DRIVING PARADIGM OPTIMIZATION FOR CLINICAL TRIALS: THE RTOC PRE-COMPETITIVE CONSORTIUM AND VALIDATION OF REWARD PROCESSING TASKS

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CONCEPT

- Reward processing tasks provide objective and quantifiable measures of anhedonia and impaired motivation[1]
- 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

ESTABLISHING RTOC

March 2017 — An initial meeting hosted by the **European College of Neuropsychopharmacology (ECNP) Experimental Medicine Network** brought together interested stakeholders, including 5 pharmaceutical industry partners, to explore opportunities for a pre-competitive collaboration

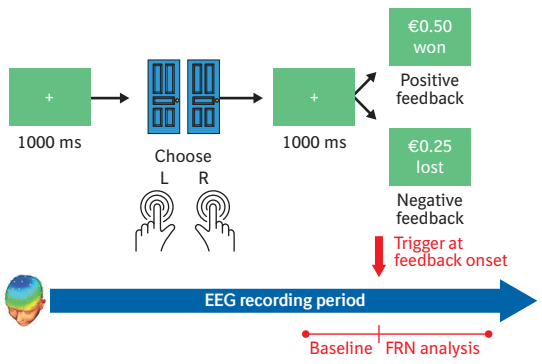
September 2017 — A meeting at the 2017 **ECNP congress** in Paris consolidated that interest, and a project work plan was developed at a subsequent meeting in March 2018

Subsequent teleconferences:
- Agreed on the scope of the project and formalized the contractual basis for the Reward Task Optimisation Consortium
- Engaged with academic experts and selected tasks based on established construct, discriminant, and test-retest validity

September 2018 — Upon completion of site selection, an investigator meeting was held at **ECNP in Barcelona** to finalize study protocol

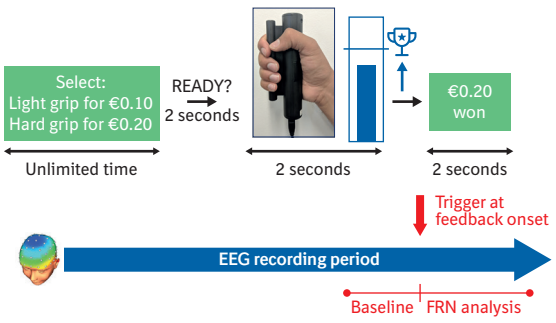
Q2 2019 — **RTOC formally launched**

THE DOORS TASK



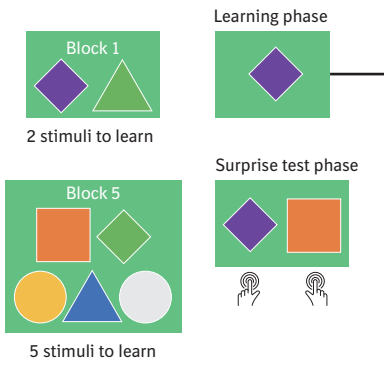
- Measures initial responsiveness to reward receipt or loss, as measured by electroencephalography (EEG) or imaging[2]
- Participants choose between two identical doors, and are presented with wins (+€0.50) and losses (-€0.25) in a pre-determined order, for a win/loss ratio of exactly 50% (choices do not influence reward)
- Each participant is presented with a total of 60 trials
- **Primary task endpoint**: Stimulus-locked feedback-related negativity (FRN) defined as activity in response to losses subtracted from activity in response to gains

THE GRIP EFFORT TASK



- Measures subjects' willingness to exert effort for variable amounts of monetary reward[3]
- 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

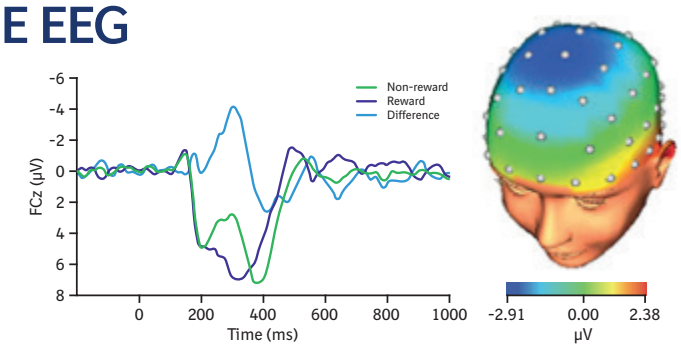
THE WM-RL TASK



- Separately identifies the contributions of reinforcement learning (effect of reward history) and working memory (load and decay effects) to reward learning[4]
- 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

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



RTOC TRIAL METHODOLOGY

This multi-center, non-interventional study across **4 EU countries (Germany, Greece, Netherlands, and Spain)** aims to recruit:

37 patients with schizophrenia **(SZ)** and **37** patients with major depressive disorder **(MDD)** and **≤80** age- and gender-matched healthy volunteers

All participants will complete all three tasks via an online platform at a single study visit, as well as the following clinical assessments:

- **Screening:**
  - Mini-International Neuropsychiatric Interview (MINI)
  - Quick Inventory of Depressive Symptomatology-Self Report (QIDS-SR)
  - Extrapyramidal Symptom Rating Scale – Abbreviated (ESRS-A) in participants with SZ
  - Positive and Negative Symptom Scale (PANSS) in participants with SZ
  - Behavioral Inhibition/Avoidance Scales (BIS/BAS)
  - Snaith-Hamilton Pleasure Scale (SHAPS)
  - Brief Negative Symptom Scale (BNSS) in participants with SZ

KEY INCLUSION CRITERIA
- Aged 20–55 years inclusive
- A primary DSM-5 diagnosis of MDD or SZ confirmed at screening

KEY EXCLUSION CRITERIA
- For healthy controls: history or presence of a primary psychiatric disorder
- For SZ and MDD groups: clinical instability or relevant co-morbid psychiatric disorder

ANALYSIS

- Primary and secondary endpoints for each task will be compared between patient groups and their age- and gender-matched controls, and with published results for these tasks. Correlations with clinical measures of severity will be explored
- **WM-RL task**: Trial-by-trial logistic regression analyses based on a previously-established model will be conducted, and individual slopes will be compared between groups to investigate variables including accuracy in the testing phase as a function of value difference (optimal minus suboptimal stimulus), delay, and set size

The RTOC trial is expected to start in September 2019 and results are expected in mid-2020

CONCLUSIONS

1 This study will optimize and validate the operational deployment of three reward-processing tasks for use in large-scale, international clinical trials

2 The pre-competitive consortium platform established for this study provides a promising framework for the development, optimization and operationalization of additional tasks in the future

For proposals of and/or participation in potential follow-up projects please contact P1vital (https://www.p1vital.com/research/rtoc/; abilderbeck@p1vital.com)

Disclosures

The authors met the criteria for authorship as recommended by the International Committee of Medical Journal Editors. **GRD**, **ACB**, **AH** and **ARa** are employees of P1vital Ltd. **RD** and **JK** are full-time employees of P1vital Products Ltd. **SP** and **AD** are full-time employees of Boehringer Ingelheim. **DU** is a full-time employee of F. Hoffmann-La Roche. **DP** is a full-time employee of Janssen Pharmaceutica. **JT** and **WJM** are full-time employees of Blackthorn Therapeutics. **CM**, **SRC**, and **ES** are full-time employees of Lundbeck. **DM** and **VB-A** are full time employees of Biotrial Neuroscience. **VP** has been a consultant to or has received honoraria or grants from AstraZeneca, Bristol-Myers Squibb, Janssen Cilag, Lundbeck, Otsuka, Servier, Medtronic, and Exeltis. **DH**, **AS**, **ARe**, **GP**, and **ME** declare no conflicts of interest.

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RTOC Reward Task Optimisation Consortium

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This version (dated October 9, 2019) is intended to support further communication on the RTOC project