - Choice 1 = ‘win’ 20% ‘lose’ 80%
  - Choice 2 = ‘win’ 80% ‘lose’ 20%

- **Reversal 1 Phase**
  - 50 trials maximum
  - Choice 1 = ‘lose’ 80% ‘win’ 20%
  - Choice 2 = ‘win’ 80% ‘lose’ 20%

- **Reversal 2 Phase**
  - 50 trials maximum
  - Choice 1 = ‘win’ 80% ‘lose’ 20%
  - Choice 2 = ‘win’ 20% ‘lose’ 80%

Feedback given on every trial
- Correct or Incorrect

**Key outcome measures**
- Total number of discrimination phases completed (out of 3)
- Total number of reversals (out of 6)
- Proportions of errors (choice of least endorsed stimulus) within the phases

Probabilistic Reversal Learning Task – baseline results (N=206)

Compared to published studies:

- Waltz JA and Gold JM. *Schizophr Res* 2007; 93(1–3):296–303
Baseline values for „understanding of/adherence to“ of task principle

<table>
<thead>
<tr>
<th>BET</th>
<th>Always hardest choice (n=17)</th>
<th>Varies choice (n=197)</th>
</tr>
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<tbody>
<tr>
<td>Age (years)</td>
<td>39.4 (7.3)</td>
<td>37.4 (7.9)</td>
</tr>
<tr>
<td>MCCB total</td>
<td>30.7(^a) (13.1)</td>
<td>28.9(^b) (12.7)</td>
</tr>
<tr>
<td>PANSS total</td>
<td>69.9 (14.4)</td>
<td>66.8 (12.7)</td>
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<tr>
<td>PANSS negative</td>
<td>17.2 (4.1)</td>
<td>18.0 (4.6)</td>
</tr>
<tr>
<td>SCoRS total</td>
<td>40.6 (11.5)</td>
<td>38.4 (8.8)</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>PRLT</th>
<th>No discrimination (n=37)</th>
<th>Learners (n=178)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (years)</td>
<td>37.6 (6.7)</td>
<td>37.6 (8.1)</td>
</tr>
<tr>
<td>MCCB total</td>
<td>22.5 (13.2)</td>
<td>30.3(^c) (12.2)</td>
</tr>
<tr>
<td>PANSS total</td>
<td>67.9 (11.8)</td>
<td>66.8 (13.0)</td>
</tr>
<tr>
<td>PANSS negative</td>
<td>19.8 (4.6)</td>
<td>17.5 (4.5)</td>
</tr>
<tr>
<td>SCoRS total</td>
<td>36.8 (7.4)</td>
<td>38.9 (9.3)</td>
</tr>
</tbody>
</table>

\(^a\)n = 15; \(^b\)n = 190; \(^c\)n = 169. Data are presented as mean (SD). Preliminary data, not QCed
Conduct experience

• Average time (incl. instructions, practice and actual task):
  PRLT about 17 minutes; BET about 21 minutes

• Raters found administrations easy; tolerability for patients appears good

• No surveillance of raters re correct verbatim instructions and patient monitoring (eg unresolvable queries if all-hard choices)

• IT: relevant to run off-line & ensure smooth data output transfer

• Monetary compensation – sometimes confusion

• Note: this substudy conducted in US only – exploratory endpoints
Precompetitive collaboration on reward processing tasks

Reward processing tasks provide objective and quantifiable measures of anhedonia and impaired motivation. Such tasks are rarely included in large, multi-site clinical trials across different diagnoses and/or countries. Trials rarely include multiple tasks assessing different sub-domains of reward processing. The available tasks do not always comply with stringent data integrity and standardization requirements for use in drug development studies.

The Reward Task Optimisation Consortium (RTOC) was formed to optimize and validate the operational implementation of three reward processing tasks, making them fit for purpose in large-scale, international, multi-site drug development studies.

1. Treadway MT and Zald DH. Transl Psychiatry 2014;4:e469.
**Doors Task**

- Measures initial responsivity to reward receipt or loss, as measured by EEG or imaging.
- Participants choose between two identical doors, and are presented with wins (+€0.50) and losses (-€0.25) in a predetermined order, for a win/loss ratio of exactly 50% (choices do not influence reward).
- Each participant is presented with a total of 60 trials.
- Primary task endpoint: Stimulus-locked FRN defined as activity in response to losses subtracted from activity in response to gains.

**Grip Effort Task**

- Measures subjects’ willingness to exert effort for variable amounts of monetary reward.
- Participants choose to carry out an easy grip (eg 50% of their max) for consistent low reward (eg €0.10) or hard grip (eg 90% of max) for variable reward (eg €0.10, €0.20, or €0.40).
- Each participant is presented with a total of 54 trials (18 for each reward level).
- Primary task endpoint: Percentage of hard grip choices at each reward level.
- Feedback-locked FRN in response to high and low rewards, with the task difficulty taken into account, will also be assessed.

**64-Electrode EEG**

- FRN occurs around 300 ms following feedback delivery and is sensitive to errors in reward prediction, negative valence and the magnitude of feedback outcomes.
- EEG will be continuously recorded to assess FRN during the Grip Effort Task and the Doors Task.

**Working Memory-Reinforcement Learning (WM-RL) Task**

- Separately identify the contributions of reinforcement learning (effect of reward history) and working memory (fixed and decay effect) to reward learning.
- Participants learn which of three actions to select in response to different stimuli, with correct responses gaining either 1 or 2 points according to a fixed probability for each stimulus (0.2, 0.5, or 0.8).
- Each participant is presented with 12 blocks, with each stimulus presented 13 times per block (for a total of 26-65 trials per block).
- During a surprise test phase, participants select which of two stimuli from the previous learning blocks is more rewarding based on learned reward associations for each stimulus.
- Primary task endpoint: Overall percentage of correct responses in the learning phase and in each block size.
RTOC pilot study details

• Pre-pilot: ~8 healthy controls (2/site) to address any major feasibility, implementation, or data issues

• Main Pilot Study: Major Depression (N=37), Schizophrenia (N=37) and age/gender matched healthy controls (max. N = 80)

• Re-Test visit: 16 participants from each group (16 MDD, 16 SZ, 16 HC)

• Four countries, one site each: Netherlands, Spain, Greece, Germany

• Clinical assessments
  • Mini-International Neuropsychiatric Interview (MINI)
  • Quick Inventory of Depressive Symptomatology – Self Report (QIDS-SR)
  • Behavioural Inhibition/Avoidance Scales (BIS/BAS)
  • Snaith-Hamilton Pleasure Scale (SHAPS)
  • In participants with SZ: Positive and Negative Symptom Scale (PANSS); Brief Negative Symptom Scale (BNSS); Extrapyramidal Symptom Rating Scale (ESRS-A)
RTOC study status

- Study start: Nov 2019
- Pre-pilot (HC N=8) confirmed operational expectations
- Acknowledging small N, output in line with reference publications
- Recruitment in main pilot study ongoing

Primary quantitative endpoint – % of hard choices by reward level

EEG results with Doors task
Conduct experience

• Overall average task duration (incl. instructions, practice and actual task):
  • Grip Strength – approx. 20 min (4 practice trials, 4 calibration trials, 54 assessment trials)
  • Doors Task – approx. 15 min (4 practice trials, 60 assessment trials)
  • WM/RL Task - approx. 40 min (43 practice trials, 507 learning trials, 156 test trials)

• Standardized face-to-face training for all key staff (hands-on, dry runs)
  • Scripted verbal instructions in local language, translated from a common English version
  • Standard practice trials - demonstrate performance at certain level before proceeding
  • Convenience of common, online platform (tasks run off-line)

• Qualitative feedback:
  • MDD need more prompting, SZ take more time to reflect responses, WM/RL can frustrate
  • Site/country specific aspects of clinical diagnosis and background treatment
Conclusions

• From a drug developer’s perspective: reward tasks in general are at a premature to near-mature stage (validity, standardisation,...); need more data

• Data output analysis and clinical interpretation is challenging, likely no simple correlations with clinical symptom severity at group (indication) level; computational approaches may help

• Inclusion of reward tasks in drug development trials should be driven by intended context of use
## Acknowledgements

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<table>
<thead>
<tr>
<th>Trial 1436-0009</th>
<th>Reward Tasks Optimization Consortium</th>
</tr>
</thead>
</table>
| **Participants and Investigators** | **Thérèse van Amelsvoort, Dennis Hernaus, Anke Sambeth**  
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| Thuy Nguyen | Victor Perez, Matilde Elies  
Institut de Neuropsiquiatria, Barcelona |
| Jana Podhora | **P1vital Ltd:**  
Amy Bilderbeck |
| Jay Soh | Andreea Raslescu |
| Yihua Zhao | Anja Hayen |
| and many more | Gerard Dawson |
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| Alexandra Atkins |  |
| Bill Horan |  |
| Rich Keefe |  |
| Heather Snyder |  |