Activation neuroimaging studies - $GABA_A$ receptor function - alcohol cues in alcoholism

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Study 1. GABA A receptor sensitivity

Hypothesis

- Alcoholics would have reduced GABA-A receptor sensitivity = tolerance

Test = challenge with midazolam – controlling for brain entry and receptor occupation – new PET pk/pd paradigm

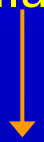
- Friston et al 1996 JCBFM

Subject characteristics

	Control ± s.d [n=10]	Alcoholics ± s.d [n=11]
Age	46.2 ± 8.1	44.45 ± 6.12
SADQ [10,10]	4.1 ± 5.7	36.5 ± 10.0
Years of heavy drinking	N/A	20.1 ± 6.1
SSAI [8,11]	27.4 ± 6.7	32.5 ± 9.4
STAI [10,11]	32.7 ± 5.8	40.4 ± 15.3
BDI [10,7]	3.1 ± 2.8	6.3 ± 3.9
Family history	2	2

Scanned at least 6 weeks after withdrawal

Inject tracer
[^{11}C]flumazenil

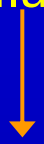


T=0

PET scan (105 min)

Inject tracer
[^{11}C]flumazenil

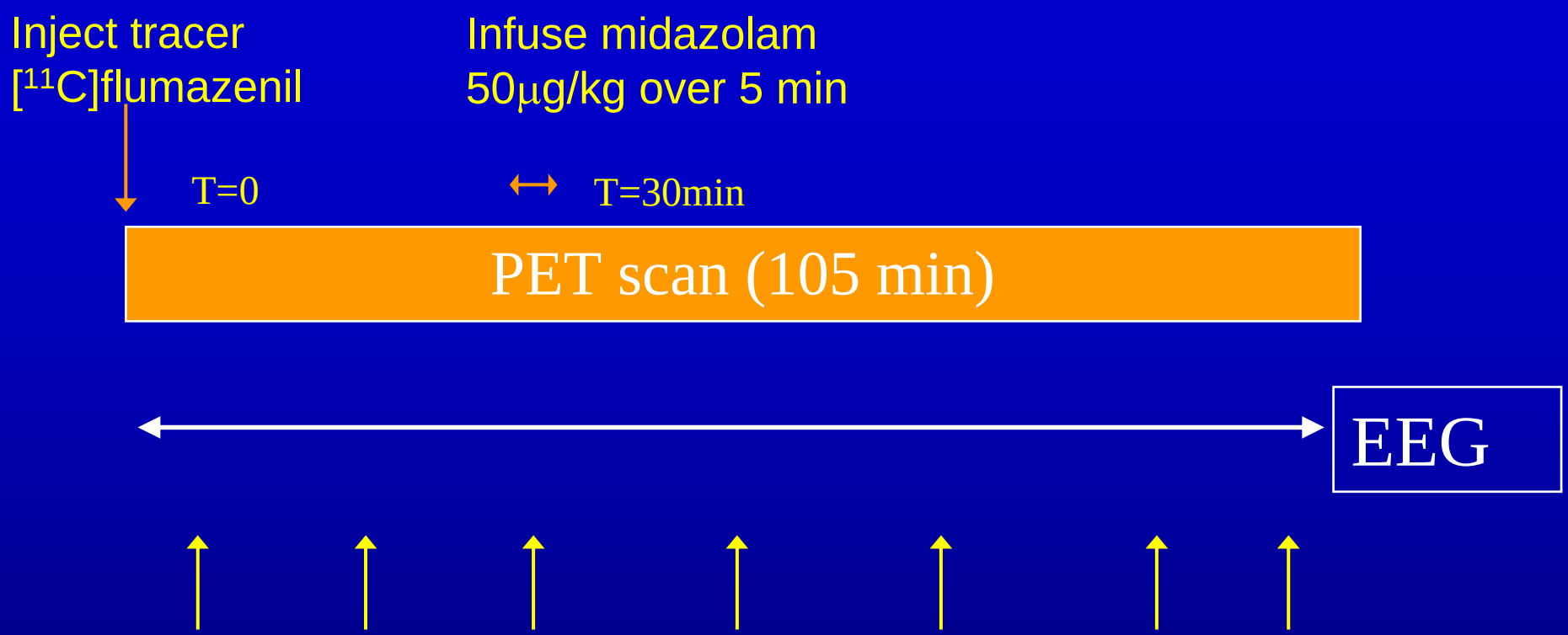
Infuse midazolam
50μg/kg over 5 min



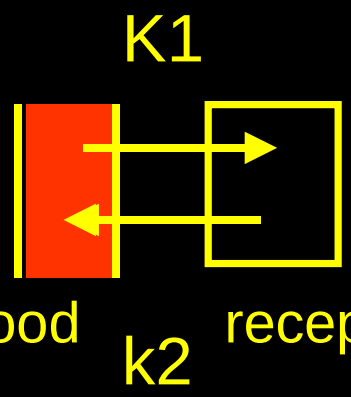
T=0

T=30min

PET scan (105 min)


Inject tracer
[11C]flumazenil
Infuse midazolam
50μg/kg over 5 min
T=0
T=30min
PET scan (105 min)
EEG
saccadic eye movements
blood for midazolam concentration

Whole head time-radioactivity curve for ^{11}C-flumazenil.

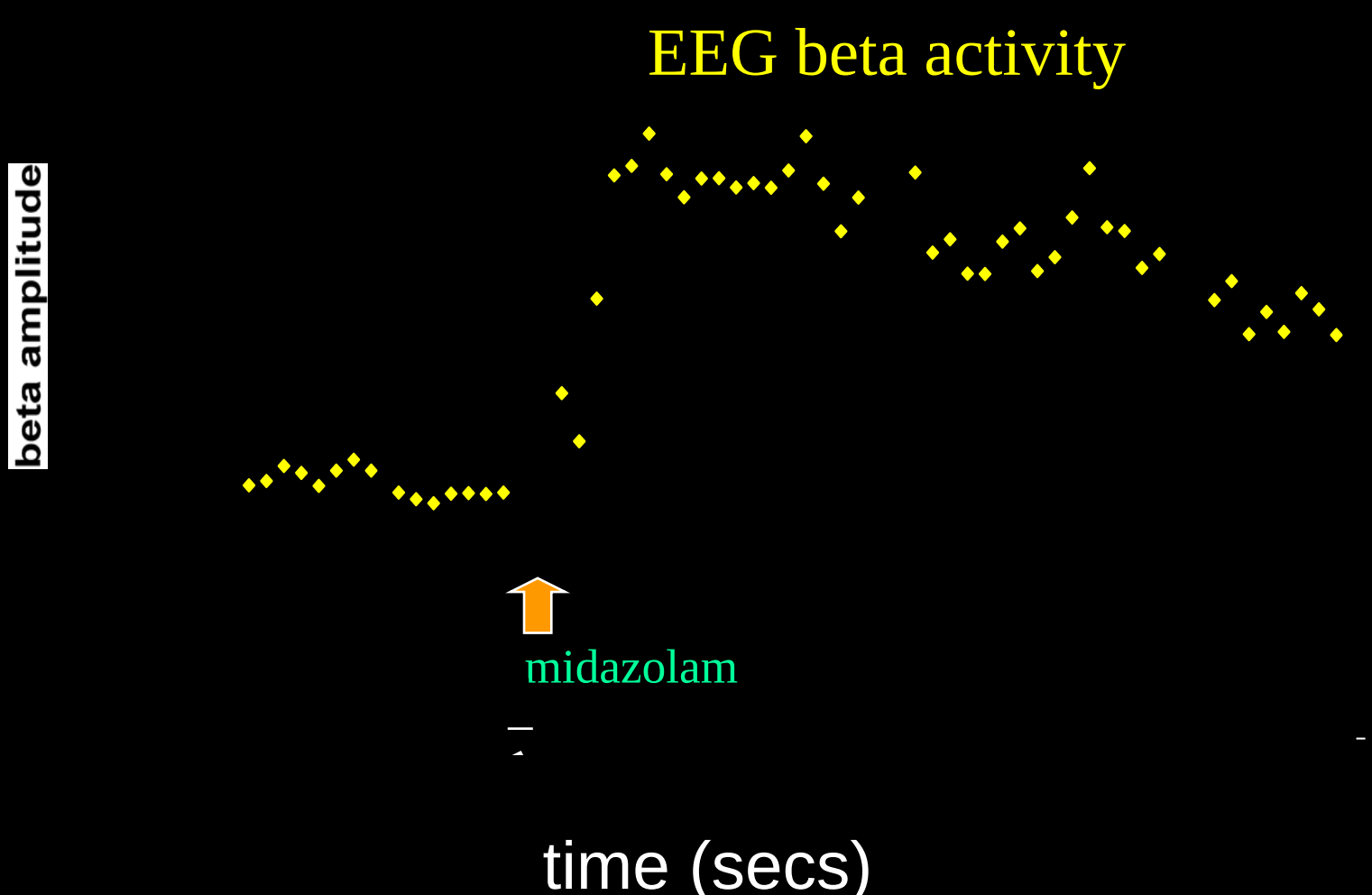


k2 increases post-midazolam [k2d]

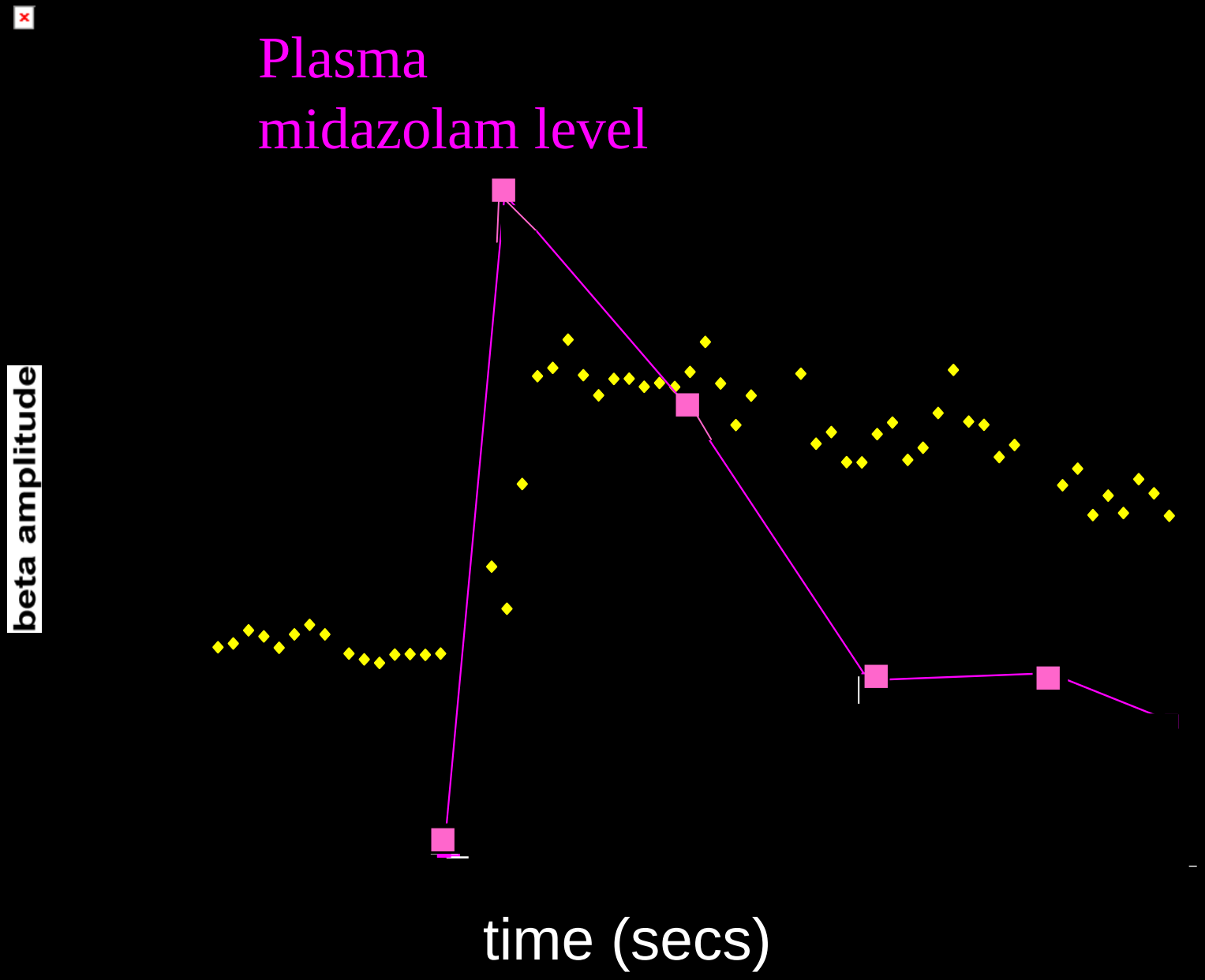
midazolam

time (secs)

EEG beta activity.



Benzodiazepine kinetics.

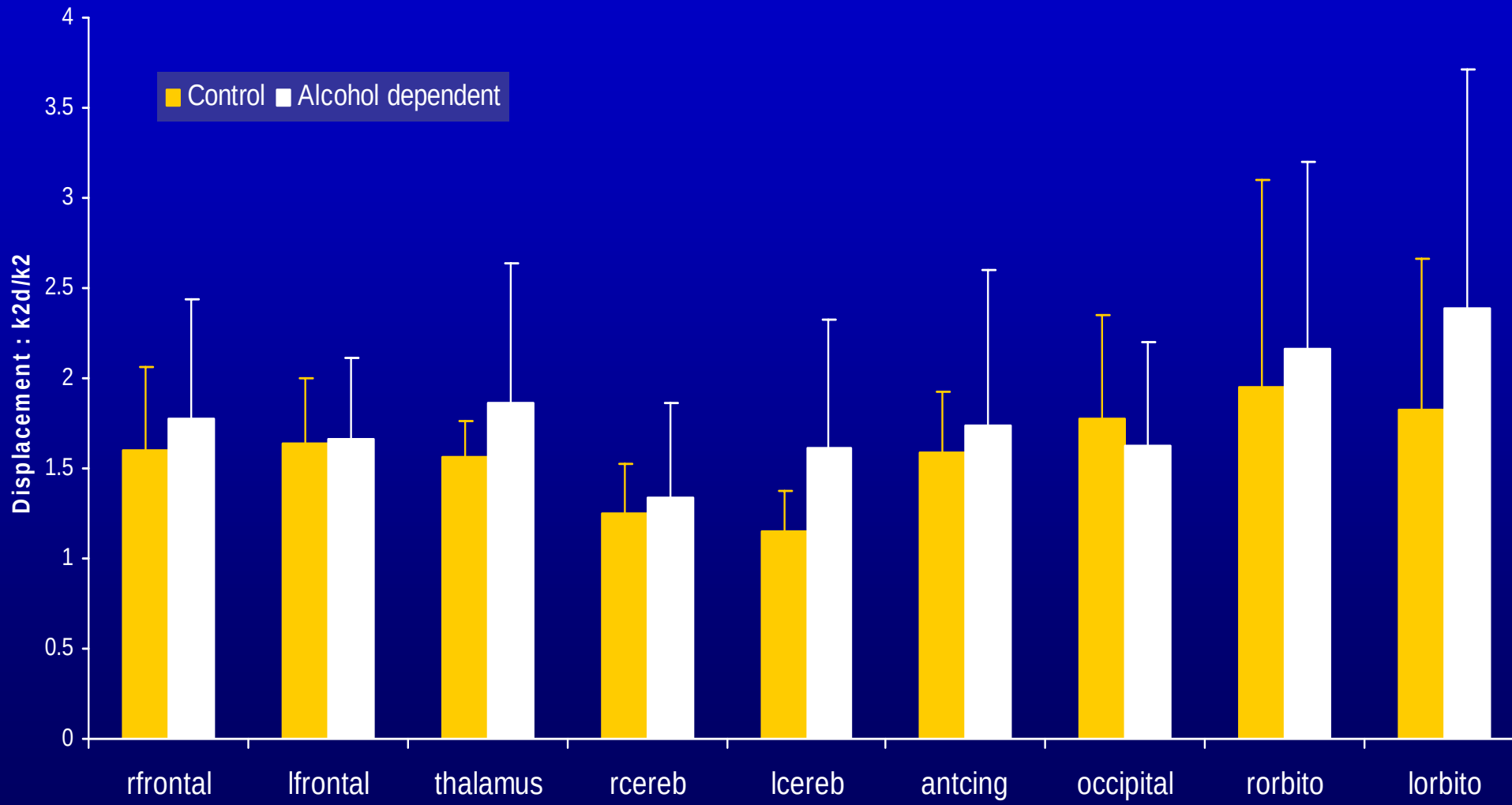


Results.

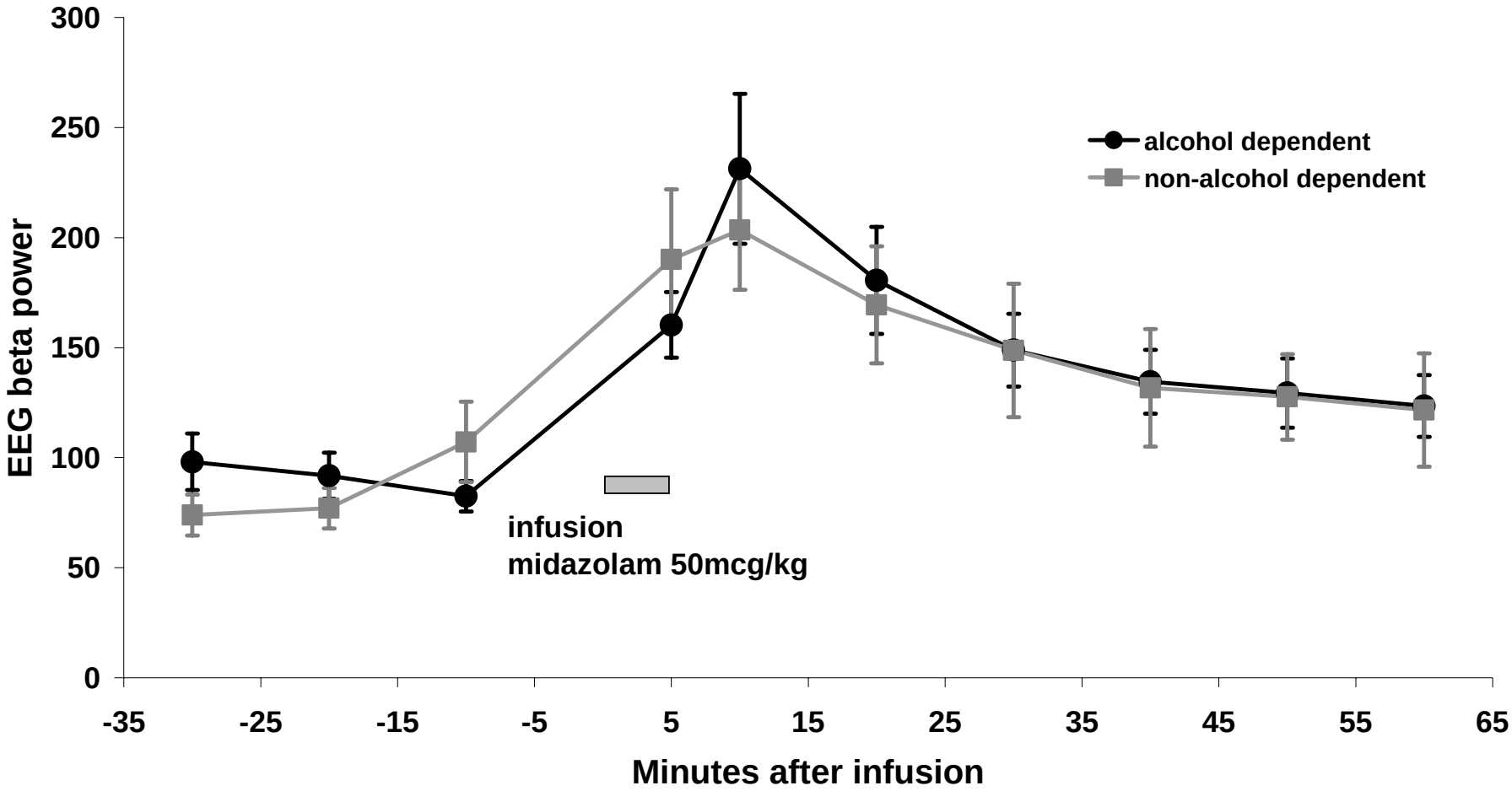
No differences in

- midazolam levels
- ^{11}C-flumazenil metabolism
- rate constants describing ^{11}C-flumazenil uptake [K1, k2, k2d]
- brain receptor occupancy

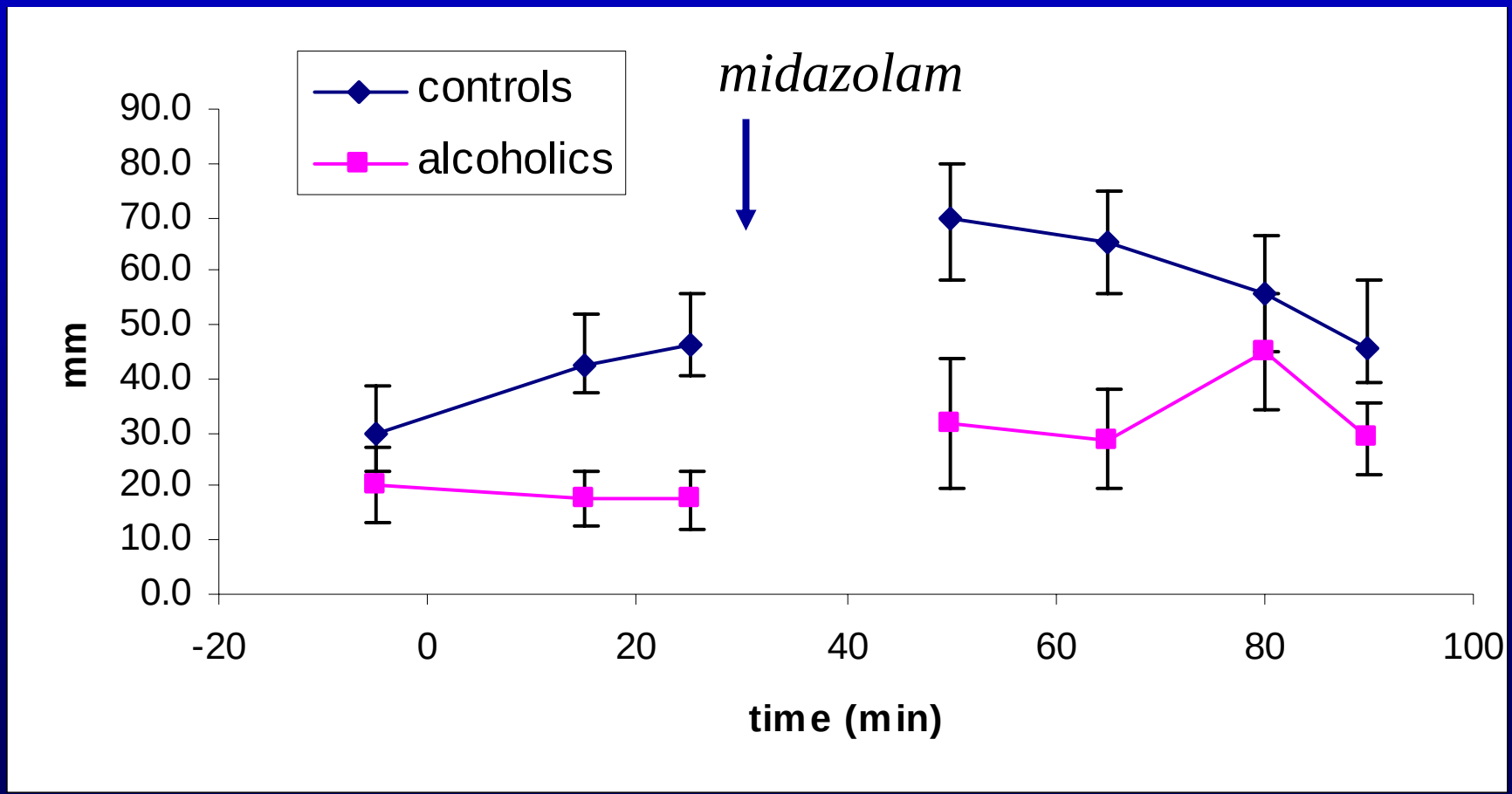
Brain receptor occupancy by midazolam



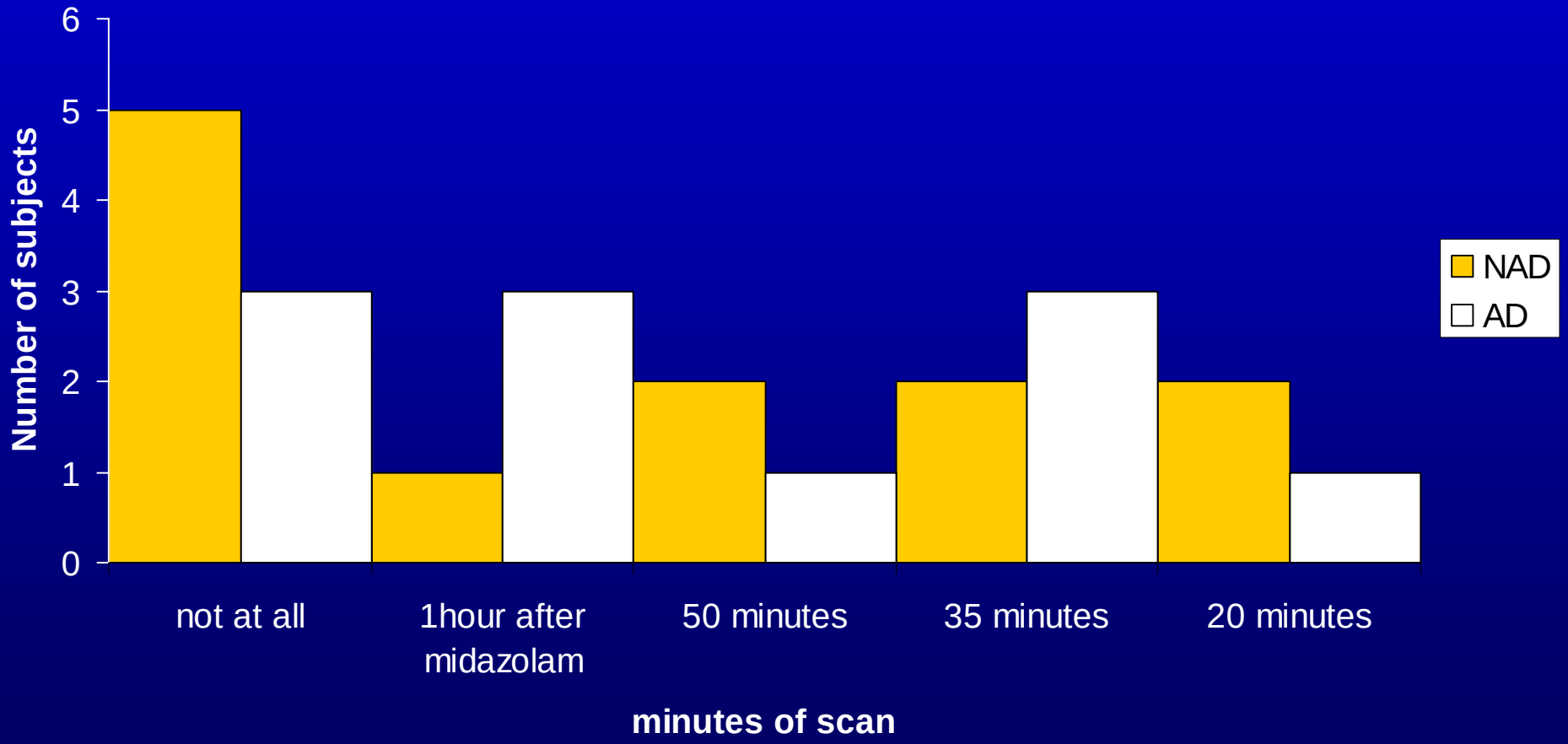
Change in EEG beta activity after midazolam infusion



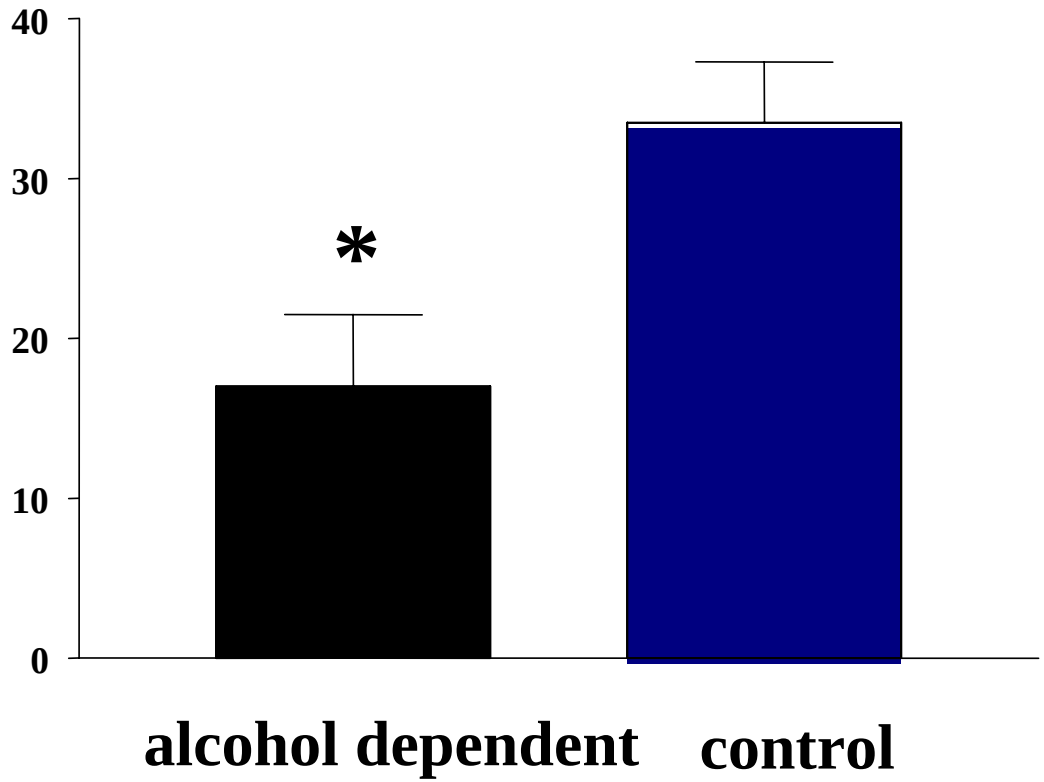
Subjective sleep ratings.



Saccadic eye movements
Time first able to perform SEMs.



Reduced total EEG sleep time after midazolam



*** : p < 0.05**

Conclusion.

Reduced function of the GABA-BZ receptor in alcohol dependence

- for induced sleep
- but not EEG beta response.

Issues

? due to changes in the subunit profile of the GABA-benzodiazepine receptor

? tolerance or predisposing trait marker

Functional neuroimaging (activation studies) to map the neural circuits associated with addiction

Abstinent alcoholics > 6 weeks

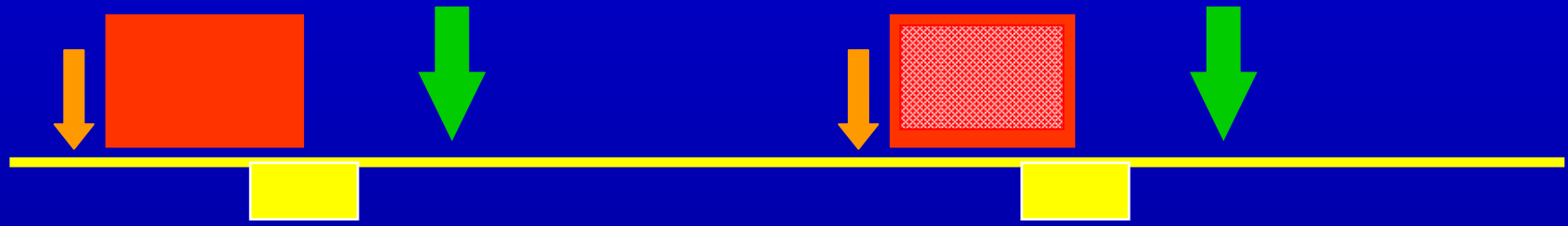
In abstinence-focussed program

Imaging of craving

- PET
  - $H_2{}^{15}O$
  - ^{18}F-FDG
- fMRI
- Drug
  - Cocaine
  - Alcohol
  - Opiate

- Paradigm (individual/generic)
  - 'Spontaneous'
  - Cue-induced
    - Visual
    - Auditory
  - Actual drug given
    - Alcohol
    - Cocaine

Cue exposure & craving: our PET protocol – six repetitions



t= 0 2 4 6 8 10 2 4 6 8 10
(mins) 0

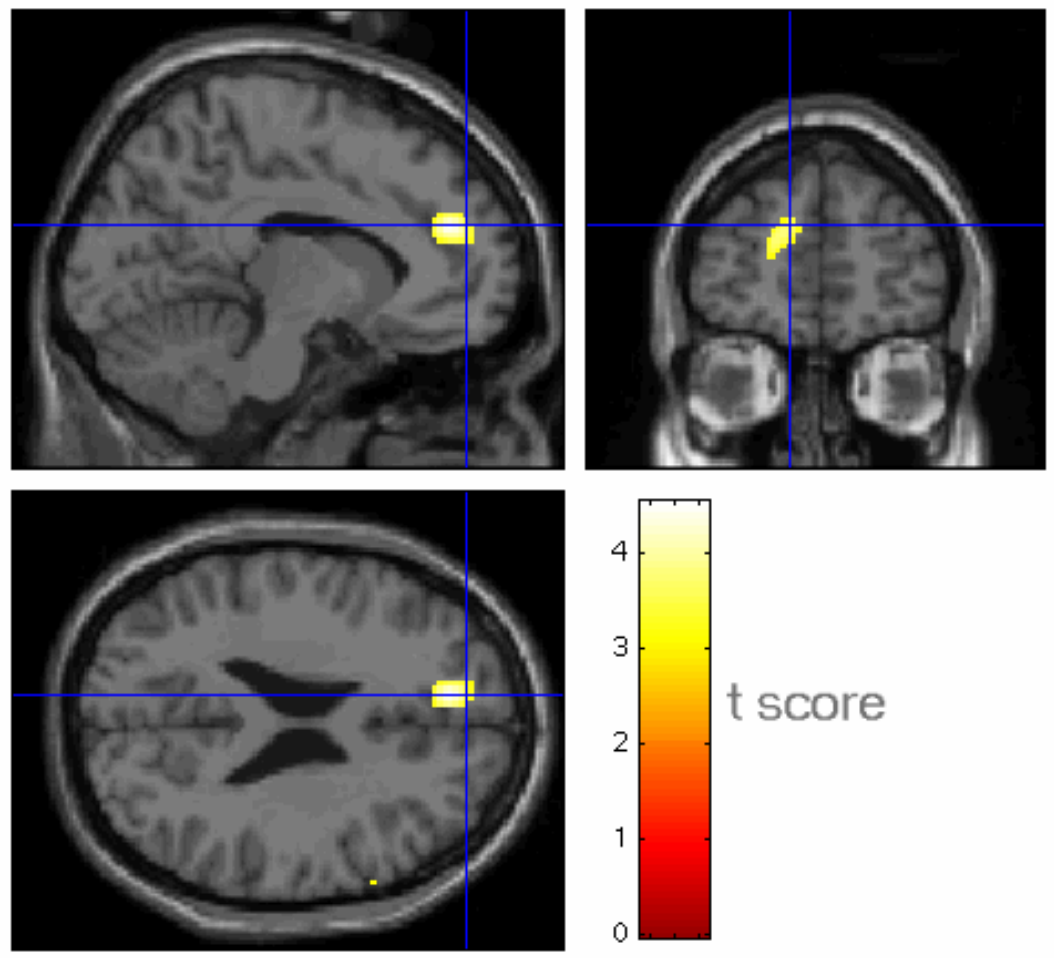
$H_2{}^{15}O$ infusion

image acquisition (90 s)

Stimulus presentation

VAS scales

Heroin addicts – cue exposure



Region of activation covering left anterior cingulate and medial pre-frontal gyri

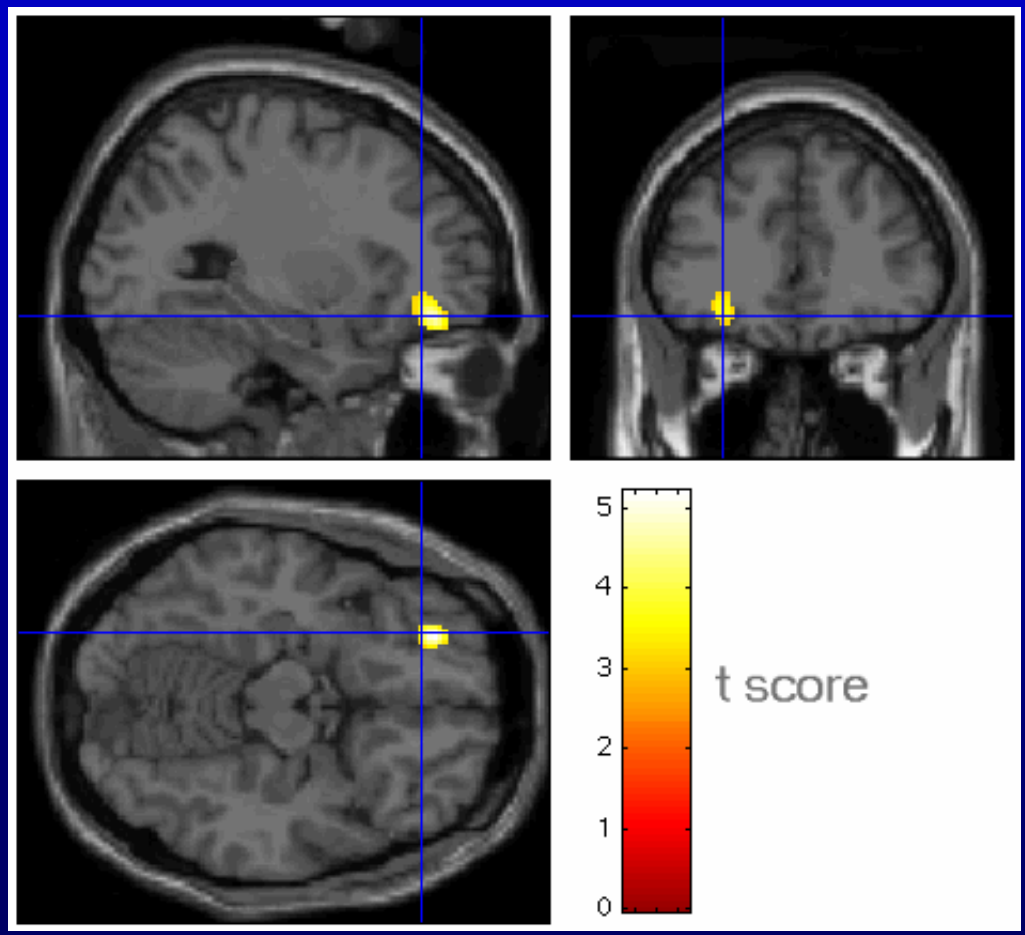
All subjects (n=12)

Activation centered on Talairach co-ordinates -10,46,24 mm

Peak t = 4.52 ($p<0.005$ corrected for multiple comparisons)

Daglish et al 2001

Activation in the left orbitofrontal cortex covaries with opiate craving

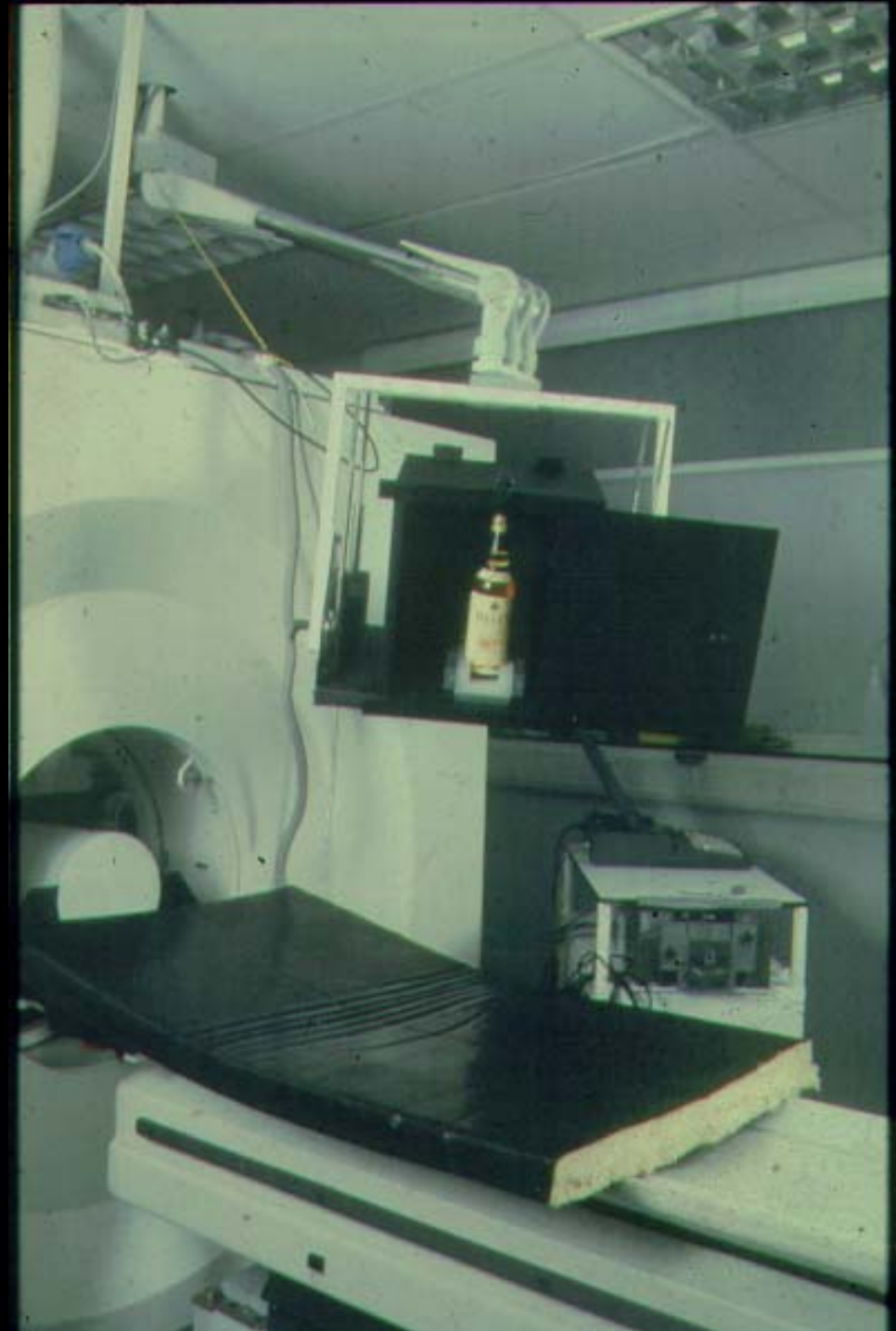


- Area of rCBF that co-varies with the composite score (craving & urge to use)
- Subjects who craved during the experiment (n=8)
- Activation centered on Talairach co-ordinates -26, 44, -14 mm
- Peak t = 5.19 ($p<0.05$ corrected for multiple comparisons)

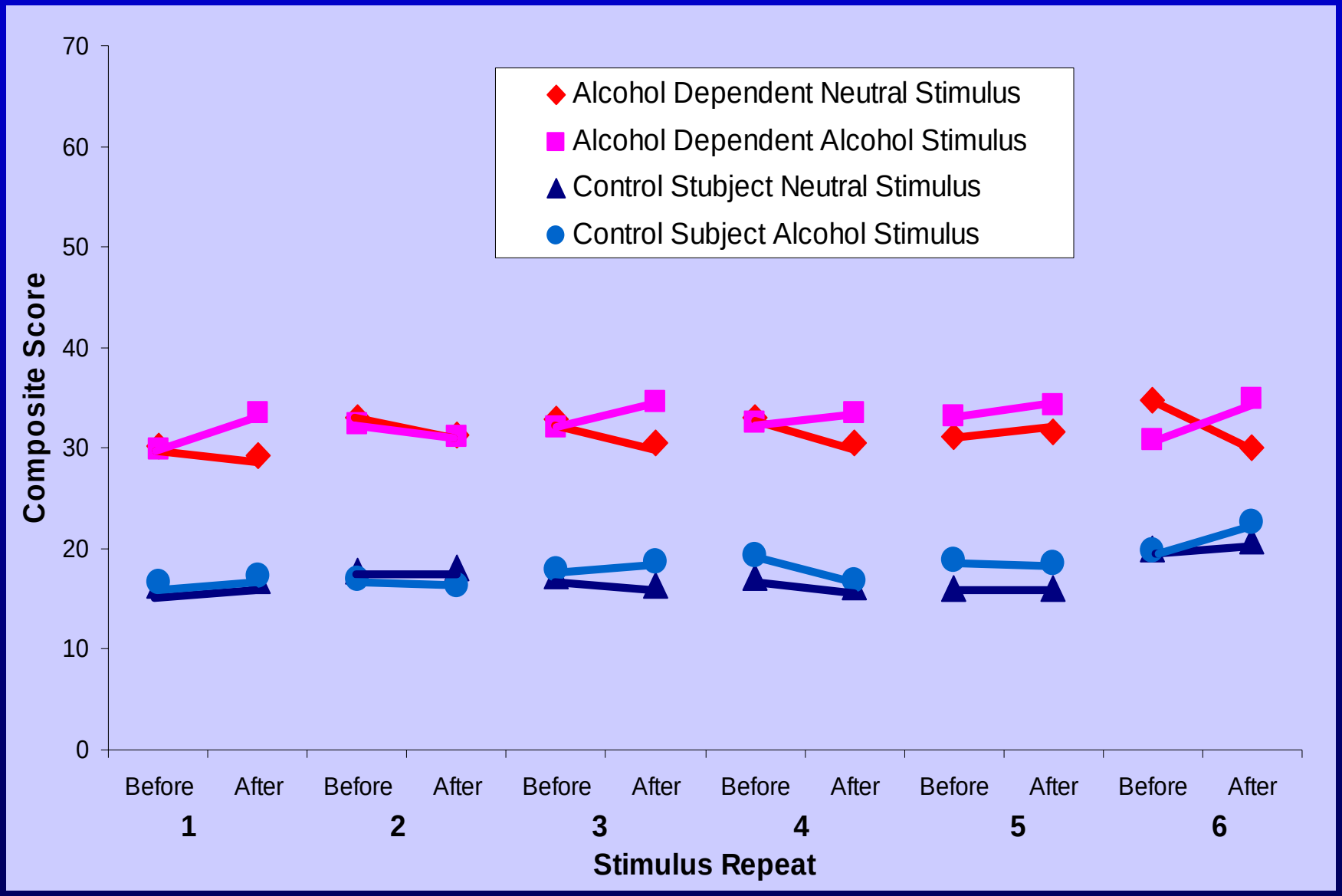
Subjects

- Alcohol Dependent Group
  - 6 male abstinent (≥ 6 weeks) alcohol dependent subjects
  - mean age : 41.5 yr
  - SADQ : 31.8 ± 12
  - OCDS: 16.7 ± 3.2
  - ACQ: 144 ± 46
- Control Group
  - 6 male control subjects
  - mean age : 36.8 years
  - SADQ : 2.25 ± 1.9
  - OCDS: 4.8 ± 2.2
  - ACQ: 69 ± 29

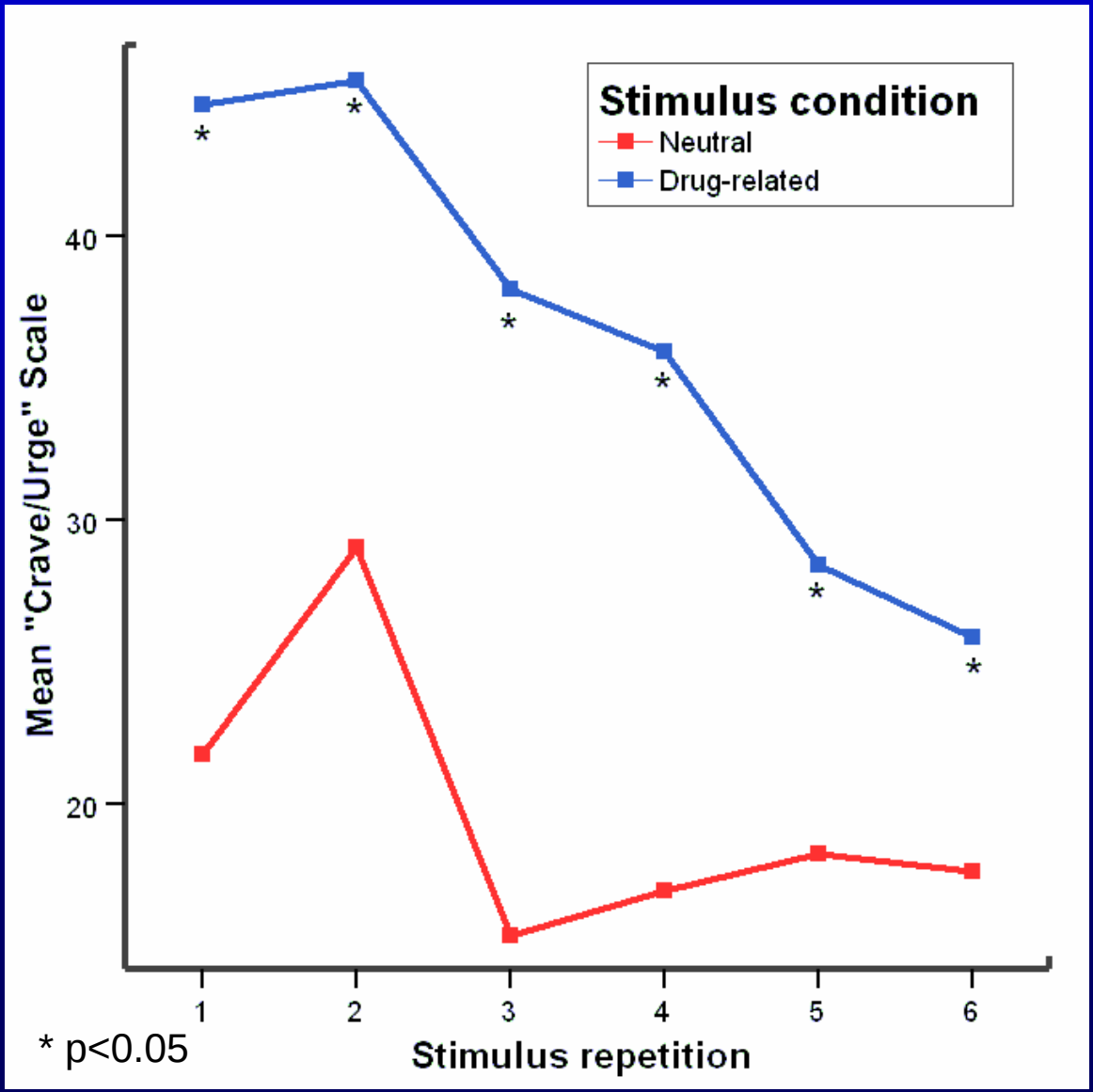
Cue exposure – real booze



Subjective Effects of Alcohol Stimuli urge to use questionnaire - Bohn



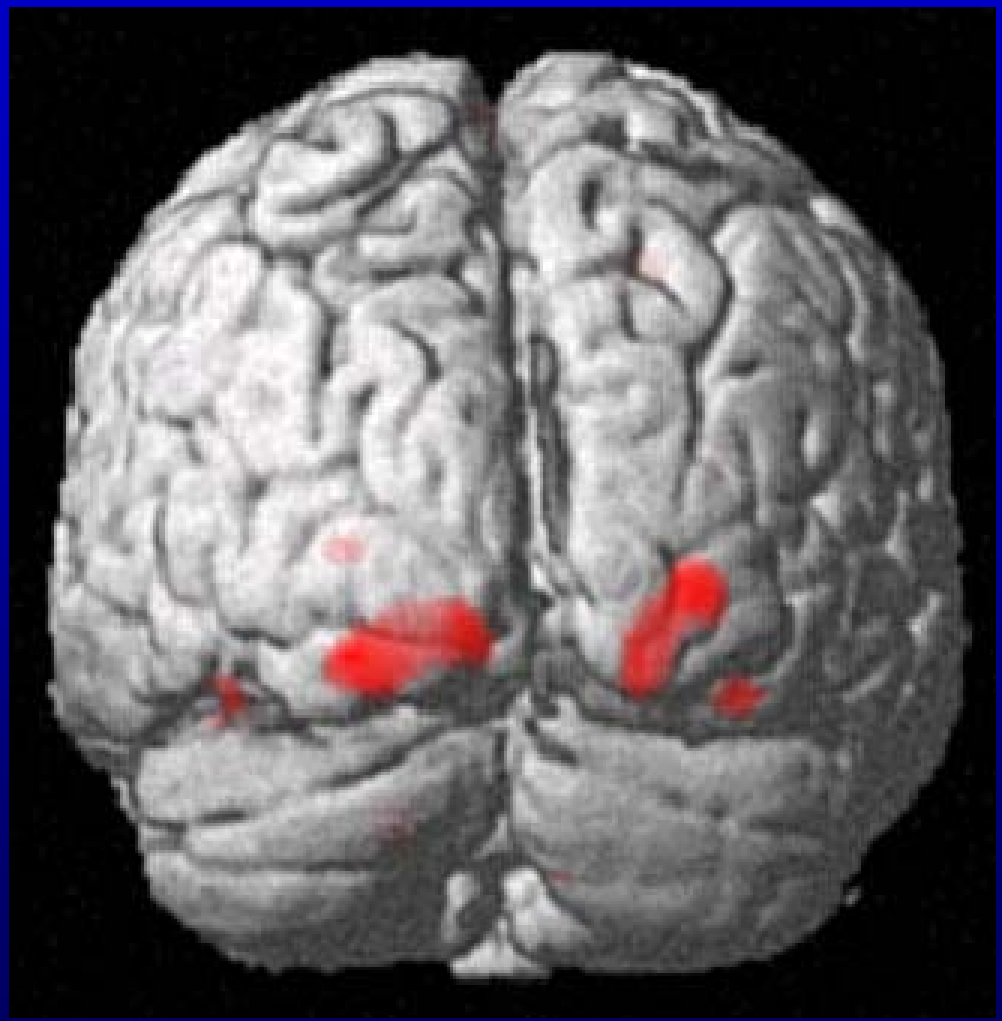
Heroin addicts' craving



Composite 'crave & urge' score derived as mean of 'crave' and 'urge to use' VAS scales

Plotted for each repetition of the neutral and craving stimuli

Activation in the occipital lobe.

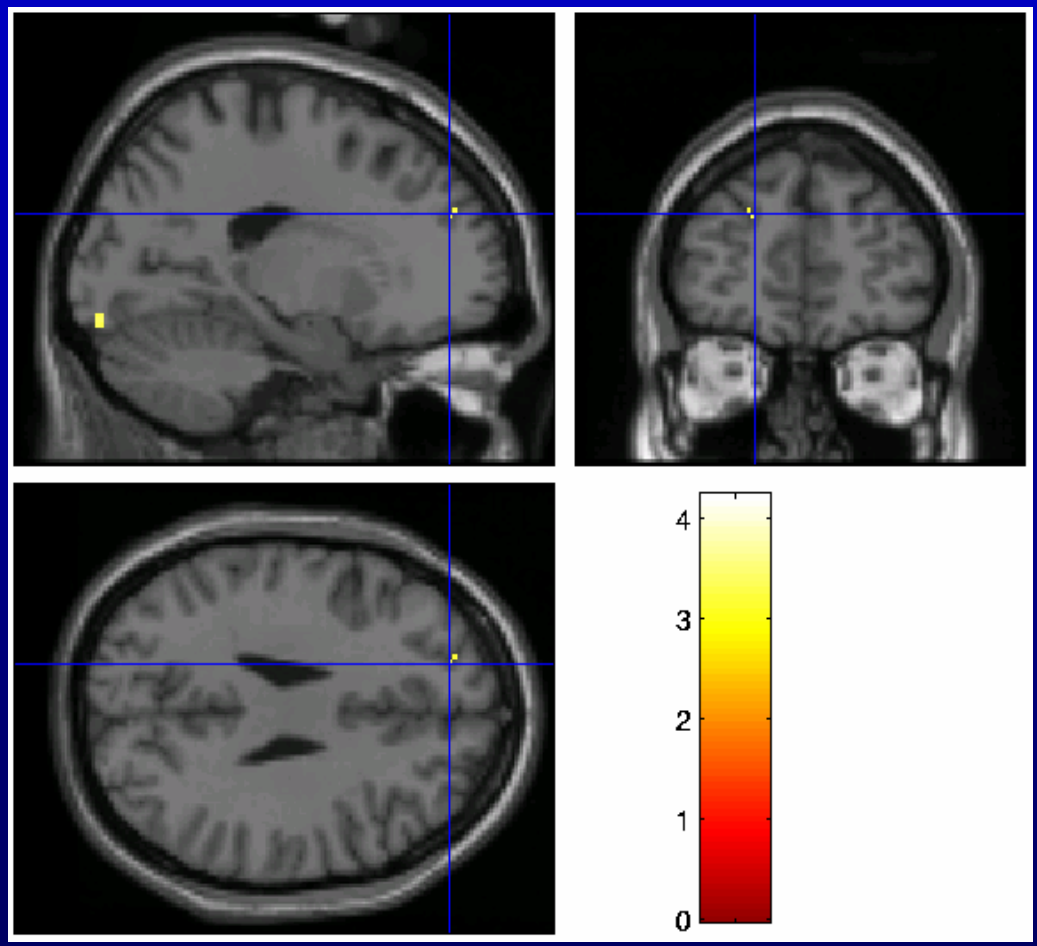


- occipital cortex activation in alcohol dependent and control subjects (n=12)

- increase in rCBF on L was statistically significant (Talairach co-ordinates –20, -94, -14mm, t= 3.81, number of voxels = 208, cluster-level $p<0.05$).

- increase in rCBF on R was smaller and almost significant (Talairach co-ordinates 24, -90, -8mm, t= 3.96, number of voxels = 168, cluster-level $p=0.09$).

Activation in alcoholics but not controls in response to the alcohol cue.

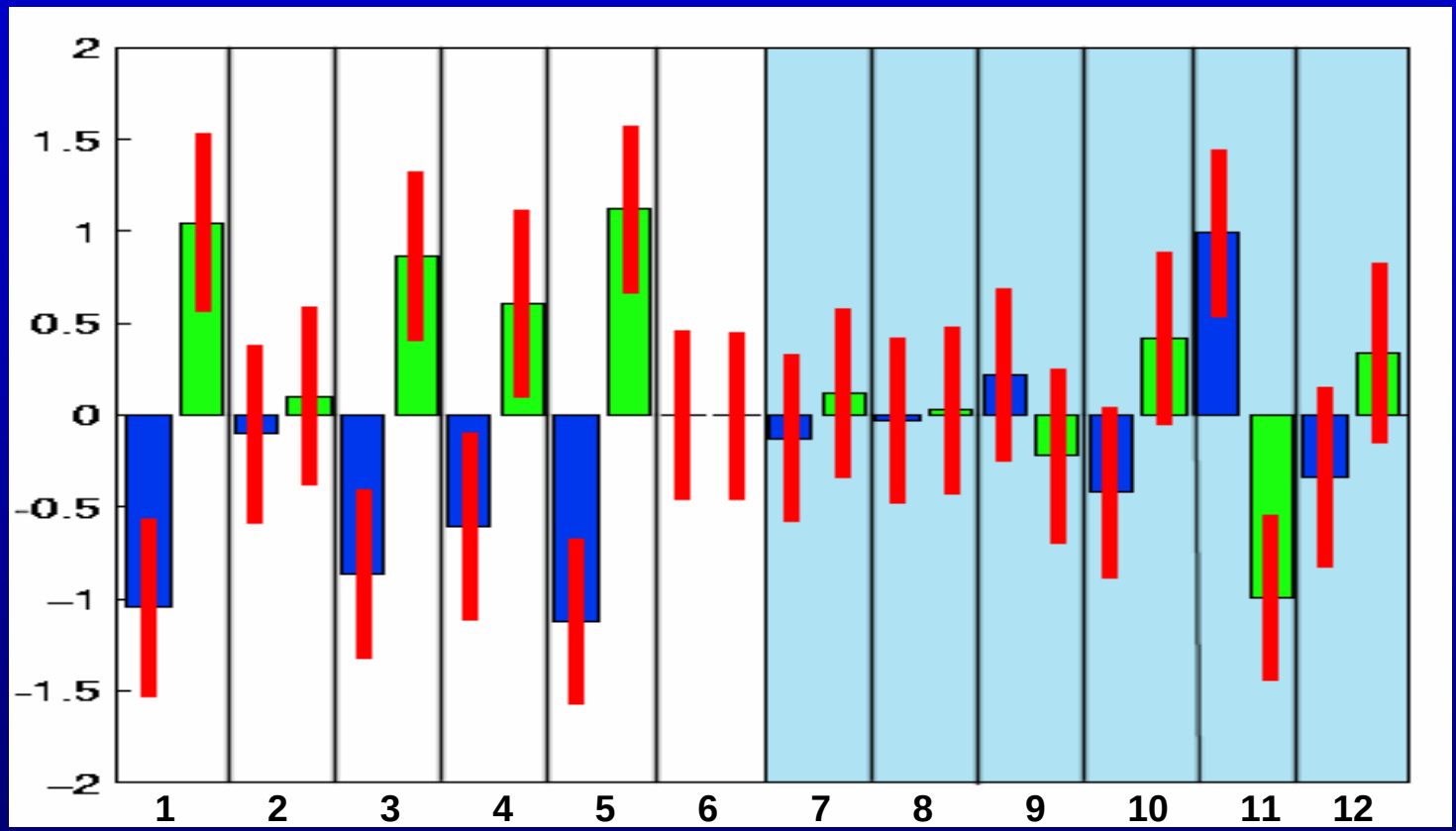


In left medial pre-frontal region : -18,48,28mm.

Significant increase in rCBF in response to alcohol stimulus [cluster-level $p<0.05$ corrected for small volume 10mm radius], but not in control group.

Activation in L medial prefrontal gyrus

Alcohol dependent subjects Control subjects



Alcohol Stimulus

Neutral Stimulus

Significant increase in alcohol dependent subjects compared to controls :
voxel level p=0.057, cluster level p=0.038

Summary.

- Robust craving for alcohol is difficult to induce in the scanner

- Activation in :
  - left medial frontal cortex in alcoholics only,
    - represents monitoring and manipulation of information within working memory and attention
  - occipital cortex in both controls and alcoholics
    - represents perception of the alcohol cue and maintenance or sustained attention to it

Why no robust craving ?

- Choice of patients
  - length of abstinence
  - severity of alcoholism, level of craving
- Choice of controls
  - unlike other neuroimaging studies in cocaine and opiates, control subjects have experienced alcohol
- Wrong paradigm
  - worked outside the scanner

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