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

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

*Scanned at least 6 weeks after withdrawal*
Inject tracer $[^{11}\text{C}]$flumazenil

T=0

PET scan (105 min)
Inject tracer \[^{11}C\text{flumazenil}\]

Infuse midazolam  
50\(\mu\)g/kg over 5 min

\(T=0\)  \(\leftrightarrow\)  \(T=30\text{min}\)

PET scan (105 min)
PET scan (105 min)

Inject tracer [\textsuperscript{11}C]flumazenil

Infuse midazolam 50\,\mu g/kg over 5 min

T=0

\leftrightarrow

T=30\,\text{min}

EEG

saccadic eye movements

blood for midazolam concentration
Whole head time-radioactivity curve for $^{11}$C-flumazenil.

- $K_1$
- $k_2$

- k2 increases post-midazolam
- $[k_2d]$

- midazolam

- time (secs)
EEG beta activity.

EEG beta activity.

midazolam

time (secs)
Benzodiazepine kinetics.

Plasma midazolam level

betta amplitude

time (secs)
Results.

No differences in
- midazolam levels
- $^{11}$C-flumazenil metabolism
- rate constants describing $^{11}$C-flumazenil uptake [$K_1$, $k_2$, $k_{2d}$]
- brain receptor occupancy
Brain receptor occupancy by midazolam

Displacement: \( \frac{k_2 d}{k_2} \)

Control
Alcohol dependent
Change in EEG beta activity after midazolam infusion

- EEG beta power
- Minutes after infusion
- Alcohol dependent
- Non-alcohol dependent

Infusion: midazolam 50mcg/kg
Subjective sleep ratings.

controls
alcoholics

midazolam
Saccadic eye movements
Time first able to perform SEMs.

![Bar chart showing the number of subjects who were able to perform SEMs at different times after midazolam administration.](chart.png)
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-focused program
Imaging of craving

- **PET**
  - $\text{H}_2\text{H}^{15}\text{O}$
  - $^{18}\text{F-FDG}$
- **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

- **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

Composite Score

- Alcohol Dependent Neutral Stimulus
- Alcohol Dependent Alcohol Stimulus
- Control Subject Neutral Stimulus
- Control Subject Alcohol Stimulus

Stimulus Repeat

Before After Before After Before After Before After Before After Before After

1 2 3 4 5 6

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

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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