Quantifiable assessment of motivational deficits and apathy in early dementia – and beyond

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- Full time employee of Boehringer Ingelheim

- This presentation represents my individual views
Clinical phenomenology & behavioural neuroscience

Reward processing paradigms for use in clinical trials

• Validation, Standardisation and Operational aspects
• Reward Task Optimisation Consortium
• PRISM

Outlook & Conclusions

Links & contacts
Clinical phenomenology of apathy, amotivation, avolition, anhedonia, social withdrawal, ...

- Descriptions and definitions are overlapping and confusing
  - Is apathy well defined as a deficit of motivation and lack of interest?

- Clinical assessment based on self- or third party-report
  - Insight?
  - Conflating components (e.g., loss of pleasure vs motivation)
  - Issues with affective forecasting (how much enjoyment to expect for a future reward)

- Clinical relevance
  - Prevalent in many neuropsychiatric disorders (MDD, Schizophrenia, abuse disorders, PTSD, ...., post-stroke, Parkinson‘s, Alzheimer dementia)
  - Associated with poor response and chronicity
Use of fMRI to study reward processing in humans
(Wang K et al, J Neurophysiol 2016)

2016: 463 papers
2017, until July 31st: 270
Behavioural neuroscience – reward processing
... Monetary Incentive Delay task (Knutson, 2000)

Stoy et al, 2012

ISCTM
THE INTERNATIONAL SOCIETY FOR CNS CLINICAL TRIALS AND METHODOLOGY

ECNP
Behavioural neuroscience – reward processing
... mapping subdomains on neurobiological substrates

Barch, Pagliaccio and Luking,
Curr Topics Behav Neurosci 2015
RDoC - Positive Valence domains & tasks
NAMH Council - Workgroup on Tasks and Measures for RDoC, April 5-6, 2016

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<td>3.2. Delay</td>
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<td>3.3. Effort</td>
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Use behavioural paradigms as bridging tools for Back- and Forward-Translation?

Diagnostic (sub)groups

Symptoms
  State - Trait

Brain Circuit Malfunction

Endpoints

Clinical scales
  (Self or Rater report)

Behavioural tasks
  (Performance measures)

Brain function measures
  fMRI, EEG, MEG,…
  (Biomarkers)

Clinical trials

Late Stage

Early Stage
Are Reward Processing Tasks ready for „prime time“ in clinical trials?

- FNIMH - Consensus Workshop on Standardization of Reward Processing Tasks, February 2016
- NAMH - Council Workgroup on Tasks and Measures for RDoC, April 2016
- Evaluation of
  - construct validity,
  - psychometric characteristics (test-retest, internal reliability, sensitivity & specificity, alternate forms, practice effects, floor/ceiling effects,...),
  - standardized administration parameters (duration, # blocks, stimuli,...),
  - cultural-language effects, pediatric use,
  - availability of analog animal test model,
  - normative data,
  - sensitive to change and lack/loss of function,
  - use with methods interrogating brain circuitry (fMRI/EEG),
  - use as stand-alone,
  - correlation with “brain signal”, correlation with “clinical” rating/severity,
  - copyright & access
Are Reward Processing Tasks ready for „prime time“ in clinical trials?

- Task software should be:
  - Suitable for international, multicentre deployment via internet
  - Flexible to meet specific study protocol requirements
  - 21 CFR Part 11 compliant including software validation, security access controls, audit trail and records retention
  - Able to pre-process and QC task data, calculate task endpoints and provide task data in multiple formats for statistical analysis (CDISC compliant)

**Data integrity**

- Comprehensive administrator and participant training programs and manuals

- Optimize task parameters and reduce task durations
Are Reward Processing Tasks ready for „prime time“ in clinical trials?

- Gaps
  - Task performance in different populations across CNS spectrum
  - Task performance in context of “battery” across domains of reward processing
  - Treatment sensitivity

Effort-Based Decision-Making Paradigms for Clinical Trials in Schizophrenia: Part 1—Psychometric Characteristics of 5 Paradigms


L. Felice Reddy*,1,2, William P. Horan1,2, Deanna M. Barch3, Robert W. Buchanan4, Eduardo Dunayevich5, James M. Gold4, Naomi Lyons1, Stephen R. Marder1,2, Michael T. Treadway6, Jonathan K. Wynn1,2, Jared W. Young7,8, and Michael F. Green1,2
Reward Task Optimisation Consortium

Precompetitive collaboration of several industry partners in collaboration with ECNP Experimental Medicine Network
- Collaboration in „status nascendi“
- Objective: optimization and standardization
- Pilot tasks for project: EEfRT and PRT, to be confirmed

**Reward Valuation**

Choose hard or easy
Probability of win: 12 – 50 – 88%

**EEfRT (Treadway, 2009)**

**Reward Learning**

Discriminate 11.5 vs 13 mm

40 /100 trials inform on reward; Bias toward rich rewarded (30:10)

**PRT (Pizzagalli, 2005)**
PRISM: Psychiatric Ratings using Intermediate Stratified Markers

Project coordinator: Martien Kas (University of Groningen, NL)
Project leader: Hugh Marston (Lilly, UK)

Deep phenotyping study of social and cognitive deficits in Alzheimer’s disease and schizophrenia to provide quantitative biological measures.

Can a set of quantifiable biological parameters cluster and differentiate SZ and AD patients characterized by low versus high levels of social withdrawal?
Longitudinal and objective measures of rodent and human social exploration

Kas (RUG) & Vorstman (UMCU)
Deep phenotyping of social withdrawal

Social Cognition tasks
- Face Emotion Processing task (fMRI and EEG)
- Facial Expression Recognition Task
- Hinting Task

Reward Processing tasks
- Monetary and Social Incentive Delay task (fMRI)
- Desk Choice Effort Task
- EEfRT

Measure of sociability and social exploration
- Smartphone application „BeHapp“
Conclusion & outlook

− Apathy and other symptoms due to reward processing dysfunctions constitute an important clinically unmet need

− Objective and quantifiable measures of reward processing provide a path forward, beyond self report measures and clinical scales, in particular also in early AD

− Psychometric characteristics need to better evaluated and tasks need to be optimized and standardized for clinical trial use
− Use as performance measures, endpoints and/or for definition of homogeneous diagnostic subgroups qualification as drug development tool for specific context of use / qualified opinion
− Towards a Reward Processing Test Battery?
Links and contacts

FNIMH hosted Consensus Workshop on Standardization of Reward Processing Tasks, February 2016:

National Advisory Mental Health Council Workgroup on Tasks and Measures for RDoC, April 5-6, 2016:

Reward Task Optimisation Consortium
  Gerry Dawson (gdawson@p1vital.com)
  Stephane Pollentier (stephane.pollentier@boehringer-ingelheim.com)

Prism website https://prism-project.eu/en/prism-study/