Biomarkers and Metabolomics of Childhood Aggression

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Aggression in Children: Unraveling gene-environment interplay to inform Treatment and InterventiON strategies

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Introduction

- Research in the biochemical basis of aggressive disorders has focused on putative biomarkers of various classes in isolation:
  - Aggression biochemistry research will benefit from a more holistic approach as provided by metabolomics (Hagenbeek, et al. 2016).
  - A previous metabolomics study suggested a relationship between serum amino acid levels with aggression and psychopathy in adult males (Gulsun, et al. 2016).
  - By identifying urinary biomarkers of aggression ACTION aims to unravel processes and pathways leading to childhood aggression.

Data collection & Pilot Studies

- ACTION aims to simultaneously collect DNA material, urine samples, health information & aggression score in children of 7 to 12 years of age registered with the Netherlands Twin Register (NTR).
- Prior to start data collection a Practical Pilot was conducted to test the urine collection protocol in 6 non-aggressive children.

Biochemical Study

Table 1. List of candidate biomarkers for ACTION

<table>
<thead>
<tr>
<th>Substance</th>
<th>Candidate biomarkers</th>
<th>ACTION metabolomics platform</th>
</tr>
</thead>
<tbody>
<tr>
<td>P</td>
<td>Cholylglycine</td>
<td>Total oxidative capacity</td>
</tr>
<tr>
<td>Enkephalin- Methionine</td>
<td>Serotoninamide albumin</td>
<td>8-hydroxydeoxyguanosine</td>
</tr>
<tr>
<td>Enkephalin-Leucine</td>
<td>Interleukin-6</td>
<td>Ox-blutin-in (biporphin)</td>
</tr>
<tr>
<td>Beta-endorphin</td>
<td>Procalcitonin</td>
<td>Hexanoyl lysine adduct</td>
</tr>
<tr>
<td>Dynorphin</td>
<td>Albumin</td>
<td>Malondialdehyde</td>
</tr>
<tr>
<td>Neurotensin</td>
<td>Creatine</td>
<td>Neopterin</td>
</tr>
<tr>
<td>C-peptide</td>
<td>Glucose</td>
<td>Cotinine</td>
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Discovery Phase

- The aim of the Discovery Phase is the establishment of putative childhood aggression biomarkers as identified by the Biochemical Study in 600 monzygotic (MZ) twin pairs selected for their aggression (dis-) concordance status.

Conclusions & Future Directives

- Metabolites can be reliably and reproducibly measured in urine samples of 7-12 year old children as shown in the Technical Pilot.
- Lasso regression for the organic acids identified a model including 4 metabolites: 2-hydroxybutyric acid, Succinic acid, Aspartic acid & Uric acid.
- The predictive value of the model including the 4 organic acids is relatively poor (see Fig 1), though it outperforms age only and adding age to the model increases the predictive accuracy.
- Univariate Follow-up: GEE models correcting for family structure and including age, vitamin use and batch effect as covariates found a significant association with aggression for 2-hydroxybutyric acid (β = 0.31, p = 0.04).
- Further Analyses: The lasso model selection analyses will be repeated in a mixed-model framework in order to correct for family structure.

We would like to thank the twins and their family members who participated in the NTR ACTION project, as well as M.M.L.J.Z. Vandenbosch & M.J. Schouten for their help with the data collection.