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

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- Full time employee of Boerhinger 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, …

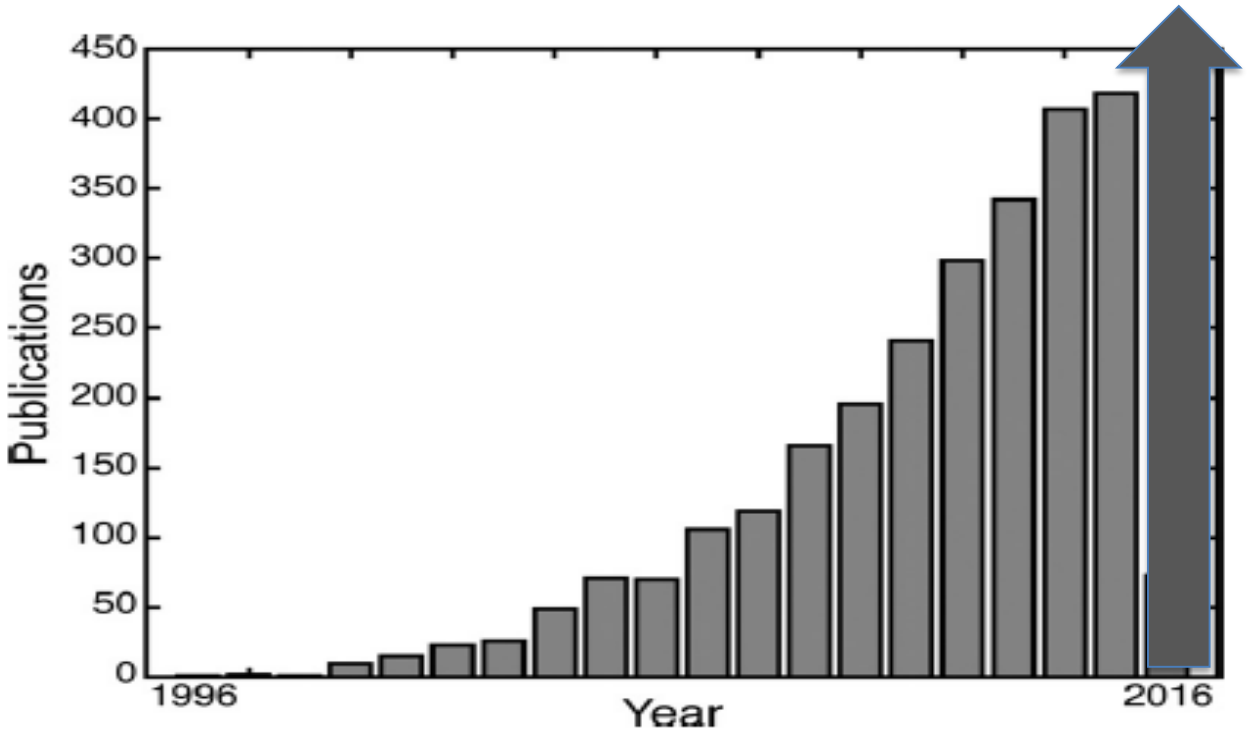
- Descriptions and definitions are overlapping and confusing
  - Is apathy well defined as a deficit of motivation and lack of interest?

- 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)

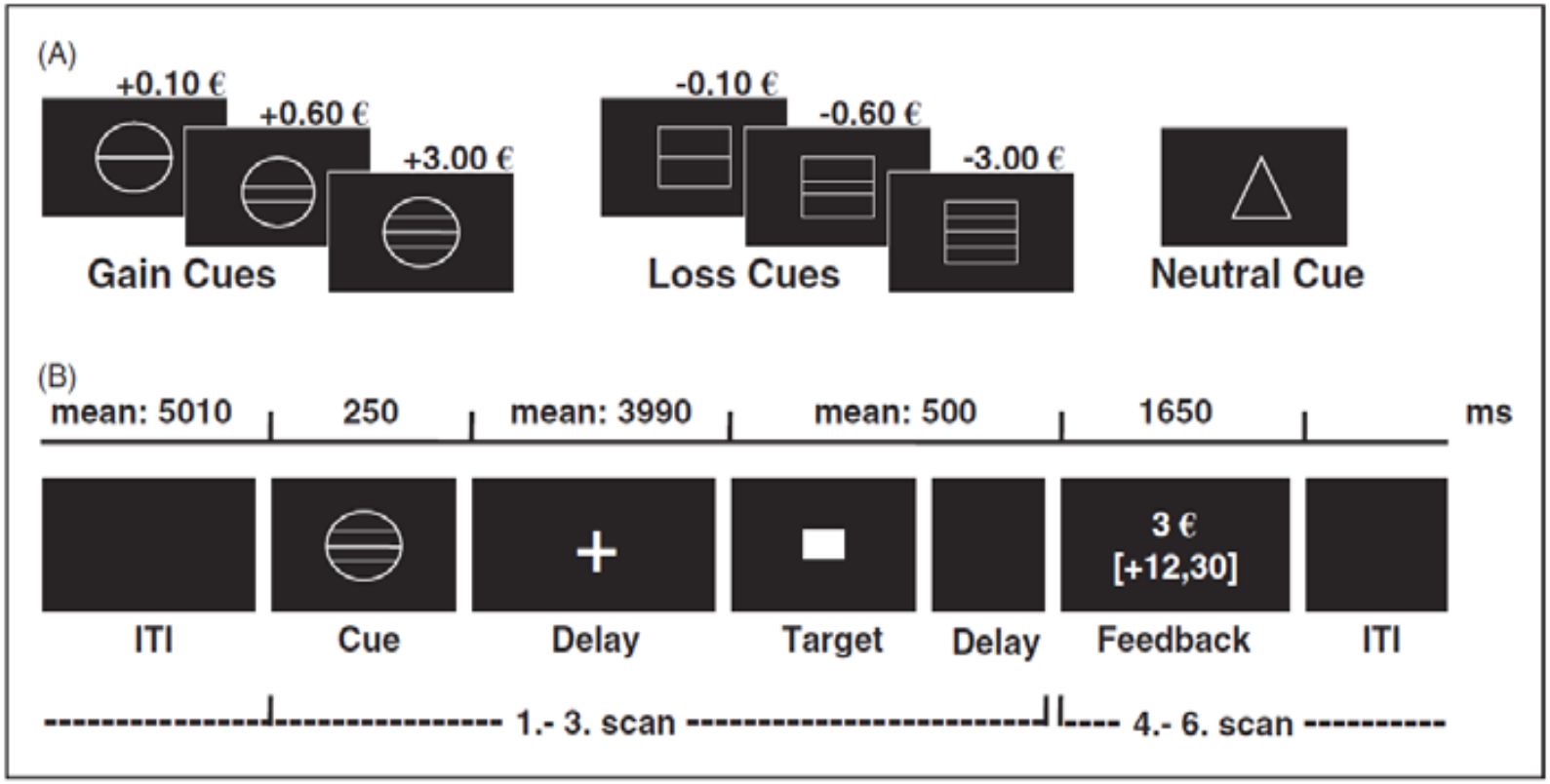


Proliferation of functional magnetic resonance imaging (fMRI) studies

2016: 463 papers
2017, until July 31st: 270

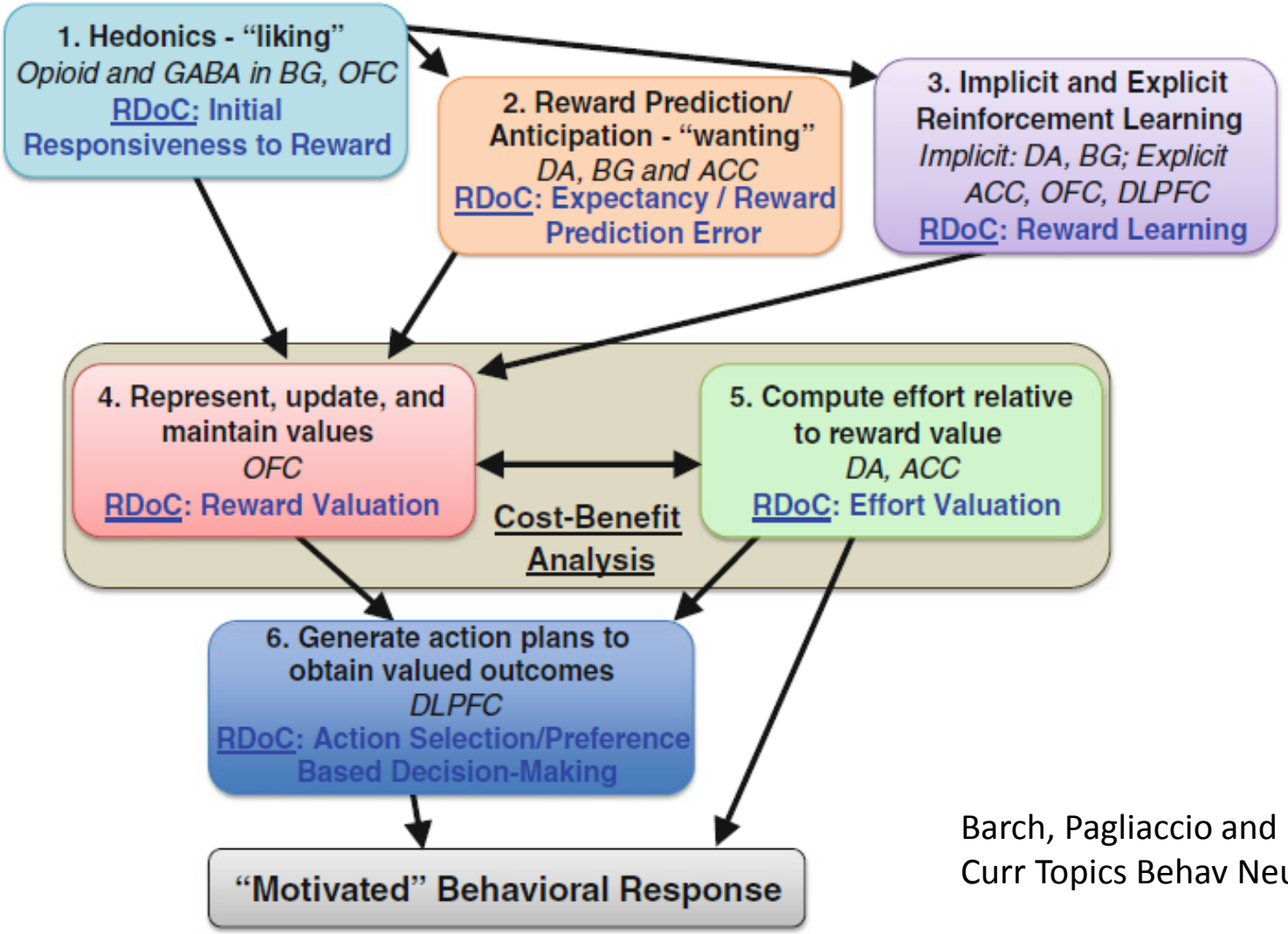
Behavioural neuroscience – reward processing

… Monetary Incentive Delay task (Knutson, 2000)



Stoy et al, 2012

Behavioural neuroscience – reward processing
… mapping subdomains on neurobiological substrates



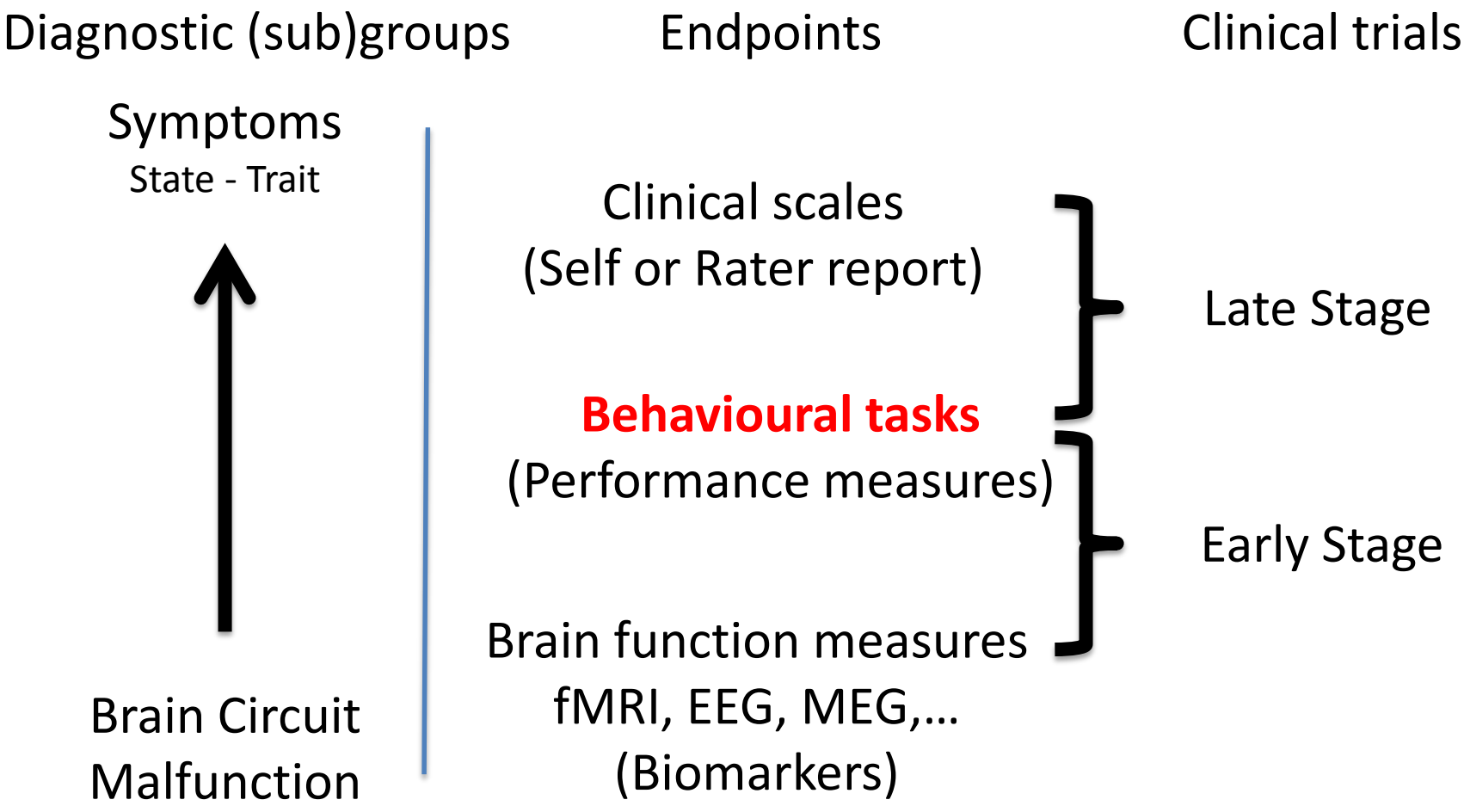
Barch, Pagliaccio and Luking,
Curr Topics Behav Neurosci 2015

RDoC - Positive Valence domains & tasks

NAMH Council - Workgroup on Tasks and Measures for RDoC , April 5-6, 2016

1. Reward Responsiveness	
1.1. Initial Response to Reward	Simple Guessing Task
1.2. Reward Anticipation	Monetary Incentive Delay Task
1.3. Reward Satiation	Fixed-ratio Satiation Schedule
2. Reward Learning	
2.1. Habit	Devaluation Task ; Habit Task
	Habit Learning Task
2.2. Probabilistic & Reinforcement Learning	Probabilistic Reward Task
	Pavlovian Conditioning
	Drifting double bandit
	Probabilistic Stimulus Selection Task
2.3. Reward Prediction Error	Rutledge Passive Lottery Task
	Drifting double bandit
3. Reward Valuation	
3.1. Reward (probability)	Probability Choice Task
	Willingness To Pay Task
3.2. Delay	Delayed Discounting Task
3.3. Effort	Effort Expenditure for Reward Task

Use behavioural paradigms as bridging tools for Back- and Forward-Translation?



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

Schizophrenia Bulletin vol. 41 no. 5 pp. 1045–1054, 2015

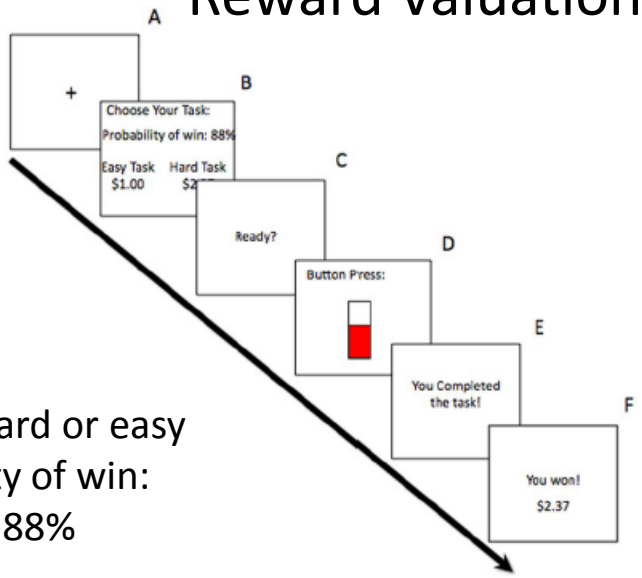
L. Felice Reddy*[,1,2], William P. Horan[1,2], Deanna M. Barch[3], Robert W. Buchanan[4], Eduardo Dunayevich[5], James M. Gold[4], Naomi Lyons[1], Stephen R. Marder[1,2], Michael T. Treadway[6], Jonathan K. Wynn[1,2], Jared W. Young[7,8], and Michael F. Green[1,2]

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

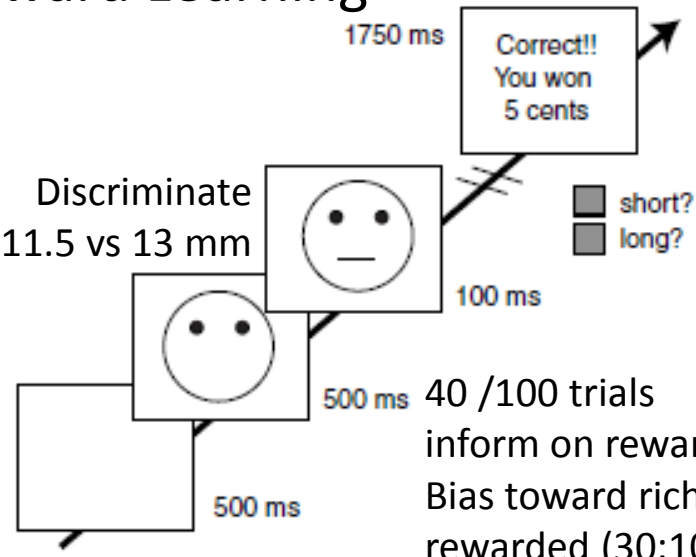
Reward Valuation



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

EEfRT (Treadway, 2009)

Reward Learning



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

PRT (Pizzagalli, 2005)

ISCTM THE INTERNATIONAL SOCIETY FOR CNS CLINICAL TRIALS AND METHODOLOGY

ECNP

PRISM: Psychiatric Ratings using Intermediate Stratified Markers

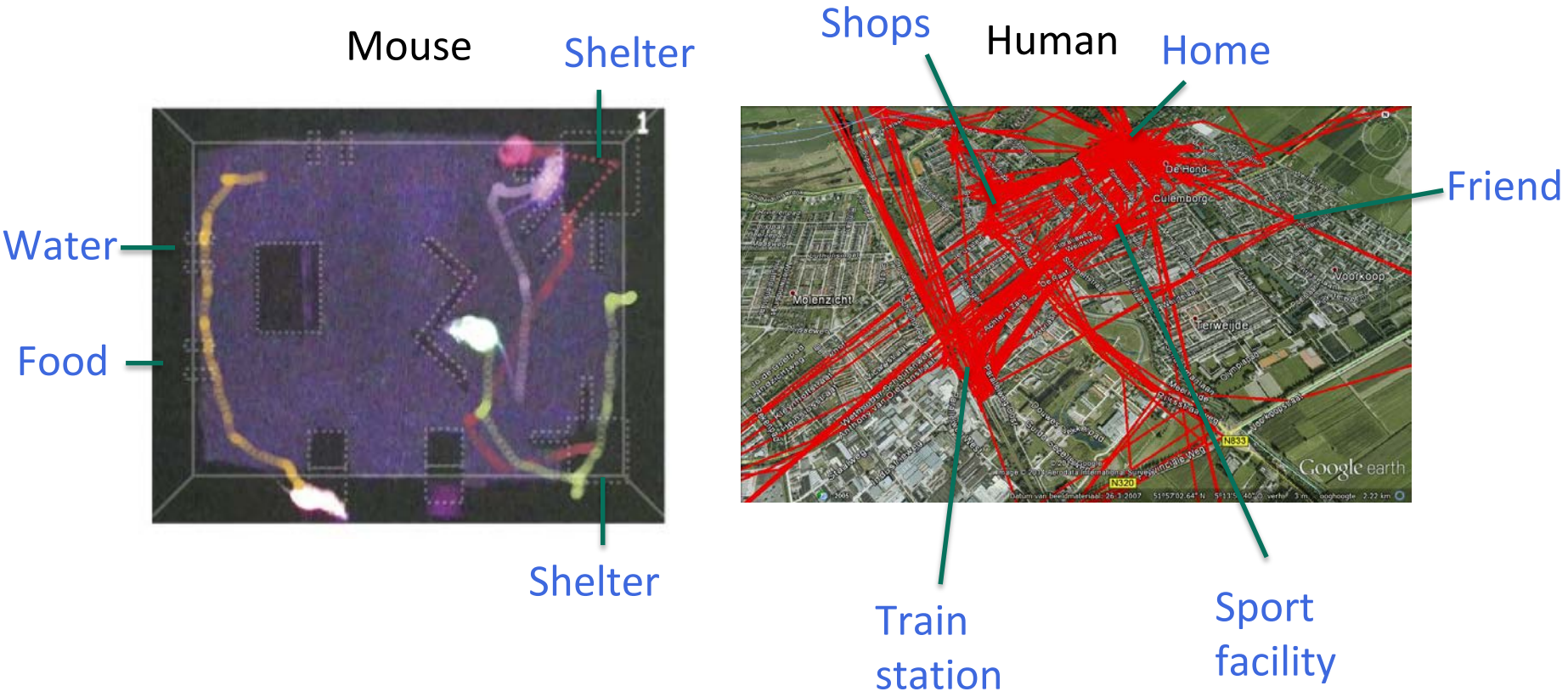
Project coordinator: Martien Kas (University of Groningen, NL)
Project leader: Hugh Marston (Lilly, UK)

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 ?**

The project leading to this application has received funding from the Innovative Medicines Initiative 2 Joint Undertaking under grant agreement No 115916. This Joint Undertaking receives support from the European Union's Horizon 2020 research and innovation programme and EFPIA.

Longitudinal and objective measures of rodent and human social exploration



Kas (RUG) & Vorstman (UMCU)

The project leading to this application has received funding from the Innovative Medicines Initiative 2 Joint Undertaking under grant agreement No 115916. This Joint Undertaking receives support from the European Union's Horizon 2020 research and innovation programme and EFPIA.

Deep phenotyping of social withdrawal

Reward Processing tasks

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

Measure of sociability and social exploration

– Smartphone application „BeHapp“

Social Cognition tasks

- Face Emotion Processing task (fMRI and EEG)
- Facial Expression Recogntion Task
- Hinting Task

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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:
http://www.fnih.org/what-we-do/current-research-programs/consensus-workshop-on-standardization-of-reward-processing-tasks

National Advisory Mental Health Council Workgroup on Tasks and Measures for RDoC , April 5-6, 2016:
https://www.nimh.nih.gov/about/advisory-boards-and-groups/namhc/reports/rdoc_council_workgroup_report_153440.pdf

Reward Task Optimisation Consortium

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