Translational Approaches in Addiction

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Stratification and prediction of at risk individuals:

“Neuropsychosocial profiles of current and future adolescent alcohol misusers”

Neuropsychosocial profiles of current and future adolescent alcohol misusers

115 Binge Drinker
Alter 14 Jahre

150 controls (no alcohol at 14 and 16 years)

121 future binge drinkers (16 years)

Classification
91% correct (p=8 x 10^{-6})

Prediction
66% correct (p=4.2 x 10^{-17})

Regularised logistic regression

Whelan et al, Nature (in press)
Praeizision:
gunter schumann, 02/05/2014
Neuropsychosocial profiles of alcohol misuse

- History
- Personality
- Genetics
- Brain
- Cognition
- Demographics

Association of brain region and alcohol abuse

Classification (14 Jahre) Prediction (16 Jahre)

Prediction of alcohol abuse
Single predictors

AUC -- ROC
Full Model
Brief, personality-targeted coping skills interventions and survival as a non-drug user over a 2-year period during adolescence.

Endophenotype concept and heritability

Reward processing: a transdiagnostic endophenotype?
Reward anticipation in 1544 individuals activates 21 distinct brain regions

Reward networks associated with reward anticipation are related to distinct clinical phenotypes.

Genome-wide association* of the reward sensitivity cluster with VPS4a rs16985736 (p=1.30×10^{-7}) and suggestive association with FRMD4a rs11258878 (p=4.30×10^{-7}). *GWAS threshold 1.92×10^{-7}
Reduction of VPS4A expression correlates with decreased presynaptic inhibition and concurrent postsynaptic sensitization. This constellation may result in increased dopaminergic neurotransmission and decreased phasic dopamine and noradrenaline peaks.

A molecular mechanism of reward deficiency?

VPS4a is an AAA ATPase providing energy for the formation of lysosomal “Multi Vesicular Bodies”. After endocytosis MVB’s transport G-protein receptors to lysosomes thus contributing to receptor turnover and regulating synaptic dopamine and noradrenaline signals.

VPS4a (-) Vermehrte Dopamin und NA Ausschüttung

Reduction of VPS4A expression correlates with decreased presynaptic inhibition and concurrent postsynaptic sensitization. This constellation may result in increased dopaminergic neurotransmission and decreased phasic dopamine and noradrenaline peaks.

Insufficient inhibitory control

Reward deficiency

Are genetic factors determinants of reward deficiency vs. insufficient inhibitory control?

Monoamine oxidase A (MAOA) is an enzyme involved in the metabolism of the monoamines, including serotonin, dopamine and noradrenaline.
MAOA rs12843268 genotype is associated with gene expression and ADHD-symptoms in boys (n=190).

Ventro striatal activation is negatively correlated with ADHD symptoms in A-carriers but not in G-carriers of rs12843268.

Left inferior frontal gyrus activation is positively correlated with ADHD symptoms in G-carriers but not in A-carriers of rs12843268.

Reward deficiency and impaired executive control are both associated with ADHD symptoms and stratified by MAOA rs12843268.

Our results suggest that both, insufficient inhibitory control and reward deficiency mechanisms contribute to ADHD symptoms, depending on MAOA genotypes.

Our study is first to dissociate distinct neurobehavioural mechanisms of ADHD symptoms by applying stratification by genotype.

Apart from its mechanistic interest, our finding may aid in developing pharmacogenetic markers for ADHD.

Conclusion:
Genome wide association study of alcohol consumption

**Excavation cohorts**
- N=28,188

**Test cohorts**
- N=21,185

**Functional Characterization**
- Gene expression
- Human brain regions
- Genotype-specific expression
- Behavioral studies
- Transcript analysis

**Exploration cohorts**
- NTRNESDA (n=3361)
- TwinUK (n=1502)
- TwinFinland (n=82)
- SSAGA (n=606)
- NFBC (n=5067)
- LOLipop (n=1237)
- KORA (n=1156)
- ERF (n=590)
- D.E.S.I.R. (n=481)
- COLAUS (n=3733)
- Cambridge (n=1896)
- Turin (n=8944)
- LRGP (n=2431)
- Lille (n=3100)
- Fenland (n=948)
- EGP (n=632)
- ARYA (n=747)

**Schumann et al. PNAS 2011**

**Association of the Guanosine Nucleotide Exchange Factor Rasgrf2 variant rs 26907 with alcohol consumption in males.**

**Functional analysis of Rasgrf2**

**Schumann et al. PNAS 2011**
*RASGRF2* haplotype containing rs26907 is associated with brain activity during reward anticipation and lifetime drinking episodes in boys.

Whole-brain analysis of *RASGRF2* haplotype and BOLD response during reward anticipation activation in the precentral gyrus (FW3, P = 0.05).

Association of V5 activation during reward anticipation with *RASGRF2* haplotype: L-V5: p=0.0495; R-V5: p=0.0697 and lifetime drinking episodes (p=0.008).

Conclusion:

Integrating genetics, neuroimaging and molecular approaches, we are investigating the molecular basis and brain physiology of reward processing.

We identified a gene *VPS4A*, which might influence dopamine homeostasis during reward processing by regulating dopamine and noradrenaline receptor turnover.

We also found a gene, *RASGRF2*, which influences reward anticipation and alcohol intake by regulating dopamine firing rate.
Genome-wide methylation analysis of monozygotic twins discordant for alcohol use disorders (AUD).

Demographics of the AUD-Discordant twin pairs at the age of 25

<table>
<thead>
<tr>
<th>Number of twin pairs</th>
<th>18</th>
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<tbody>
<tr>
<td>Male/Female ratio</td>
<td>7/11</td>
</tr>
<tr>
<td>Alcohol Dependence (A) / Alcohol Abuse (AA)</td>
<td>3/6/2</td>
</tr>
<tr>
<td>24-Hr Symptom Score AA/AU twin, mean (SD)</td>
<td>8.6 (3.36)</td>
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Top hypermethylated Differentially Methylated Regions in the AUD twin compared to the unaffected twin (p<1x10^-5)

Interplay of nociceptin receptors with stress pathways, and neuropeptide and non-peptide neurotransmitters

Jeffrey et al. 2014
A CpG island in the 5' UTR of OPRL1 was differently methylated in the monozygotic twins and associated with binge drinking in 14 year old participants of the IMAGEN study (n=499). Methylation was assessed through Sequenom Mass ARRAY system and measured in peripheral blood.

Methylation of nociceptin receptor gene (OPRL1) is associated with psychosocial stress and binge drinking in 14 year old IMAGEN participants.

Ventral striatal activation during reward anticipation is associated with nociceptin receptor gene (OPRL1) methylation and binge drinking.
Reward anticipation:

Extended reward system:
FRMD4
VPS4A

Cortical/environmental regulation:
RASGRF2

VTA:

Potential for stratified medicine:

- Target identification
- Identification of risk groups
- Neurobehavioural stratification
- Transdiagnostic characterisation of reward processing

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