previous results: CFN PET

Elevated Carfentanil uptake in abstinent alcoholics

p = 0,05 unilateral corrected for whole volume
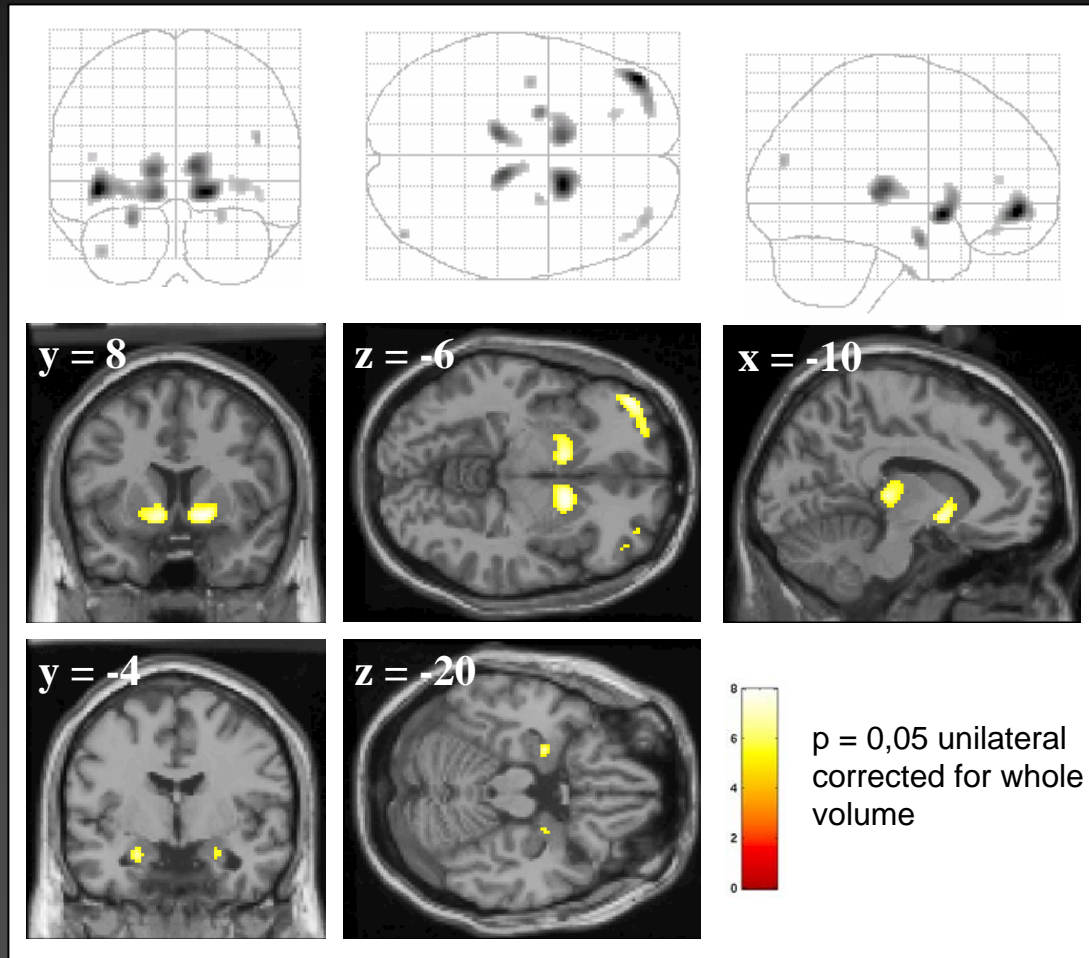
Background: [^{11}C]Carfentanil

- **selective µ-opiate 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 ß-endorphines)?**

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

	1st PET Scan (two weeks of abstinence)	2nd PET Scan (five weeks after PET1)
Alcoholics (group 1)	15 (2*)	12 (1*)
Alcoholics (group 2)	10 (3*)	10 (3*) Naltrexone medication
healthy controls	10 (1*)	

*genetic variant A118G

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

<u>Reference tissue quantification of $V_3''=k_3/k_4$:</u>

- **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*=18min)

<u>Primary study goals:</u> LGA (ROI and voxel-level)

<u>Validation / Discussion:</u> LGA, SRTM, MRTM2, interindividually averaged TAC (heterogeneity error from variable perfusion negligible in simulations)

Methods: ROI definition

ROI	Size
ventral striatum	2 * 0.36ml
putamen	2 * 0.67ml
caudate	2 * 0.40ml
prefrontal cortex	2 * 3.4ml
parietal cortex	2 * 4.4ml

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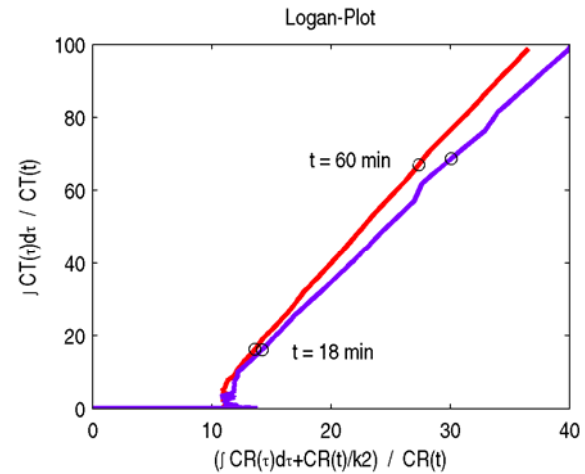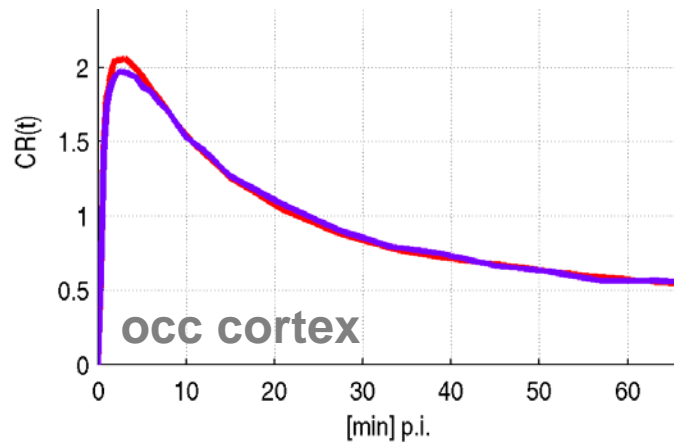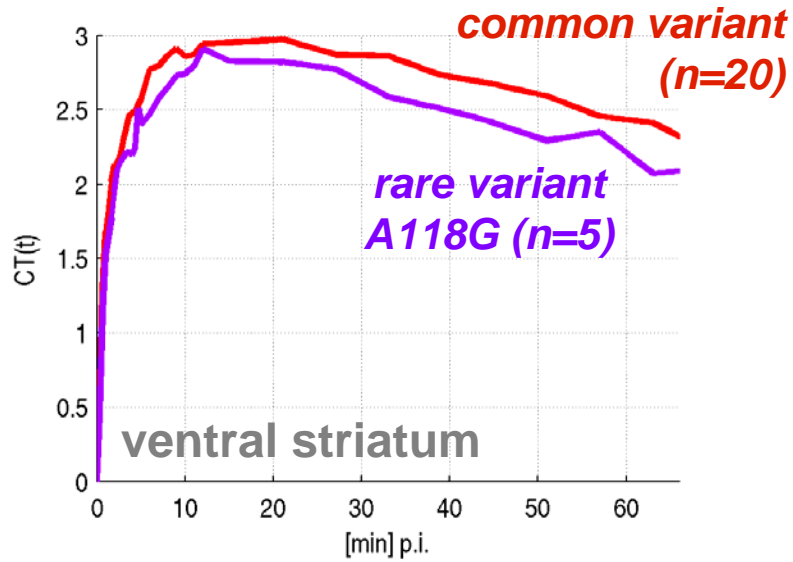
Results: CFN delivery and washout

y-axis: CFN concentration, normalized by occipital area under curve 0-60 min. p.i.
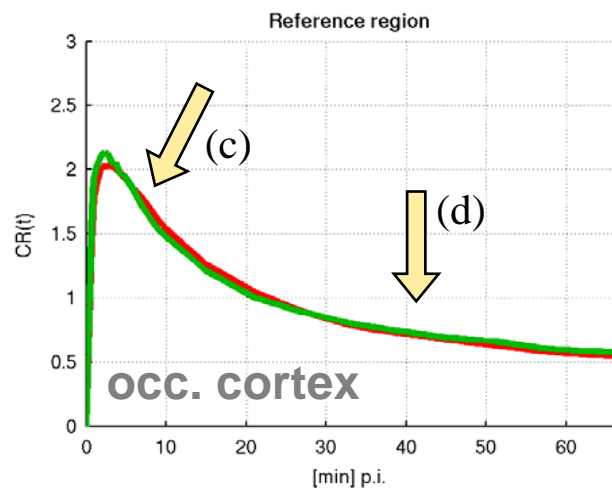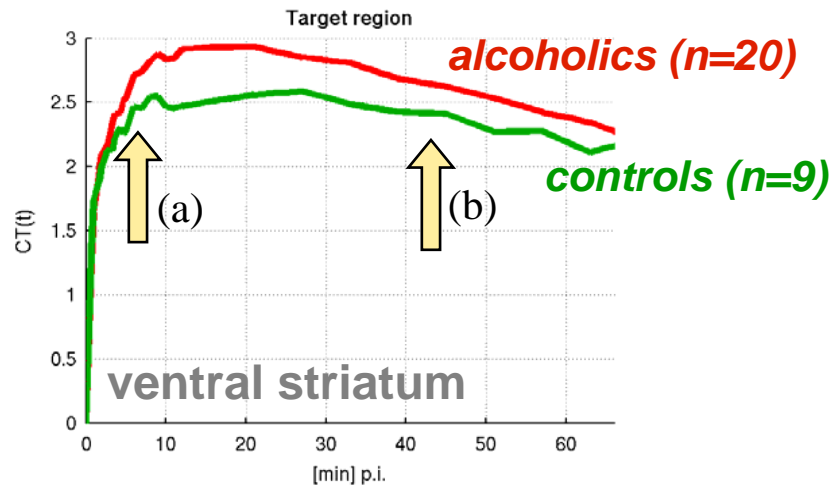
(a) **higher perfusion (K_1) in alcoholics**
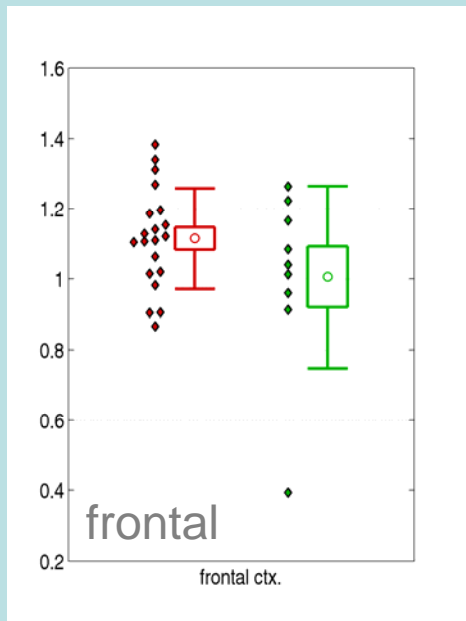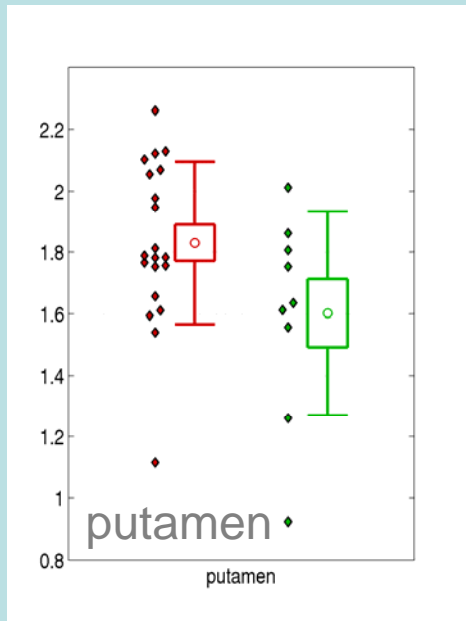
(b) **higher receptor availability k_3/k_4**

(c) **negligible difference in washout k_2'**

(d) **negligible difference in distribution volume :**

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

Results: CFN delivery and washout

VS — *T=2.83, p=0.009* — ventral striatum

putamen

n.c. — N.c.

frontal — frontal ctx.

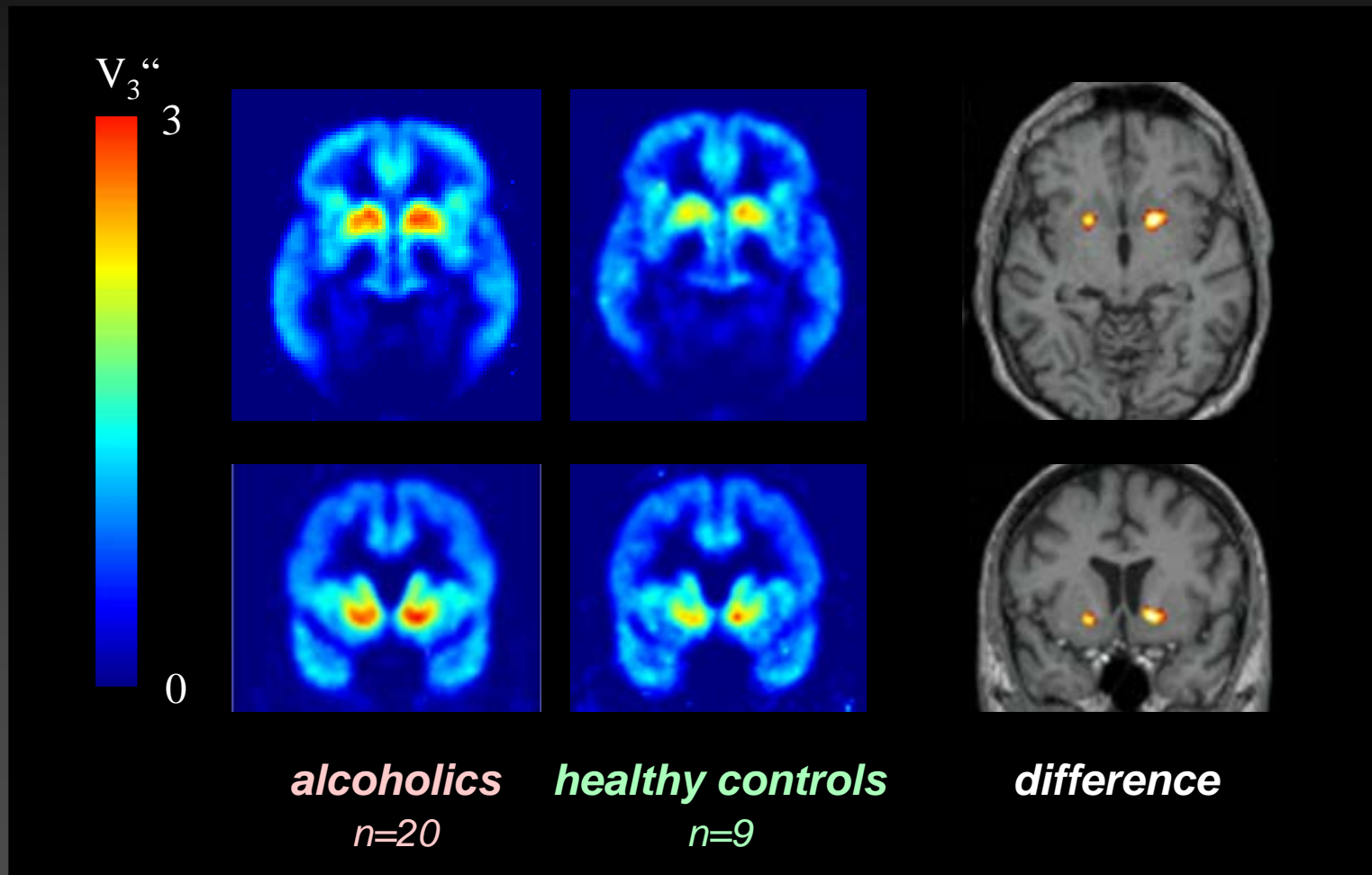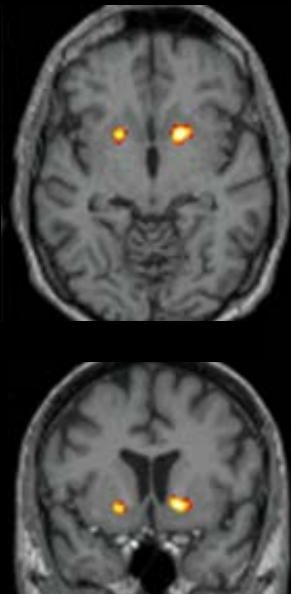parietal — parietal ctx.
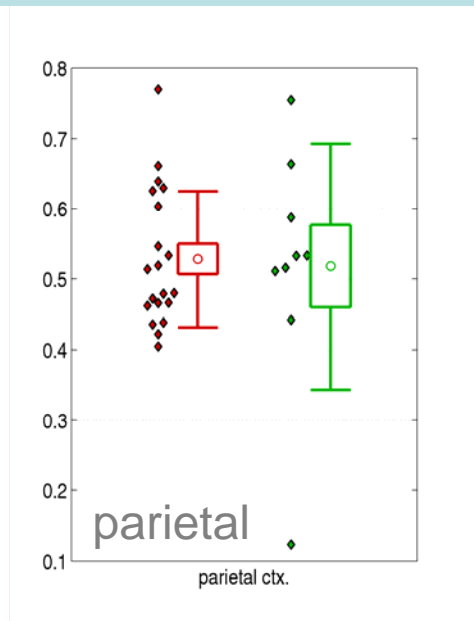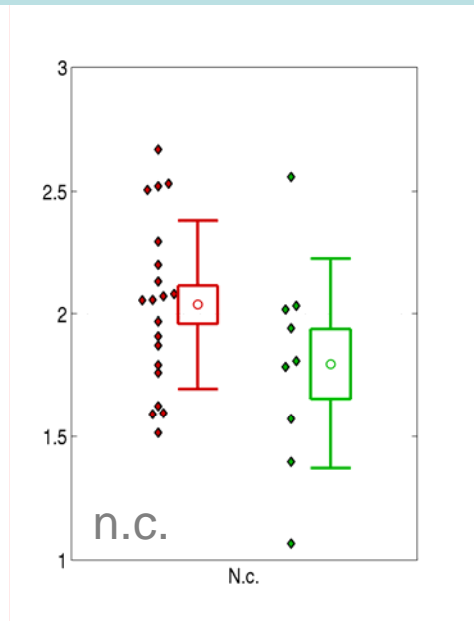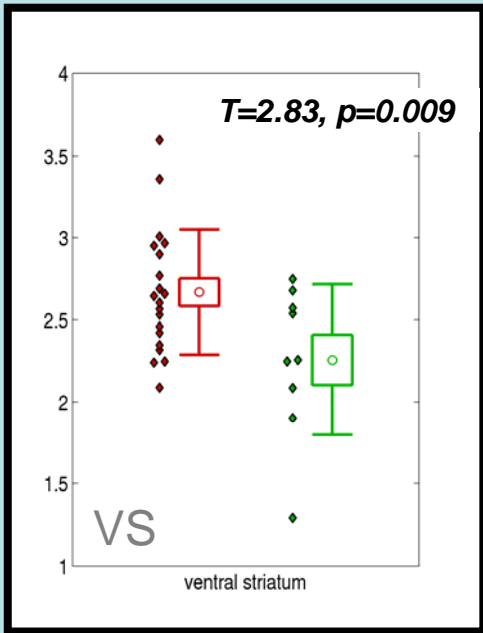
Results: ROI-analysis (LGA): V_3''

Region of Interest (ROI)	Alcoholics 3 weeks after detoxification	Alcoholics 8 weeks after detoxification	control subjects
Ventral Striatum	2.67 ± 0.38	2.80 ± 0.43	2.25 ± 0.43
Putamen	1.83 ± 0.26	1.85 ± 0.28	1.58 ± 0.32
Caudate	2.04 ± 0.34	2.11 ± 0.32	1.75 ± 0.43
Prefrontal cortex	1.08 ± 0.14	1.11 ± 0.15	1.01 ± 0.27
Parietal Cortex	0.53 ± 0.10	0.52 ± 0.09	0.51 ± 0.17

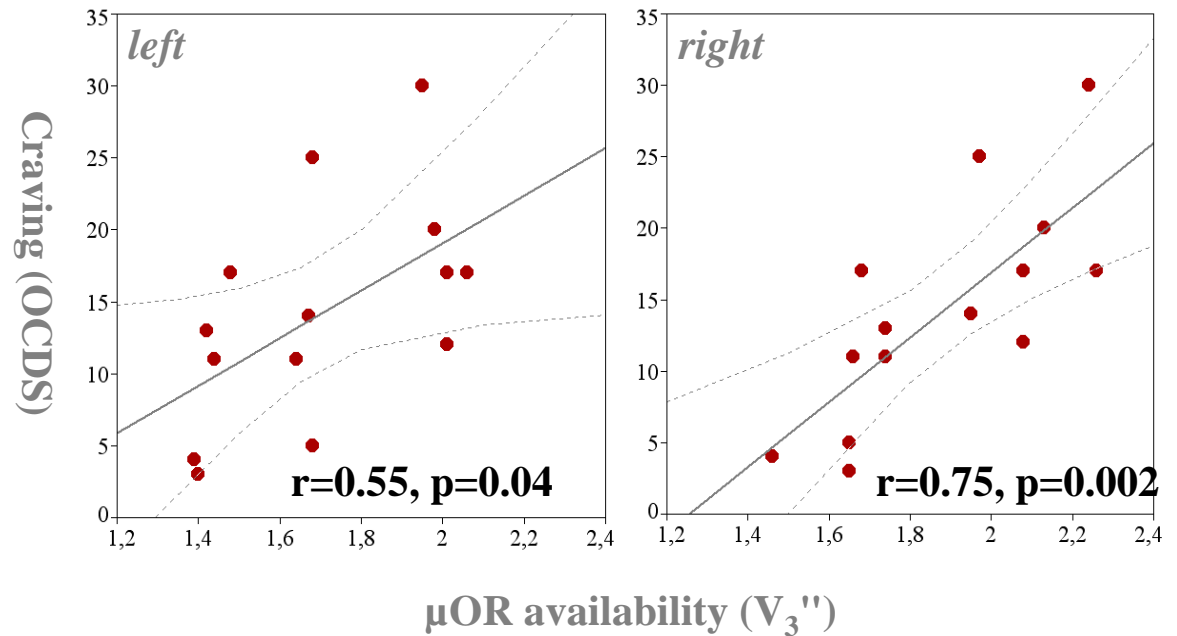# Results: parametric group images ($V_3''=k_3/k_4$)

Results: 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:
- Familiy history   positive: 2.80±0.32 (n=8)
  negative: 2.76±0.24
- age of onset   early: 2.92±0.26 (n=4)
  late: 2.73±0.27
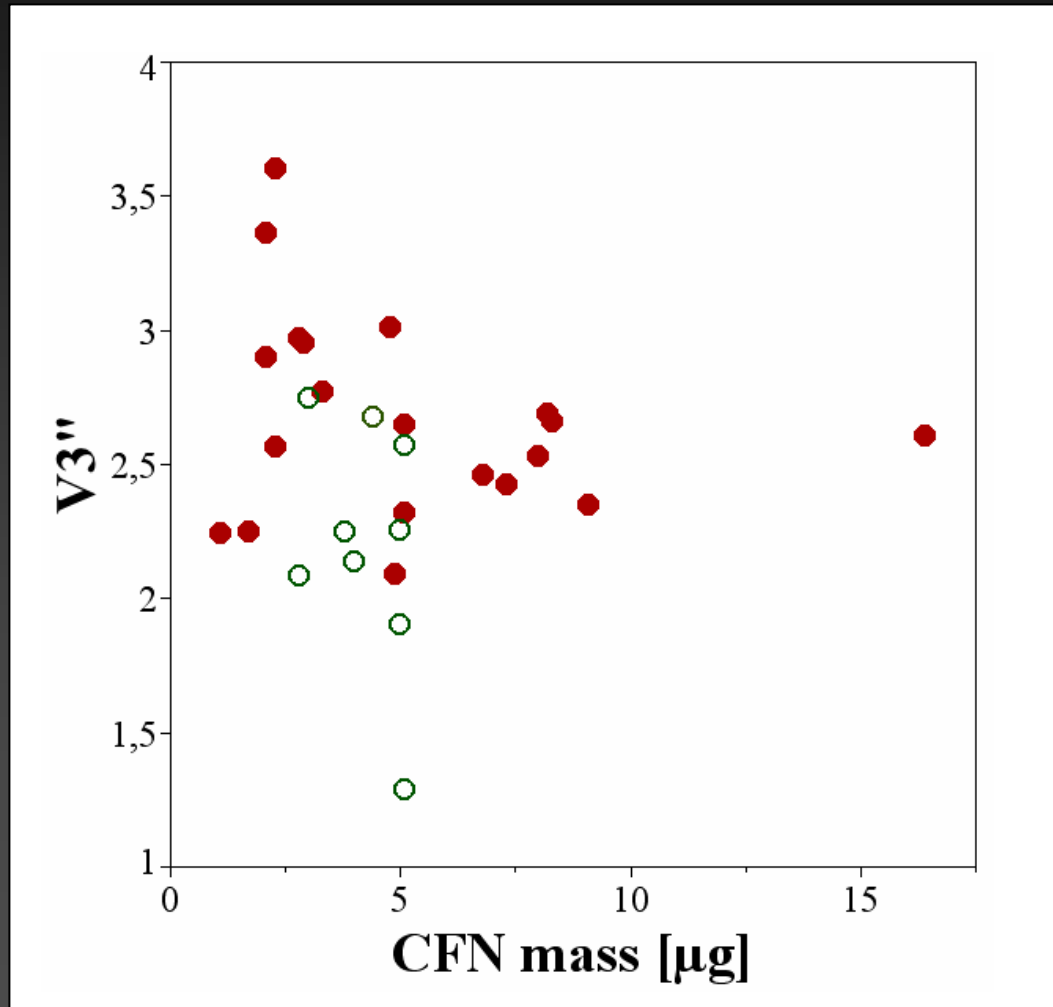- Smoker   no: 2.79±0.10 (n=3)
  yes: 2.77±0.31
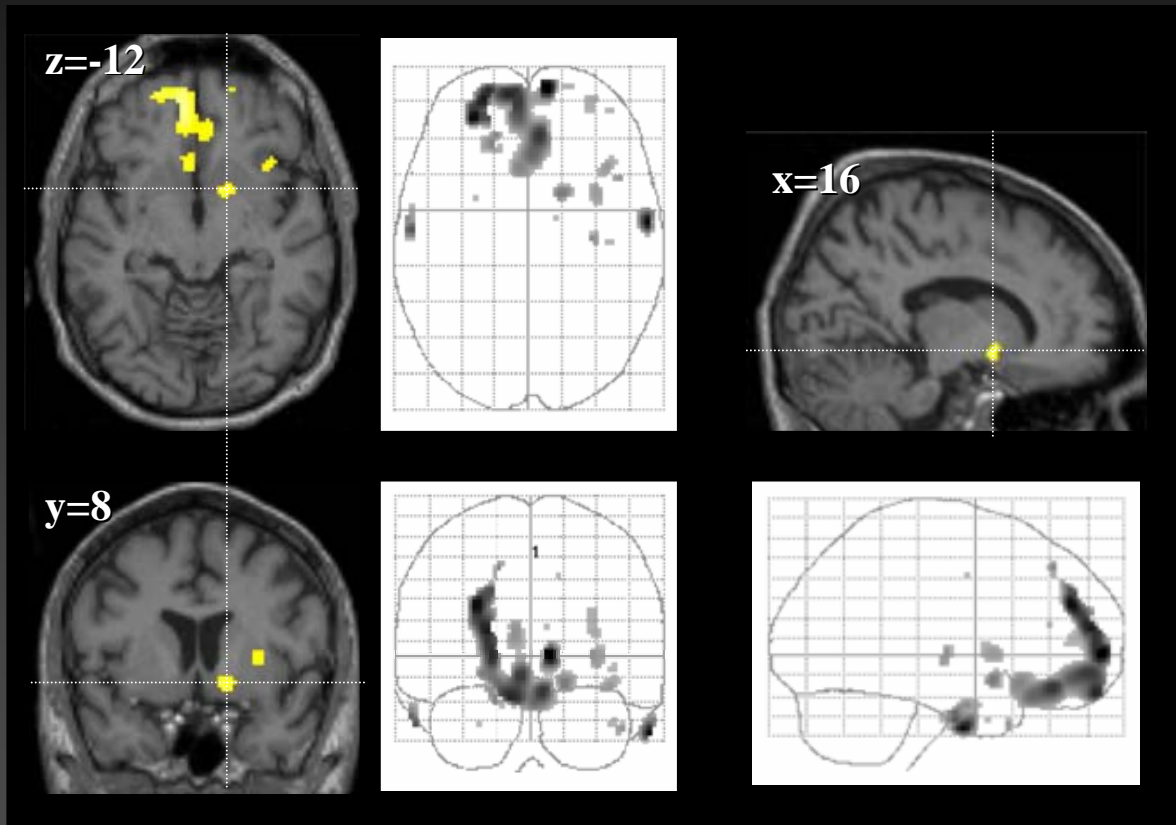
Discussion

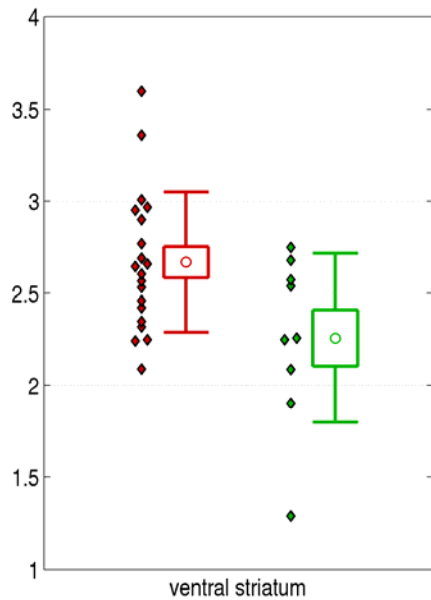↑µ-Receptor availability corresponds to

(1) ↑Receptor density *or*
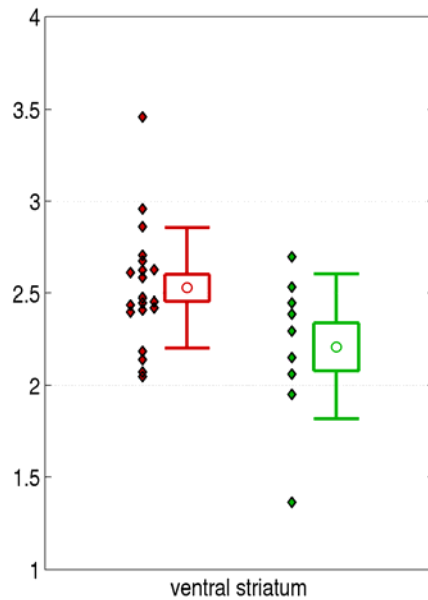
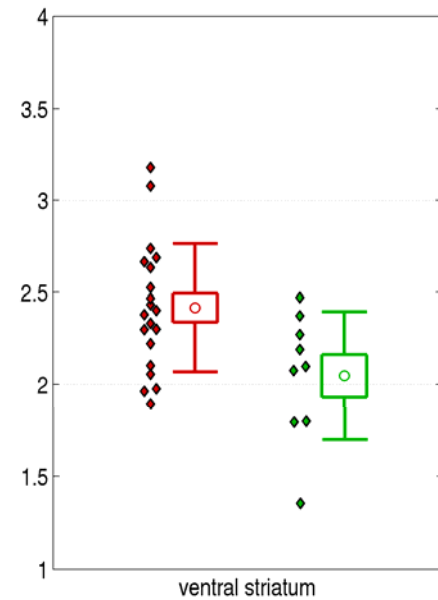(2) ↓Competition with endogeneous ligand

Discussion: mass effect?

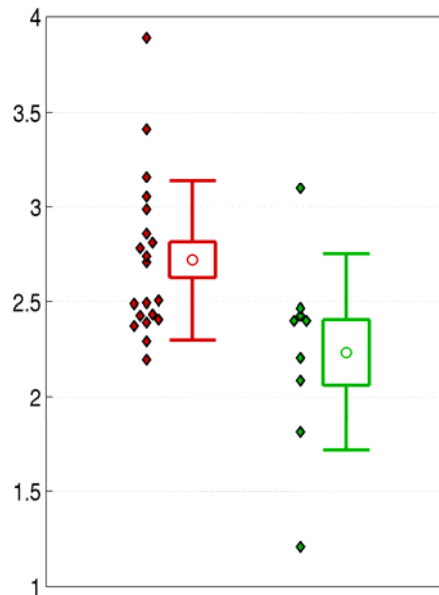# **Discussion**: comparison of quantification methods

Logan   SRTM   MRTM2
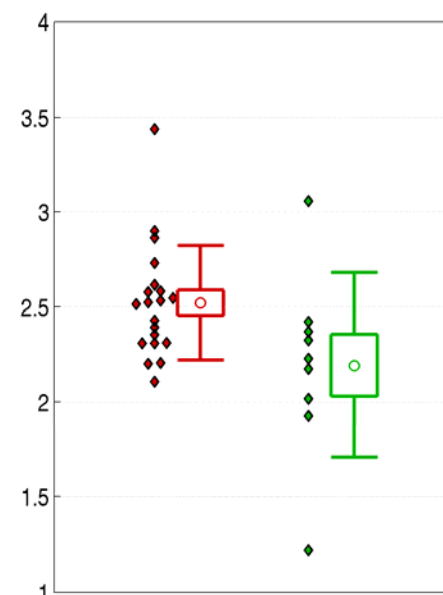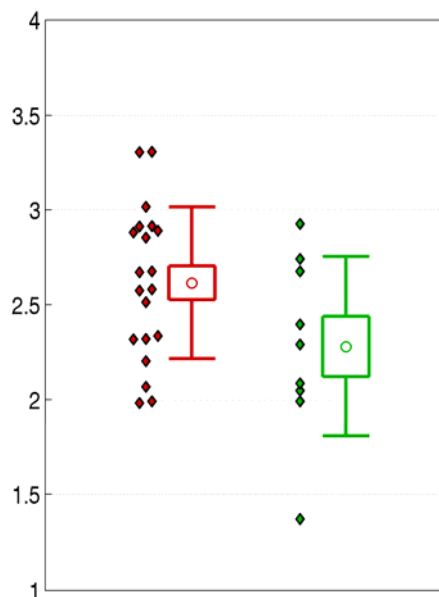
Discussion
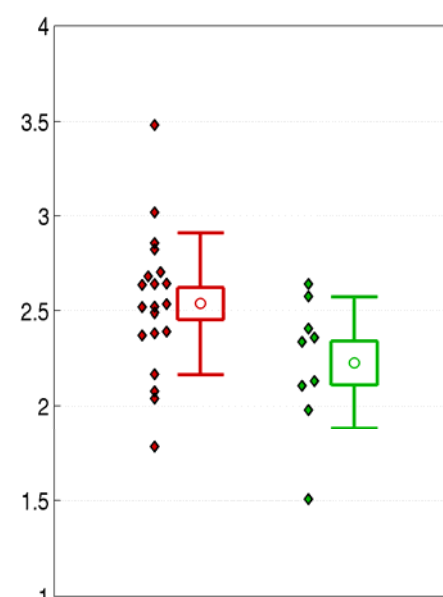
higher variability in Logan's graphical analysis

Logan   SRTM

ventral striatum (left)   ventral striatum (left)

Discussion: negligible noise dependent bias

	mean V_3'' (Logan GA)	V_3'' from average curve (Logan GA)
controls (n=9)	2.25	2.26
alcoholics (n=20)	2.67	2.68
alcoholics (n=5, A118G)	2.27	2.30

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