PRISM: Psychiatric Ratings using Intermediate Stratified Markers

Project Coordinator: Prof. dr. Martien Kas (University of Groningen, NL)
Project Leader: Dr. Hugh Marston (Lilly, UK)
From diagnose to biology
Disease diversity
PRISM’s general concept:
“Providing quantitative biological measures to facilitate the discovery and development of new treatments for social and cognitive deficits in Alzheimer’s disease, schizophrenia and depression”

Adapted from: Thomas R. Insel and Bruce N. Cuthbert, Science, May 2015

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.
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Human and rodent homologies

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Homologies in evoked related potentials

Kas, Penninx, Sommer, Serretti, Arango, & Marston, Neuroscience & BioBehavioural Reviews, in press

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Neuroscience & Biobehavioral Reviews: Special Issue
Quantitative neurosymptomatics; linking quantitative biology to Neuropsychiatry

Guest Editors:
Martien Kas* (University of Groningen, Groningen, The Netherlands) *Managing editor
Hugh Marston (Eli Lilly & Company, Windlesham, UK)
Alessandro Serretti (University of Bologna, Bologna, Italy)

Manuscripts:
1. A quantitative approach to neurosymptomatics: the why and the how M Kas et al – in press
3. Commentary: Operationalization of RDoCs as an approach to the study of social withdrawal in schizophrenia and Alzheimer’s disease B Cuthbert (NIMH) – in press
4. Defining and objective assessments of social withdrawal in schizophrenia and Alzheimer’s dementia patient populations N van der Wee et al – in press
5. Quantitative and translational measures of attention in schizophrenia, Alzheimer’s disease, and major depressive disorder A Serretti et al – in press
6. Electrophysiological assessments of sensory processing dysfunction in schizophrenia and Alzheimer’s dementia P Danjou et al in press
7. Commentary: The challenges of quantitative biology in the study of social withdrawal in schizophrenia and Alzheimer’s disease W T Carpenter – in press
8. Overview of the clinical implementation of a study exploring social withdrawal in schizophrenia and Alzheimer’s disease Amy Bilderbeck et al – in press
9. Commentary: PRISM project viewed from the regulatory perspective Maria Tome et - in press
10. The reverse translation of a quantitative neuropsychiatric framework into pre-clinical studies B Hengerer et al – in press
11. Sleep disturbances and (other) neuropsychiatric symptoms in neurodegeneration Winsky-Sommerer et al - in press
12. Multisensory cortical processing and dysfunction across the neuropsychiatric spectrum Hornix et al – in press

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Clinical deep phenotyping study
Study design

Screening and Assessment Day 1
- 5.5 hours duration
- Full screening
- Inclusion/Exclusion
- Questionnaires
- Behavioural testing
- BEHAPP
- Blood draw

Pre-screening:
- Telephone/internet screen
- Roughly 40% eligible

Assessment Day 2
- 5 hours duration
- MRI / EEG practice
- fMRI 1 (80 min)
- EEG 1 (60 min)

Assessment Day 3
- 5 hours duration
- MRI / EEG practice
- fMRI 2 (80 min)
- EEG 2 (50 min)

Follow-up (+42 days):
BEHAPP
WHODAS
SFS

Max 12 weeks study length (aim for all data collected within 6 weeks)
Recruitment Estimated vs. Actual

- Estimated actual
- Actual

Recruitment as of 20/10/2018

n = 128

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Futility analysis
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## Endpoints

<table>
<thead>
<tr>
<th>Modality</th>
<th>Endpoint</th>
</tr>
</thead>
<tbody>
<tr>
<td>EEG Visit 2</td>
<td>various</td>
</tr>
<tr>
<td>Anatomical MRI</td>
<td>volume</td>
</tr>
<tr>
<td></td>
<td>thickness</td>
</tr>
<tr>
<td></td>
<td>area</td>
</tr>
<tr>
<td>BOLD fMRI Resting State</td>
<td>DMN</td>
</tr>
<tr>
<td></td>
<td>seed-maps</td>
</tr>
<tr>
<td>BOLD fMRI Facial Expression</td>
<td>mean z-score in regions of interest</td>
</tr>
<tr>
<td>Processing Task (FEP)</td>
<td></td>
</tr>
<tr>
<td>BOLD fMRI Virtual Morris Water</td>
<td>mean z-score in regions of interest</td>
</tr>
<tr>
<td>Maze (VMWM)</td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Modality</th>
<th>Endpoint</th>
</tr>
</thead>
<tbody>
<tr>
<td>BOLD fMRI Monetary and Social Incentive Delay task (MSID)</td>
<td>mean z-score in regions of interest</td>
</tr>
<tr>
<td>Diffusion Imaging</td>
<td>FA, MD, MO</td>
</tr>
<tr>
<td>Facial Expression Recognition Task (FERT; Behaviour)</td>
<td>various</td>
</tr>
<tr>
<td>Hinting Task (Behaviour)</td>
<td></td>
</tr>
<tr>
<td>Digit Symbol Substitution Task (DSST; Behaviour)</td>
<td>various</td>
</tr>
<tr>
<td>Effort Expenditure for Rewards Task (EEfRT; Behaviour)</td>
<td>various</td>
</tr>
<tr>
<td>Continuous Performance Test (CPT; Behaviour)</td>
<td>various</td>
</tr>
</tbody>
</table>

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Futility results for individual endpoints

Regional Volume

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How to assess longitudinal and objective measures of social withdrawal in a trans-diagnostic manner?
Think back over the past 30 days and answer these questions, thinking about how much difficulty you had doing the following activities. For each question, please circle only one response.

### Getting along with people

<table>
<thead>
<tr>
<th>D4.1</th>
<th>Dealing with people <strong>you do not know</strong>?</th>
<th>None</th>
<th>Mild</th>
<th>Moderate</th>
<th>Severe</th>
<th>Extreme or cannot do</th>
</tr>
</thead>
<tbody>
<tr>
<td>D4.2</td>
<td>Maintaining a friendship?</td>
<td>None</td>
<td>Mild</td>
<td>Moderate</td>
<td>Severe</td>
<td>Extreme or cannot do</td>
</tr>
<tr>
<td>D4.3</td>
<td>Getting along with people who are <strong>close</strong> to you?</td>
<td>None</td>
<td>Mild</td>
<td>Moderate</td>
<td>Severe</td>
<td>Extreme or cannot do</td>
</tr>
<tr>
<td>D4.4</td>
<td>Making new friends?</td>
<td>None</td>
<td>Mild</td>
<td>Moderate</td>
<td>Severe</td>
<td>Extreme or cannot do</td>
</tr>
</tbody>
</table>

### Participation in society

In the past 30 days:

<table>
<thead>
<tr>
<th>D6.1</th>
<th>How much of a problem did you have in <strong>joining in community activities</strong> (for example, festivities, religious or other activities) in the same way as anyone else can?</th>
<th>None</th>
<th>Mild</th>
<th>Moderate</th>
<th>Severe</th>
<th>Extreme or cannot do</th>
</tr>
</thead>
</table>
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BEHAPP – passive remote behavioural monitoring

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BEHAPP features

Current features:
- Call History
- SMS Messaging History
- Interval based WiFi Scans
- Interval based Bluetooth Device Scans
- Location Data
- App Usage

Upcoming features:
- Accelerometer
- Ambient noise
- Ambient light

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BEHAPP: Home stay scores

preliminary results
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**BEHAPP: correlation with scales**

*preliminary results*
Preclinical battery
Alignment and harmonization of the pre-clinical and clinical behavioral test batteries

<table>
<thead>
<tr>
<th>Human task</th>
<th>Rodent equivalent</th>
<th>Contribution by</th>
</tr>
</thead>
<tbody>
<tr>
<td>Smartphone application</td>
<td>Social group behavior</td>
<td>RUMC, RUG, BI</td>
</tr>
<tr>
<td>Social Functioning scale</td>
<td>Social group behavior</td>
<td>RUMC, RUG, BI</td>
</tr>
<tr>
<td>Social incentive delay – MRI: 15 min. MID, incl. motivation – (outside the scanner)</td>
<td>Social conditioned place preference</td>
<td>RUMC, RUG, BI, Biotrial No task coupling to MRI</td>
</tr>
<tr>
<td></td>
<td>Three chamber task</td>
<td></td>
</tr>
<tr>
<td>Resting State eyes open and closed</td>
<td>Resting state EEG.</td>
<td>RUG, Eli Lilly, Janssen, Biotrial</td>
</tr>
<tr>
<td>MMN Auditory (passive)</td>
<td>MMN auditory</td>
<td>RUG, (Eli Lilly), Janssen, Biotrial</td>
</tr>
<tr>
<td>Steady-state auditory-evoked potential</td>
<td>Steady-state auditory-evoked potentials</td>
<td>RUG, Eli Lilly, Janssen, Biotrial</td>
</tr>
<tr>
<td>N-back – with fMRI</td>
<td>Odor Span Task</td>
<td>Biotrial, Eli Lilly</td>
</tr>
<tr>
<td>Arena Task- with fMRI</td>
<td>Morris Water Maze</td>
<td>Biotrial, Eli Lilly</td>
</tr>
<tr>
<td>Continuous Performance task</td>
<td>5C-CPT</td>
<td>RUMC</td>
</tr>
</tbody>
</table>
Automated longitudinal analyses of social behaviours
Identification of biological substrates underlying transdiagnostic domains
Genome wide association studies

= preliminary GWAS of a SW measure in 342,490 adult participants from the UK Biobank → 584 genome-wide significant SNPs → 20 independent loci

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Some deliverable highlights

- Implemented a transdiagnostic clinical study that passed futility analysis
- Upcoming Neuroscience & Biobehavioural Reviews special issue on the PRISM project (with 9 manuscripts and 3 commentaries)
- Implemented a parallel preclinical test battery to enable the back translation of findings from PRISMs clinical study.
- Genetic studies of social withdrawal in humans revealing significant hits in known and novel pathways
- Starting discussions on initiating the regulatory path for a transdiagnostic biomarkers
- Excellent engagement with public, patients and researchers through ECNP led dissemination activities
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