Neuroimaging studies of opioid and $GABA_A$ receptors in alcoholism.

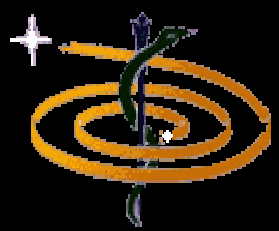
Dr Anne Lingford-Hughes

Psychopharmacology Unit,

University of Bristol &

MRC CSC Cyclotron Unit,

Imperial College School of Medicine.

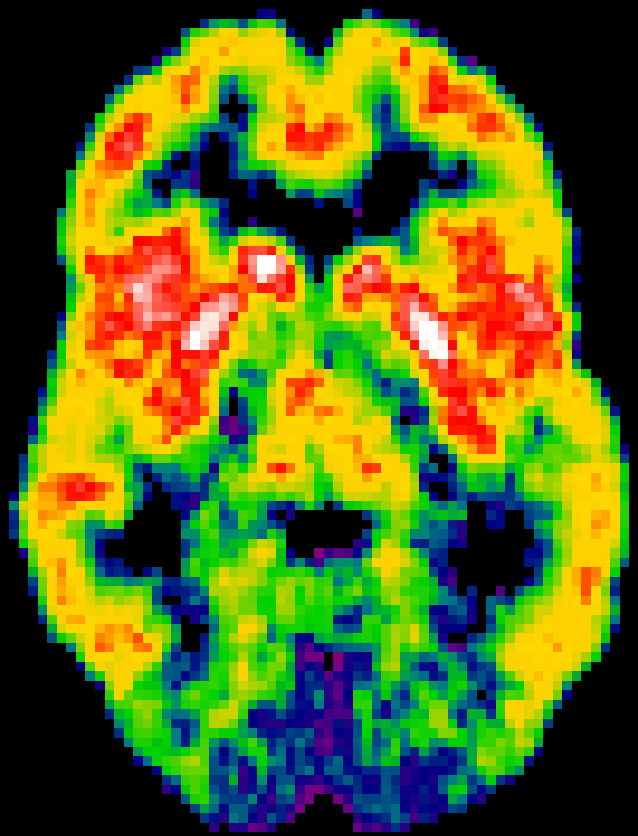


Our alcohol dependent subjects.

- Outpatient programs
- No clinically apparent cognitive, neurological or other medical problems
- Other drug use – apart from nicotine, no dependence allowed, but previous use permitted.
- Not currently depressed but previous history permitted; antidepressant use.
- Undergone benzodiazepine detox. completed at least 6 weeks previously.

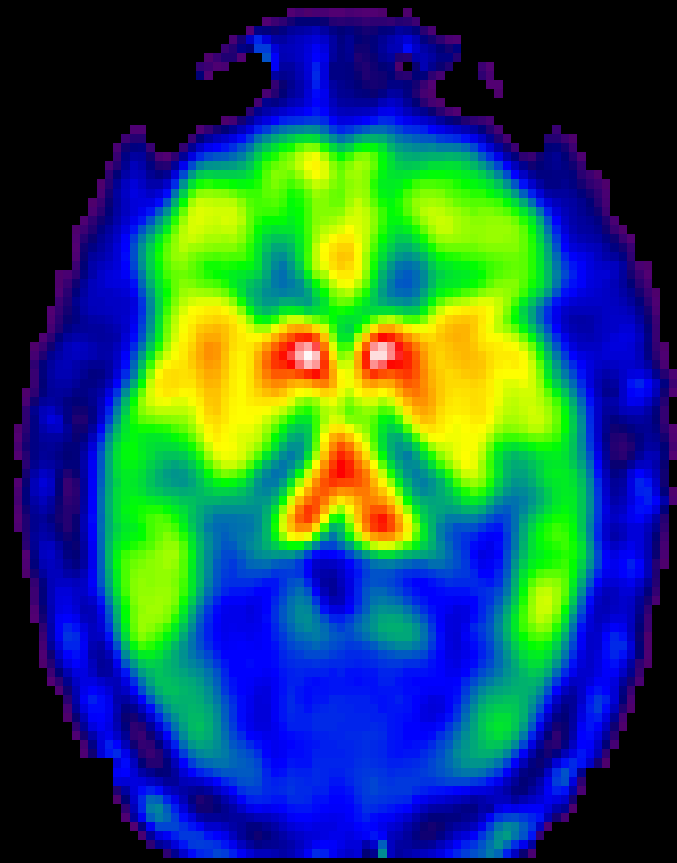
Imaging opiate receptors

μ,κ,δ



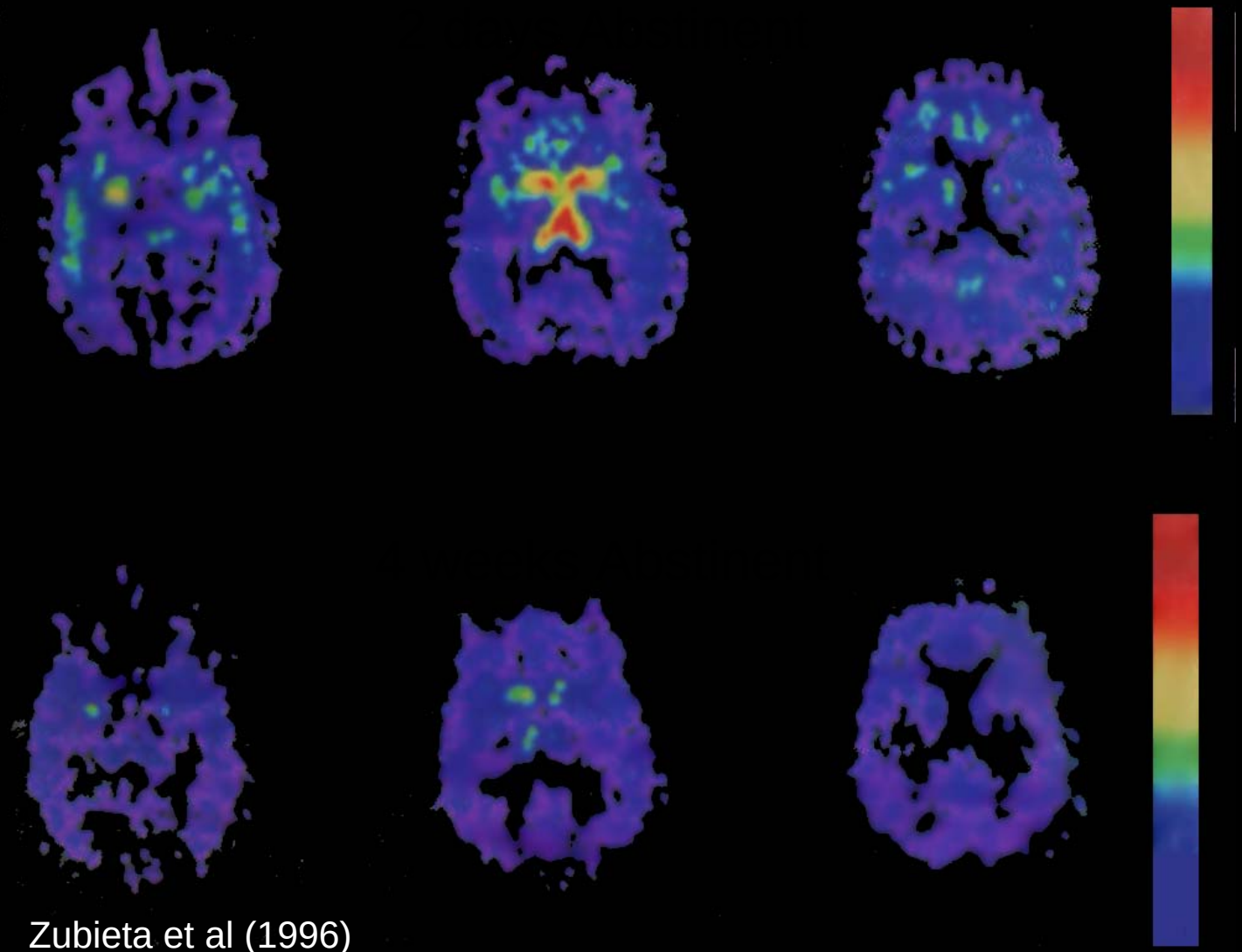
Diprenorphine

μ



Carfentanil

Increased ^{11}C-carfentanil binding in cocaine abstinence.

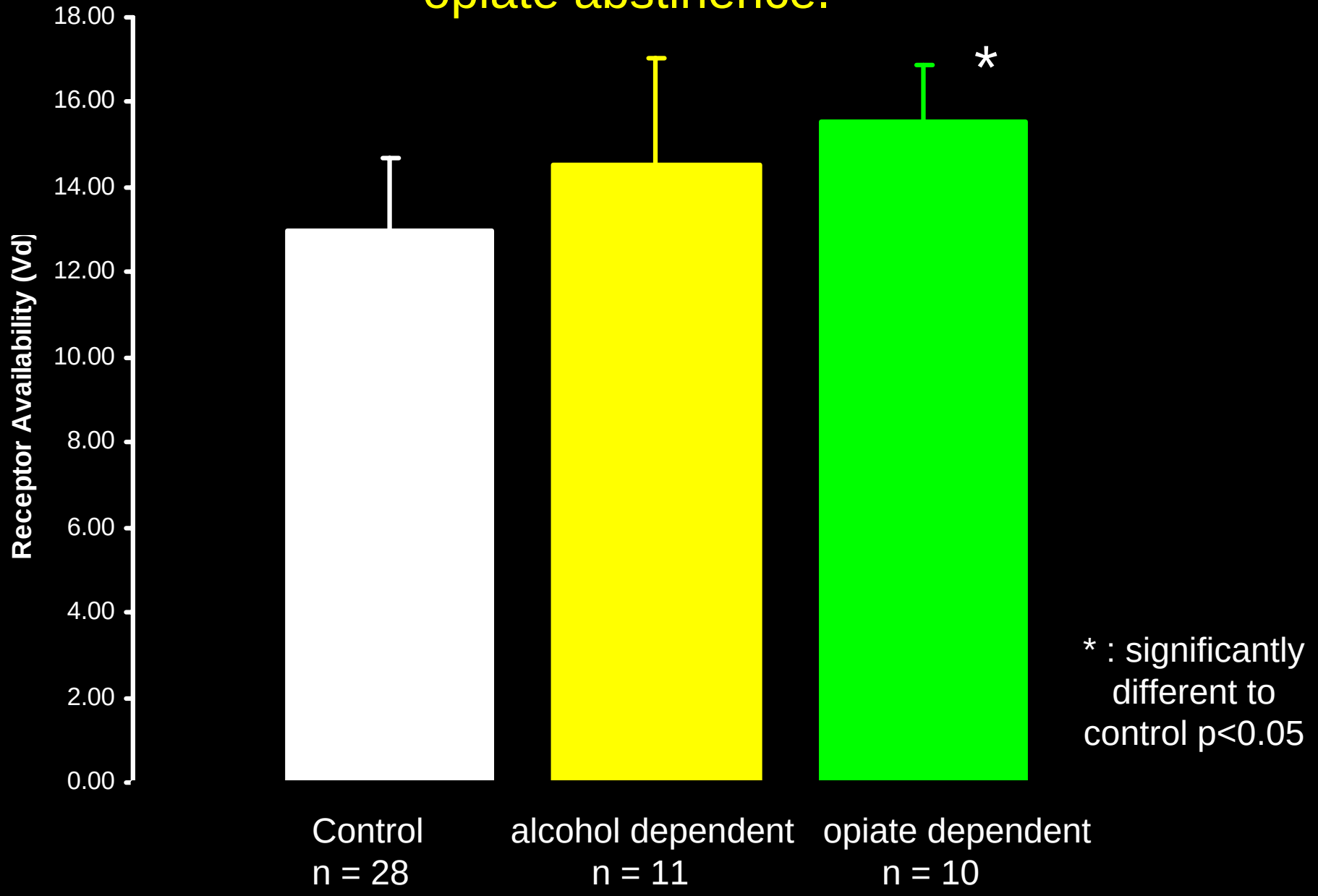


Cocaine craving correlated with mu receptor levels in :

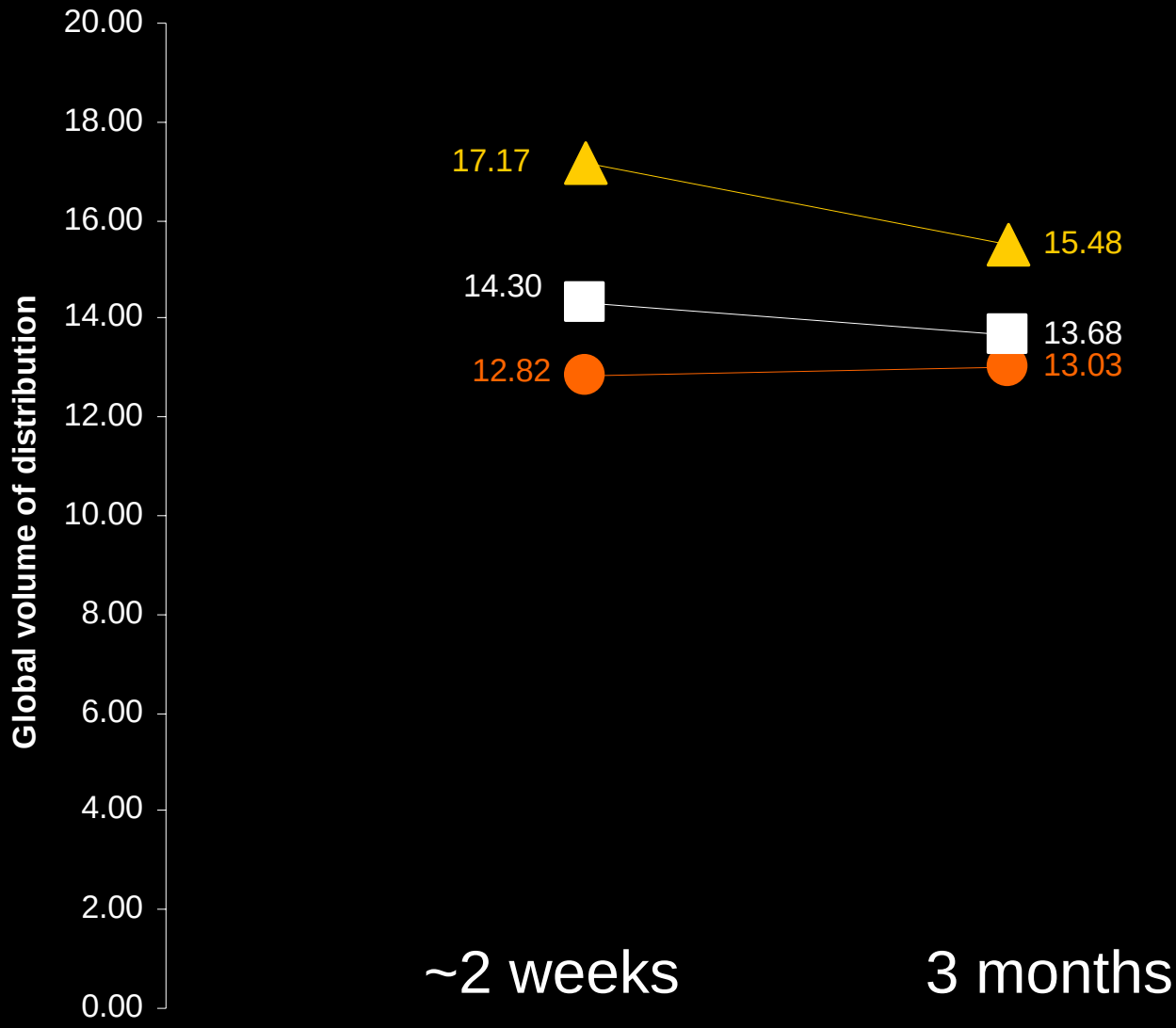
- Amygdala
- Anterior Cingulate
- Frontal cortex
- Temporal cortex

Zubieta et al (1996)

Global increase in opiate receptors in early alcohol and opiate abstinence.



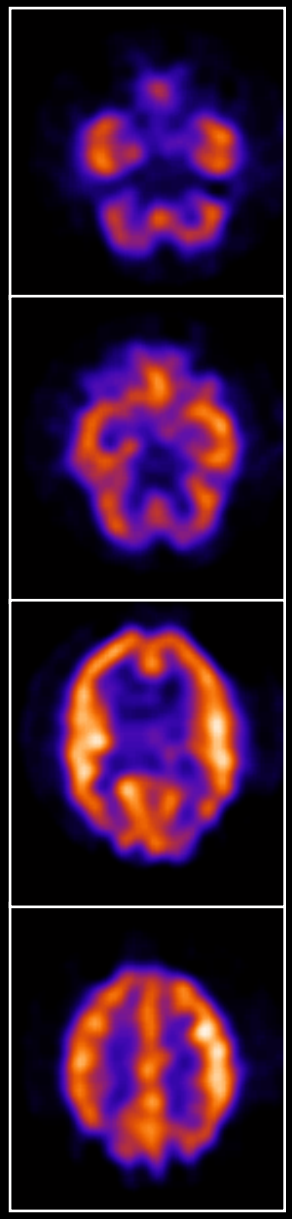
Change in global [^{11}C]-diprenorphine binding during abstinence from alcohol.

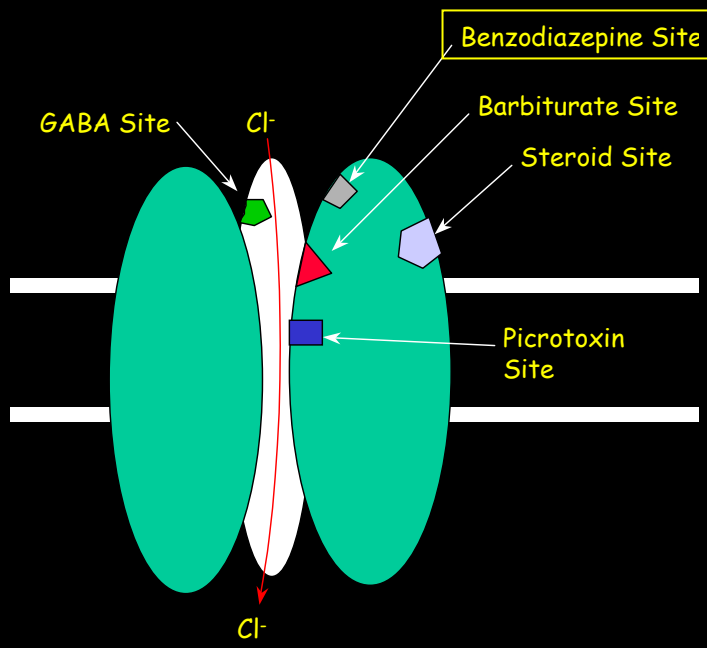


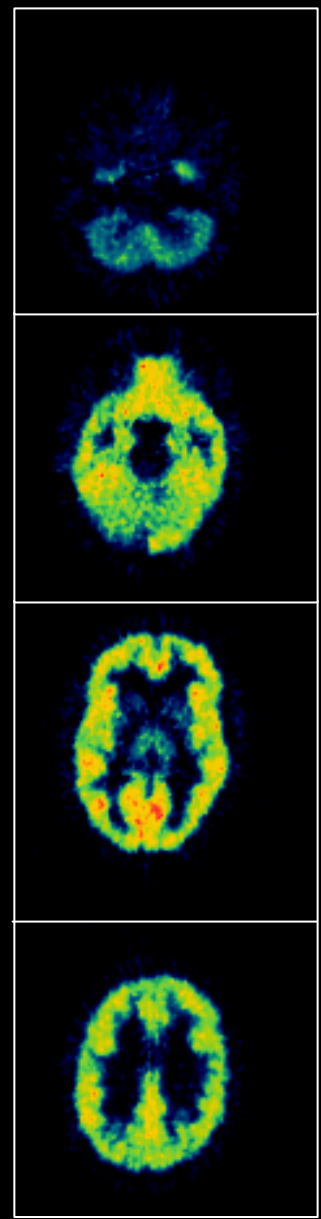
Opioid receptors and addiction.

- Increased availability of opioid receptors reported in early abstinence
  - cocaine
  - opiates
  - alcohol
    - changes occur with lengthening abstinence.
- May be fundamental to addiction

Neuroimaging the GABA-benzodiazepine receptor.







SPET
[^{123}I]-iomazenil

PET
[^{11}C]-flumazenil

Hypothesis.

- that alcohol dependence is associated with reduced GABA-benzodiazepine receptor levels

- recruited medically and cognitively healthy abstinent [> 3 months] alcohol dependent patients.

Comparison between male abstinent alcohol dependent and non-dependent subjects.

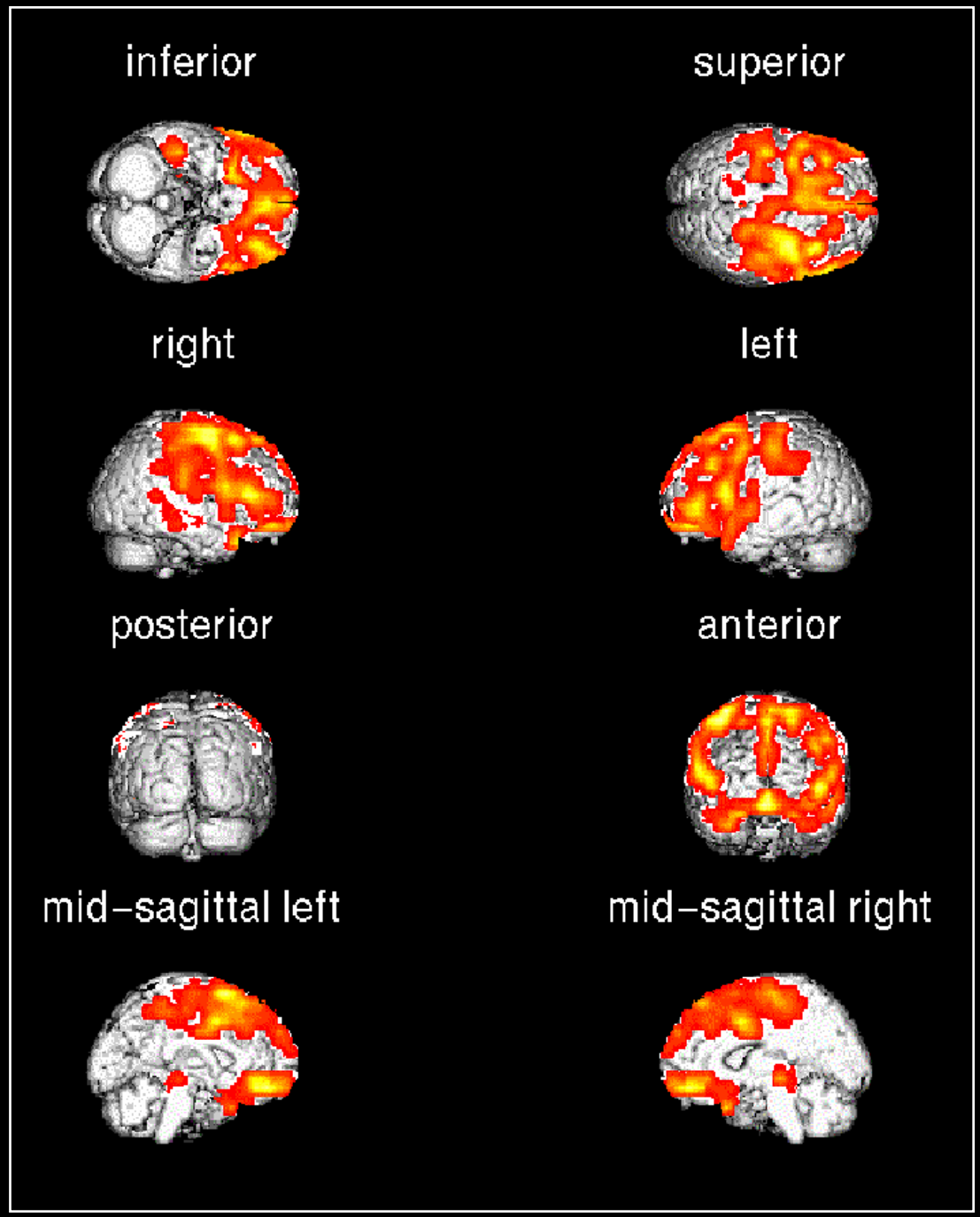
	alcohol (sd)	control (sd)
n	12	14
Age	43.2(11)	39.9 (9)
SADQ	36.6 (17)	1.9 (2)
Yrs drinking	25.25 (11)	22.4 (7)
Total alcohol(kg)	720 (407)	287 (141)
Abstinence (mo)	22.5 (50)	
Weekly alcohol (g)		282 (141)

[^{123}I]-iomazenil SPET :

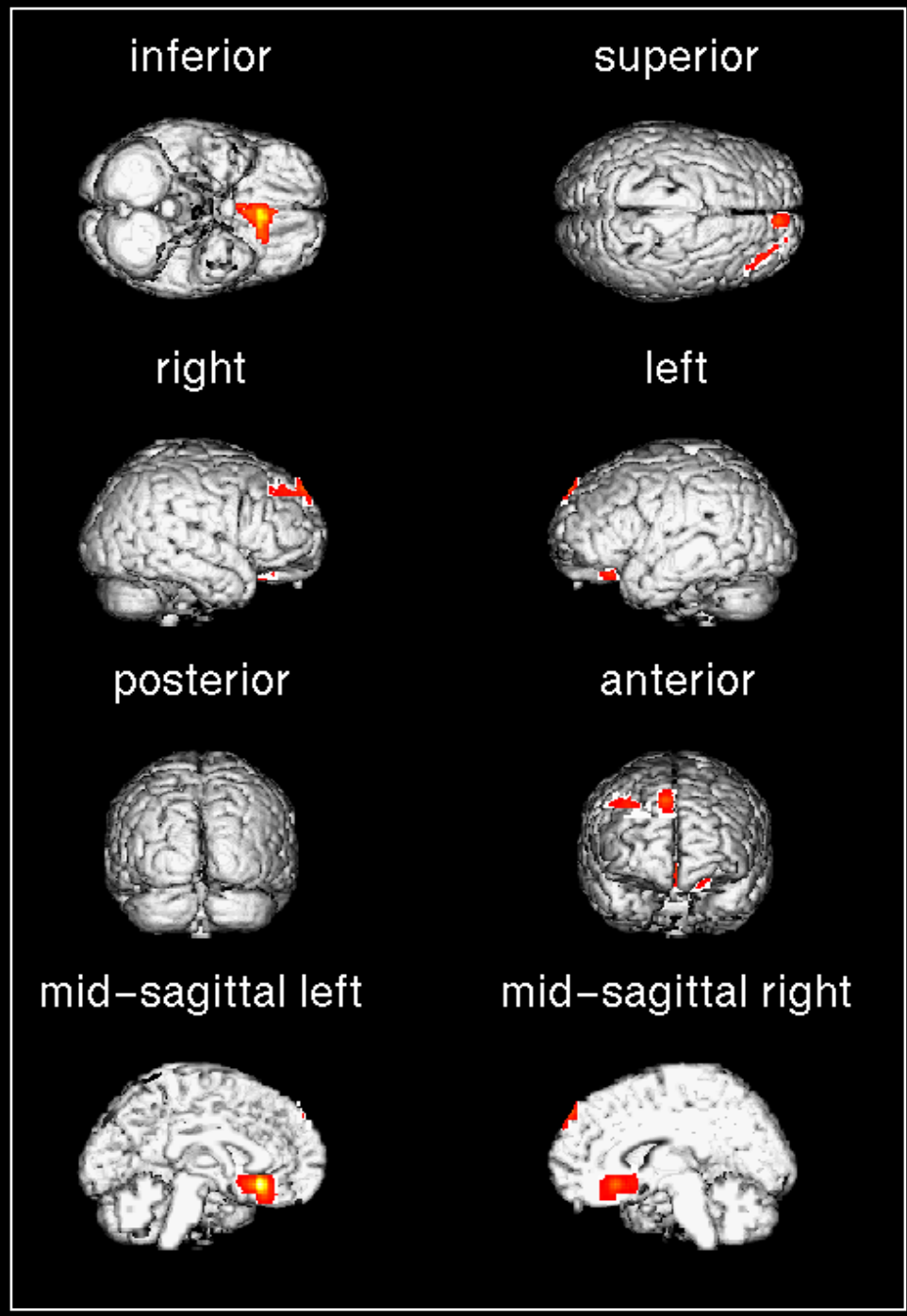
Regions showing significant reductions in GABA-BDZR in alcohol-dependent male subjects :

cluster-level significance $p<0.05$

Lingford-Hughes et al 1998
B J Psychiatry



Minimal grey matter reductions in these alcohol dependent male subjects.



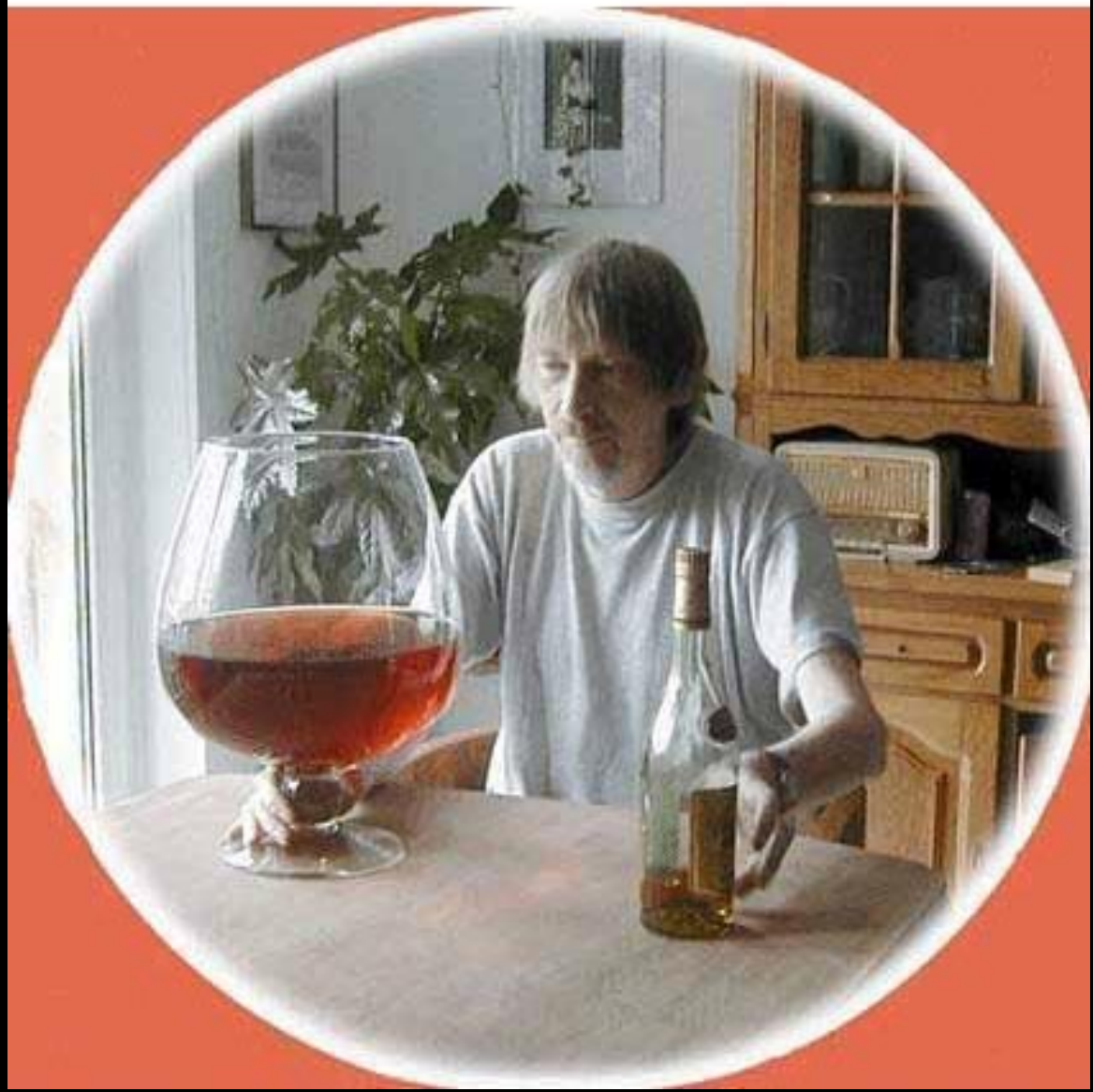
cluster-level significance
$p<0.05$

Lingford-Hughes et al 1998
B J Psychiatry

- This reduction was not related to
  - age
  - length of abstinence
  - anxiety levels [Spielberger state and trait]

- but was associated with increases in
  - lifetime amount of alcohol consumed
  - severity of dependency
    - implications : cannot determine if ‘cause’ or ‘consequence’

My Doctor said "Only 1 glass of alcohol a day". I can live with that.



Gender Differences in Alcohol Dependency.

In females :

- Structural imaging
  - increase in ventricular volume, sulcal widening
  - occurs after shorter drinking history than in males

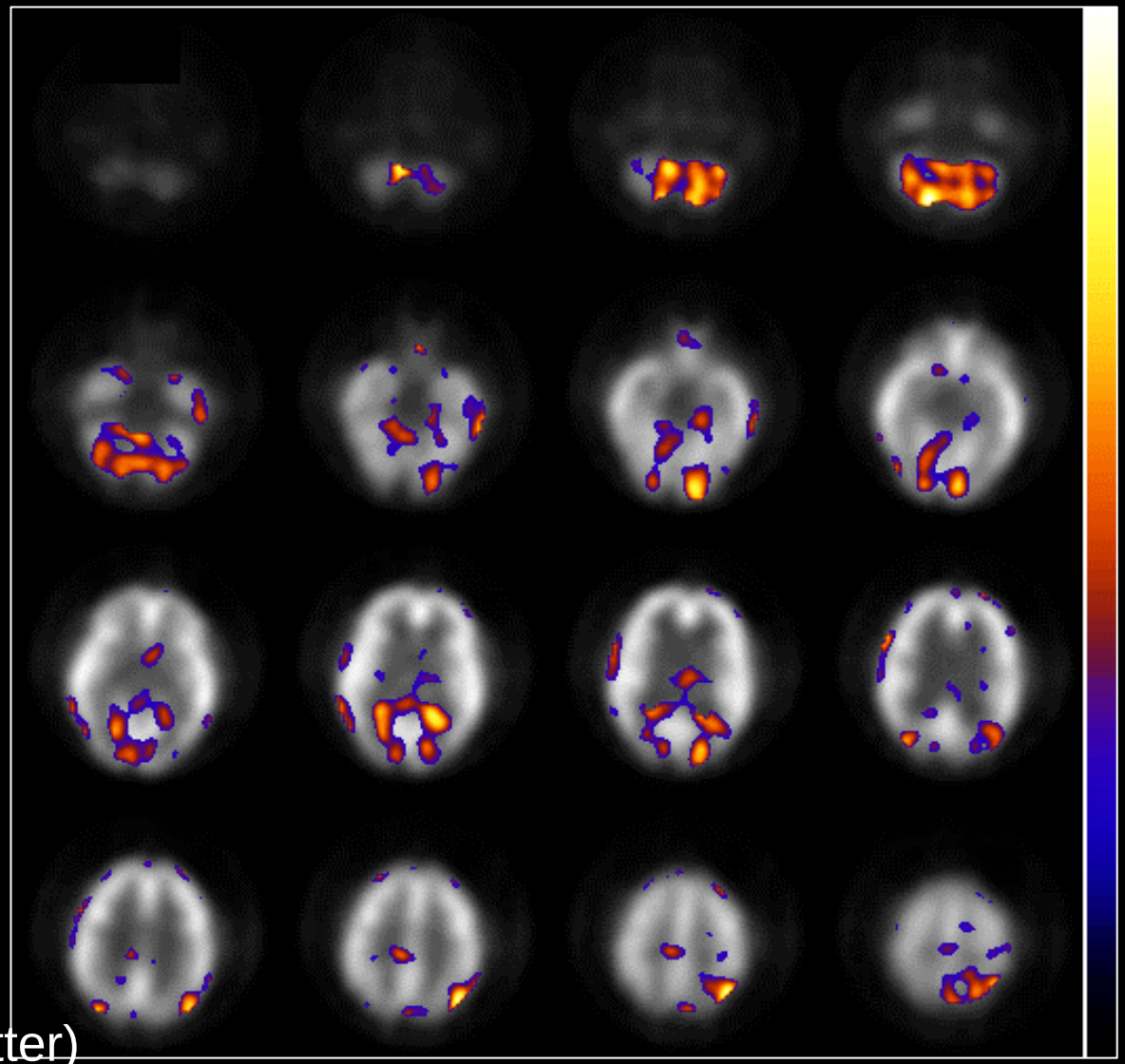
- Neuropsychology
  - perform worse than males with equivalent drinking histories

Comparison between male and female abstinent alcohol dependent subjects.

	male (sd)	female(sd)
n	11	9
Age	43.2(11)	42.9 (8)
SADQ	36.6 (17)	39.1 (8)
Yrs drinking	25.25 (11)	24.9 (7)
Total (kg)	720 (407)	722 (433)
Abstinence (mo)	22.5 (50)	30.4 (53)

Different pattern of reduction in GABA-BDZR levels in female alcoholics.

Reductions are seen in the cerebellum but not in the frontal cortex as seen in male alcohol dependence.

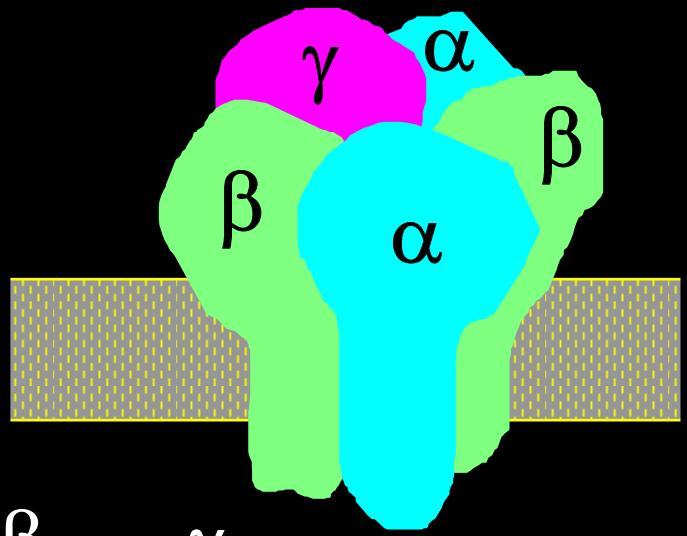


(normalised to white matter)

Putative mechanisms underlying gender differences.

- Different patterns of alcohol consumption
- Differential aging effects
- GABA-BDZ receptor system is less vulnerable in females
  - reduced α1 subunit peptide levels in ethanol dependent male but not female rat cortex *[Devaud et al 1998]*

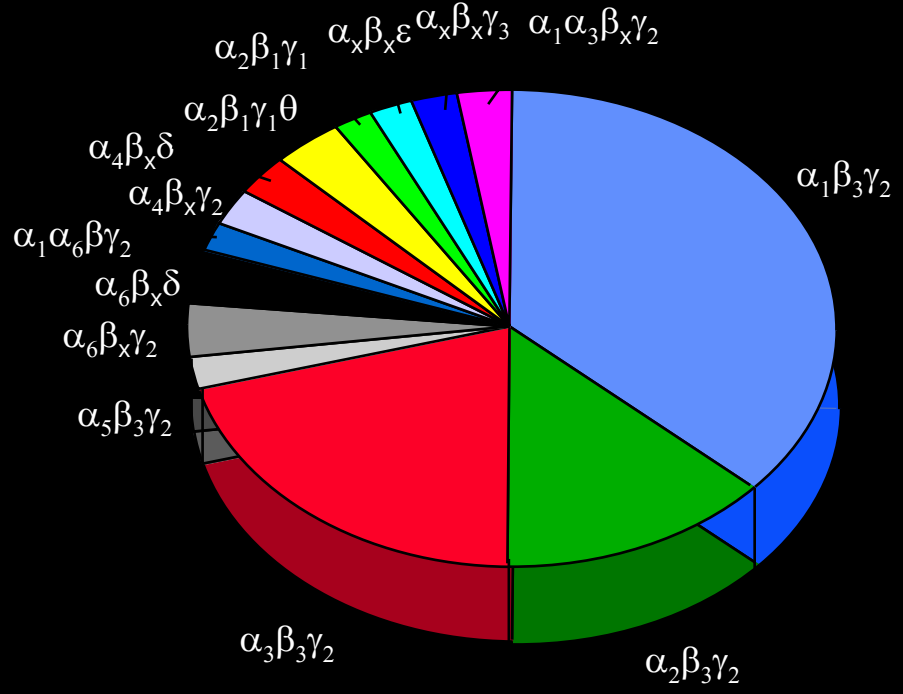
The GABA-BDZR: subtypes



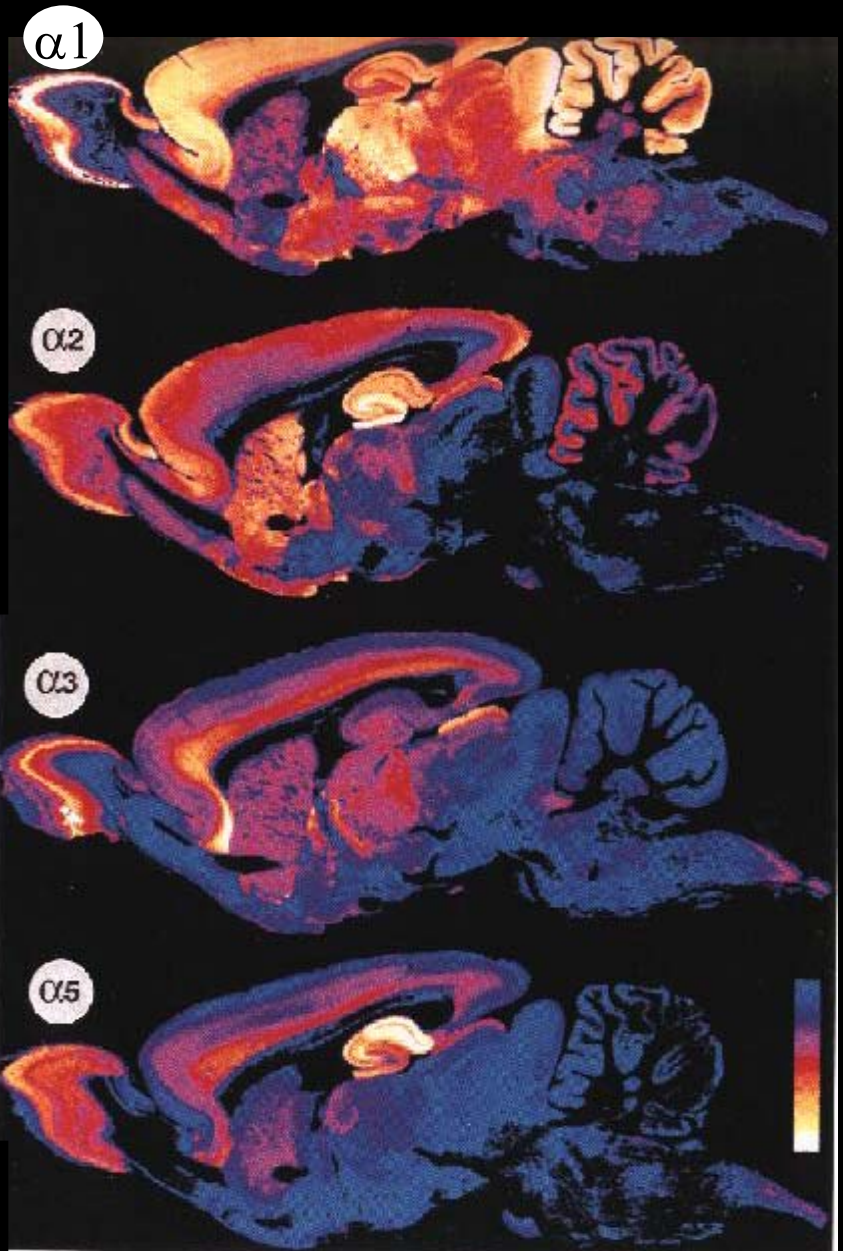
α_{1-6}, β_{1-3}, γ_{1-3},

Most common :

$\alpha_1\beta_2\gamma_2$

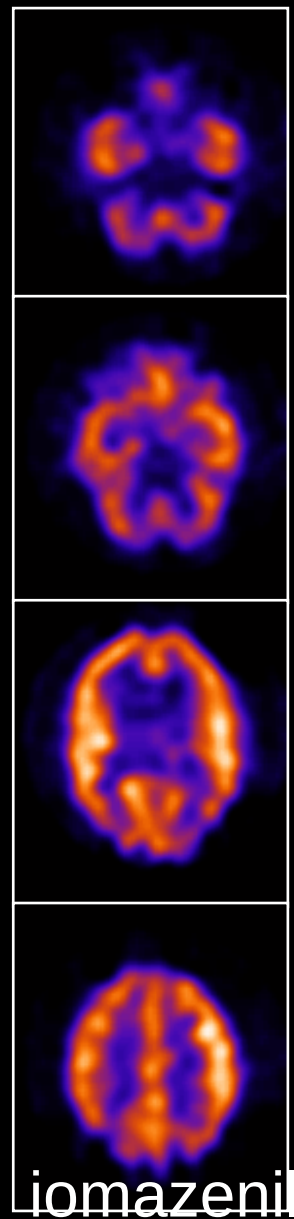


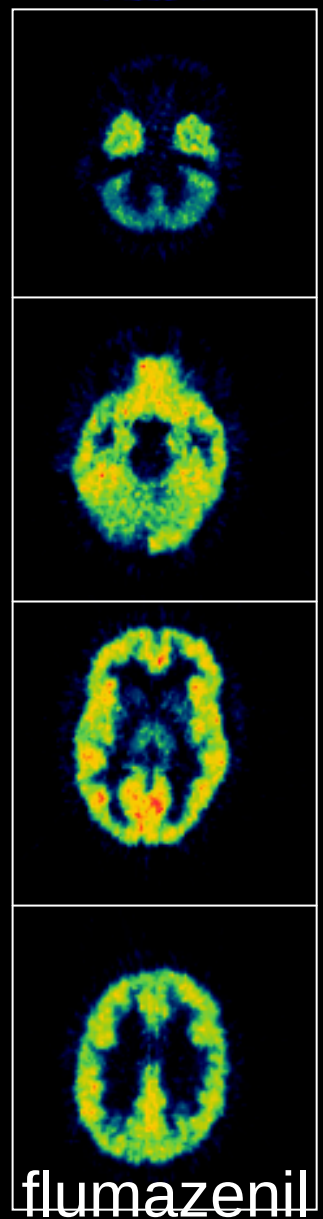
$GABA_A$ subunits are differentially distributed in the brain



SPET

PET





iomazenil

flumazenil

Roles of GABA-BDZR subtypes in benzodiazepine function.

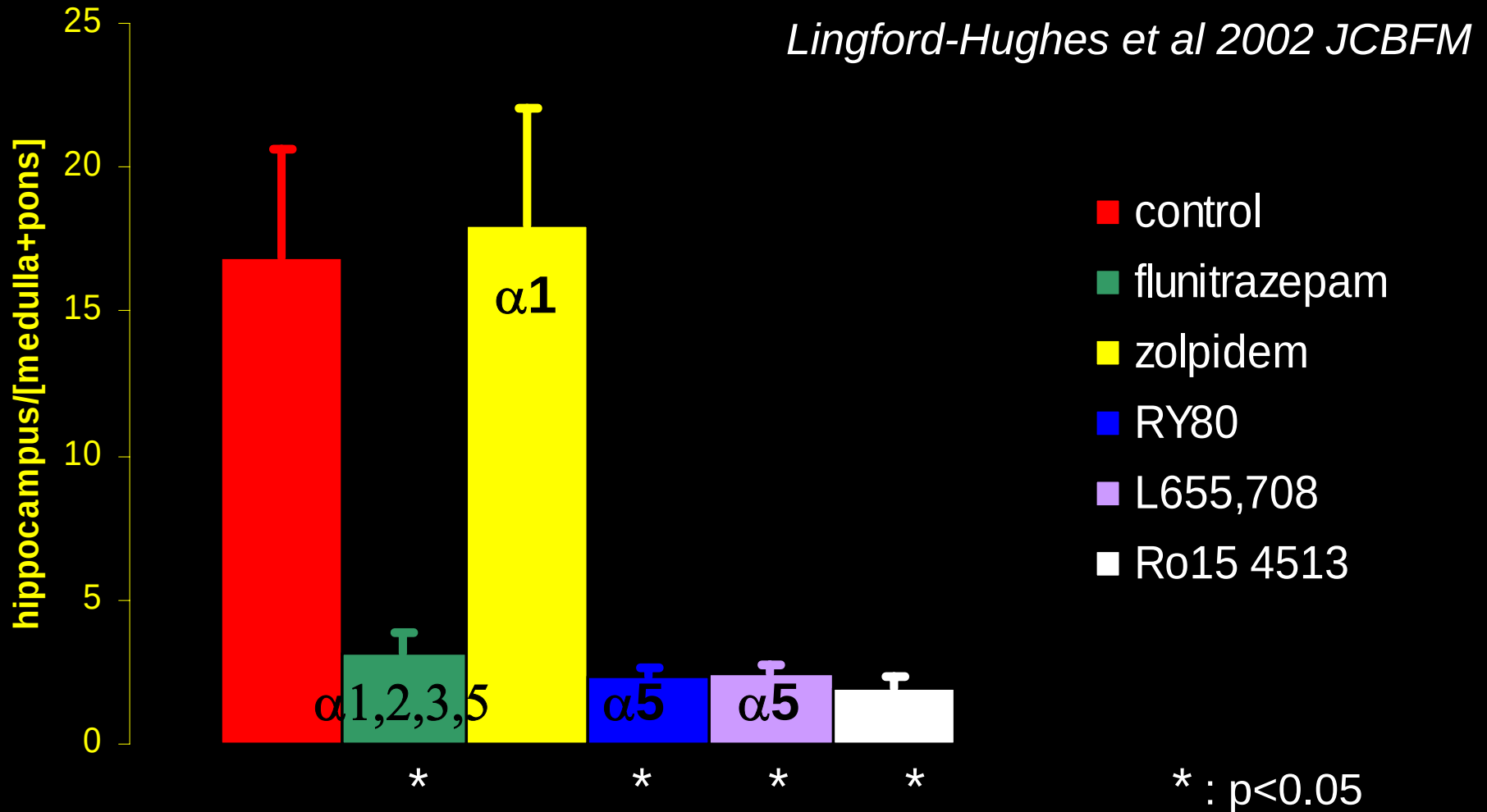
	α1	α2, α3, α5
sedation	+	-
amnesia	+	-
seizure threshold	+	+
anxiolysis	-	+
myorelaxation	-	+
motor impairment	-	+ [α6]
ethanol potentiation	-	+ [α5]
memory / learning	-	+ [α5]

Competition studies in the rat :

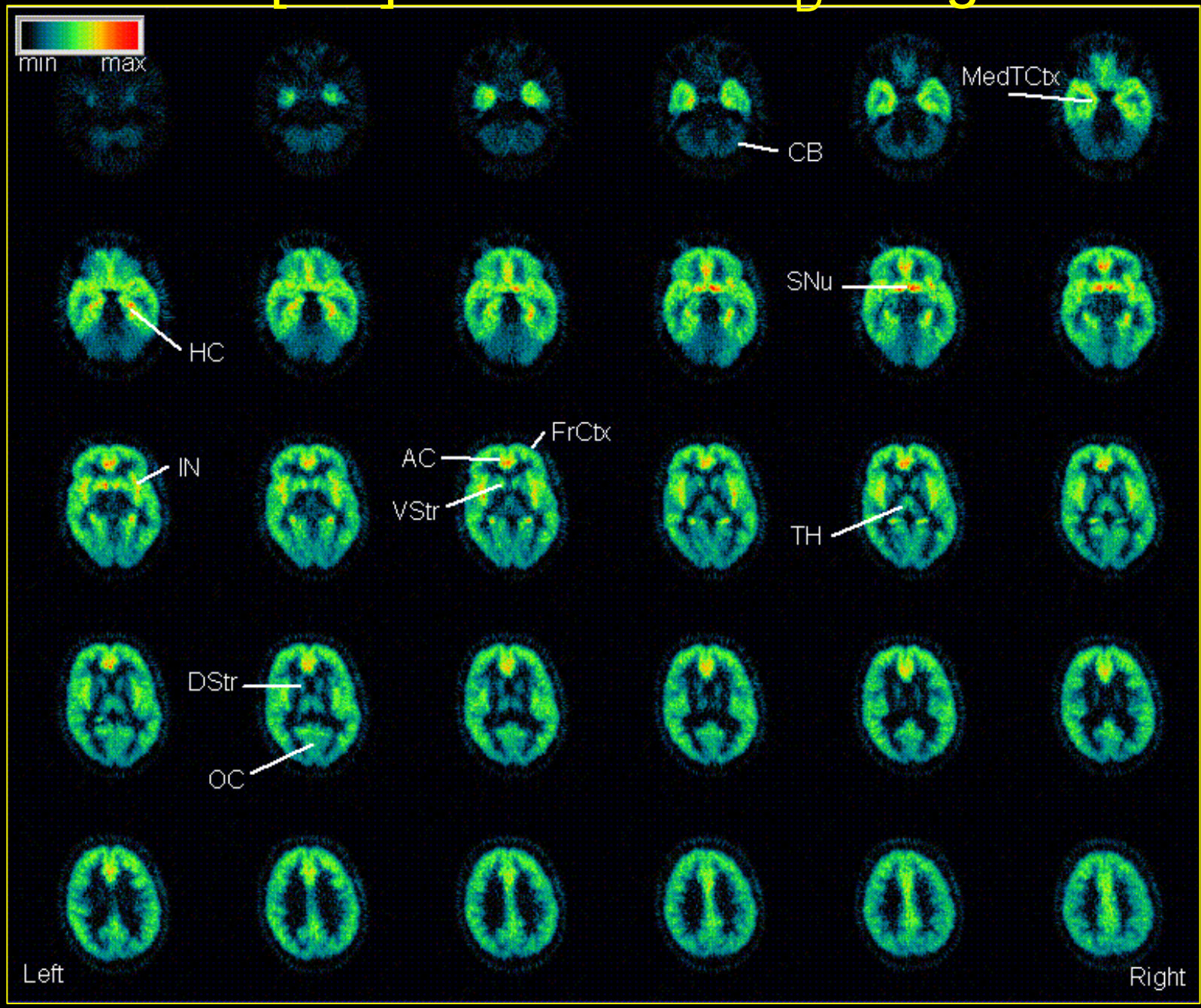
Binding of [^{11}C] / [^{3}H]Ro15 4513 in the hippocampus.

α5 selective compounds reduce Ro15 4513 binding

Lingford-Hughes et al 2002 JCBFM

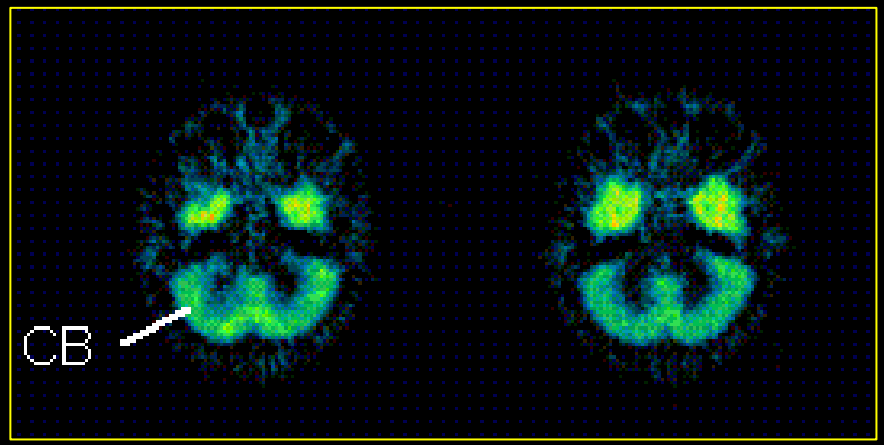


A [^{11}C]-Ro15 4513 V_D image

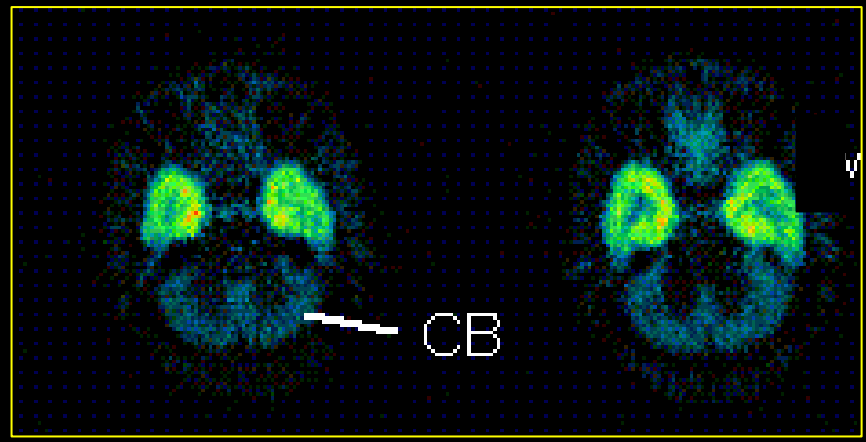


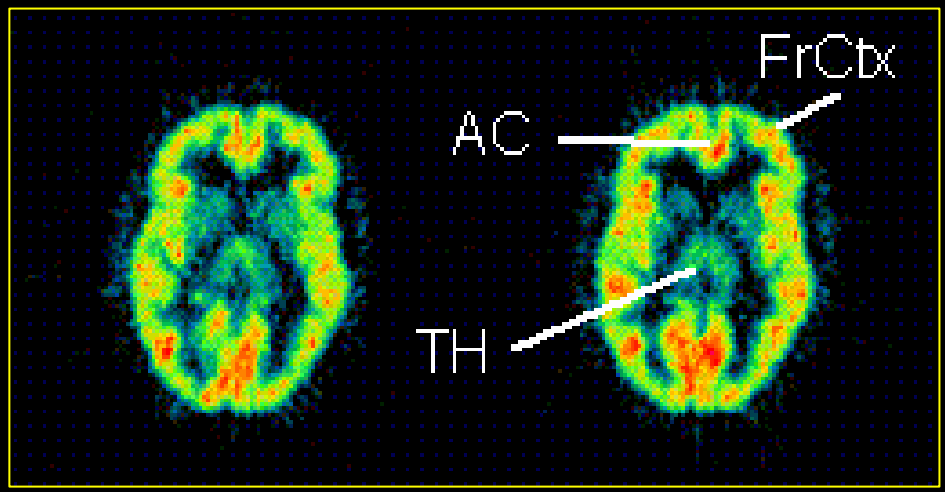
Comparing images of

[^{11}C]flumazenil

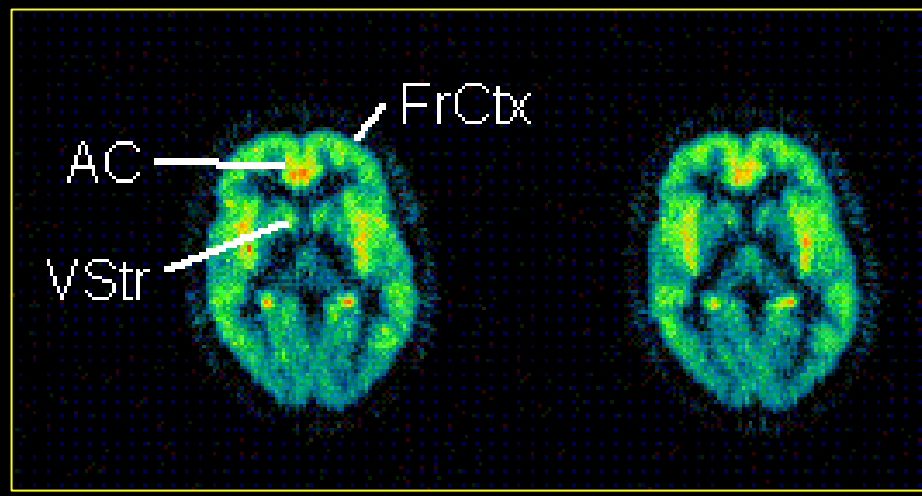


[^{11}C]Ro15 4513





Non-specific cortex



Limbic cortex / system

Acknowledgements.

- Institute of Psychiatry
  - Prof Robert Kerwin
  - Dr Peter Woodruff
  - Dr Jane Marshall
  - Dr John Suckling
  - Dr Ed Bullmore
  - Dr Lyn Pilowsky
- Psychopharmacology Unit, University of Bristol
  - Prof David Nutt
  - Dr. Sue Wilson
  - Dr. Mark Daglish
  - Dr Adrian Feeney
  - Dr. Simon Davies
- Institute of Nuclear Medicine
  - Prof Peter Ell
  - Dr Paul Acton
  - Dr Durval Costa
  - Dr Sveto Gacinovic
- MRC CSC Cyclotron Unit, Hammersmith Hospital
  - Prof Paul Grasby
  - Prof David Brooks
  - Prof Vin Cunningham
  - Dr. Sue Hume

Supported by Wellcome and MRC

All staff and patients at London and Bristol Addiction Services.