previous results: CFN PET

Elevated Carfentanil uptake in abstinent alcoholics

y = 8  z = -6  x = -10
y = -4  z = -20

p = 0.05 unilateral corrected for whole volume
Background: $[^{11}\text{C}]$Carfentanil

- selective $\mu$-opioid receptor ligand

- Agonist
Aim

• Pharmacokinetic analysis of group differences (dependency on delivery?)

• Correlation with Alcohol craving (OCDS)?

• *Exploratory*: impact of A118G genotype (increased affinity of μOR to β-endorphin)?
Methods

Inclusion criteria (patients):

- Alcohol dependence according to ICD-10 and DSM IV
- 1st PET scan: 2-3 weeks after (in-patient) detoxification
- No past history of drug dependence or current drug abuse
- No psychotropic medication for >1 week
## Methods: Subjects

<table>
<thead>
<tr>
<th>Subjects</th>
<th>1st PET Scan (two weeks of abstinence)</th>
<th>2nd PET Scan (five weeks after PET1)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Alcoholics (group 1)</td>
<td>15 (2*)</td>
<td>12 (1*)</td>
</tr>
<tr>
<td>Alcoholics (group 2)</td>
<td>10 (3*)</td>
<td>10 (3*)</td>
</tr>
<tr>
<td>healthy controls</td>
<td>10 (1*)</td>
<td></td>
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</tbody>
</table>

*N* genetic variant A118G

Alcoholics (group 2) received Naltrexone medication.
Methods: PET

**CFN-Injection**: Bolus, 400-800MBq, 1.7-9.1µg

**PET-Scanner**: GE Advance

**Acquisition**: 2D mode, 0-72 min. p.i.

**Image reconstruction**: 128*128 pixel = 30cm

**Realignment**: SPM99 (three fiducial markers)

**Spatial normalisation**: SPM99 (CFN 0-5min p.i. versus SPM perfusion template)

- for ROI analysis: linear transformation only
- for voxelwise analysis: linear and nonlinear transformation
**Methods**: kinetic modelling

**Reference tissue quantification of $V_3'' = k_3/k_4$**:

- **Logan graphical analysis (LGA)**
  (2 d.o.f., $k_2' = 0.1\text{min}^{-1}$, regression interval 18-60min p.i.)
- **SRTM** (Lammertsma and Hume)
  (3 d.o.f.)
- **MTRM2** (Ichise)
  (2 d.o.f., $k_2' = 0.1\text{min}^{-1}$, $t^* = 18\text{min}$)

**Primary study goals**: LGA (ROI and voxel-level)

**Validation / Discussion**: LGA, SRTM, MRTM2, interindividually averaged TAC (heterogeneity error from variable perfusion negligible in simulations)
Methods: ROI definition

<table>
<thead>
<tr>
<th>ROI</th>
<th>Size</th>
</tr>
</thead>
<tbody>
<tr>
<td>ventral striatum</td>
<td>2 * 0.36ml</td>
</tr>
<tr>
<td>putamen</td>
<td>2 * 0.67ml</td>
</tr>
<tr>
<td>caudate</td>
<td>2 * 0.40ml</td>
</tr>
<tr>
<td>prefrontal cortex</td>
<td>2 * 3.4ml</td>
</tr>
<tr>
<td>parietal cortex</td>
<td>2 * 4.4ml</td>
</tr>
</tbody>
</table>

Optionally individual adjustment of ROI position to early summation images (0-5 min p.i.)
Results: CFN delivery and washout

(a) higher perfusion ($K_1$) in alcoholics
(b) higher receptor availability $k_3/k_4$
(c) negligible difference in washout $k_2'$
(d) negligible difference in distribution volume:

- mean CFN concentration 30-60min
  - alcoholics (n=20): $10.4\pm2.3*10^{-4}\%ID/ml$ (alc)
  - controls (n=9): $9.6\pm1.6*10^{-4}\%ID/ml$ (controls)

y-axis: CFN concentration, normalized by occipital area under curve 0-60 min. p.i.
Results: CFN delivery and washout

- rare variant A118G (n=5)
- common variant (n=20)

Ventral striatum

Occ cortex
$T=2.83, p=0.009$
**Results: ROI-analysis (LGA): V₃"**

<table>
<thead>
<tr>
<th>Region of Interest (ROI)</th>
<th>Alcoholics 3 weeks after detoxification</th>
<th>Alcoholics 8 weeks after detoxification</th>
<th>control subjects</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ventral Striatum</td>
<td>2.67 ± 0.38</td>
<td>2.80 ± 0.43</td>
<td>2.25 ± 0.43</td>
</tr>
<tr>
<td>Putamen</td>
<td>1.83 ± 0.26</td>
<td>1.85 ± 0.28</td>
<td>1.58 ± 0.32</td>
</tr>
<tr>
<td>Caudate</td>
<td>2.04 ± 0.34</td>
<td>2.11 ± 0.32</td>
<td>1.75 ± 0.43</td>
</tr>
<tr>
<td>Prefrontal cortex</td>
<td>1.08 ± 0.14</td>
<td>1.11 ± 0.15</td>
<td>1.01 ± 0.27</td>
</tr>
<tr>
<td>Parietal Cortex</td>
<td>0.53 ± 0.10</td>
<td>0.52 ± 0.09</td>
<td>0.51 ± 0.17</td>
</tr>
</tbody>
</table>
**Results:** parametric group images ($V_3'' = k_3/k_4$)

- Alcoholics: $n=20$
- Healthy controls: $n=9$
- Difference

![Image showing parametric group images for alcoholics and healthy controls with a color scale from 0 to 3.](image-url)
**Results:** correlation with craving

**difference: alcoholics versus control**

*TT coordinates of max. diff.:*

- right: [17.8/9.2/-9.7]
- left: [20.8/9.2/-9.7]

μOR availability ($V_3'$)

<table>
<thead>
<tr>
<th>Craving (OCDS)</th>
<th>left</th>
<th>right</th>
</tr>
</thead>
<tbody>
<tr>
<td>$r=0.55, p=0.04$</td>
<td></td>
<td>$r=0.75, p=0.002$</td>
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Graph showing correlation with craving.
Results: SPM analysis (correlation with craving)
Results: V3" in the voxel-of-interest

Correlation with...

- **OCDS**: $r = 0.55$, $p = 0.04$ (left) $r = 0.75$, $p = 0.002$ (right)
- Age of onset $r = -0.35$
- Number of cigarettes smoked: $r = -0.26$
- SADQ score: $r = 0.18$
- Age: $r = 0.01$

Subgroups:

- Family history
  - positive: $2.80 \pm 0.32$ (n=8)
  - negative: $2.76 \pm 0.24$
- Age of onset
  - early: $2.92 \pm 0.26$ (n=4)
  - late: $2.73 \pm 0.27$
- Smoker
  - no: $2.79 \pm 0.10$ (n=3)
  - yes: $2.77 \pm 0.31$
Discussion

↑μ-Receptor availability corresponds to

(1) ↑Receptor density or
(2) ↓Competition with endogenous ligand
Discussion: mass effect?
Discussion: comparison of quantification methods

- Logan
- SRTM
- MRTM2
Discussion

higher variability in Logan's graphical analysis
**Discussion**: negligible noise dependent bias

<table>
<thead>
<tr>
<th></th>
<th>mean $V_3''$ (Logan GA)</th>
<th>$V_3''$ from average curve (Logan GA)</th>
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</thead>
<tbody>
<tr>
<td>controls (n=9)</td>
<td>2.25</td>
<td>2.26</td>
</tr>
<tr>
<td>alcoholics (n=20)</td>
<td>2.67</td>
<td>2.68</td>
</tr>
<tr>
<td>alcoholics</td>
<td>2.27</td>
<td>2.30</td>
</tr>
<tr>
<td>(n=5, A118G)</td>
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</table>
Conclusions

• Abstinent alcoholics show significantly elevated μOR availability in the (ventral) striatum (and prefrontal cortex)

• Elevated μOR are closely correlated with alcohol craving

• Further investigations of functional relations between the μ-opiate system and alcohol dependence seem possible with CFN-PET