Depression

- Depression affects 3.5 m UK citizens and 21 m US citizens
  - Twice as common in women (12%) as in men (7%)
- Current therapies (e.g. SSRIs, NRIs, SNRIs) have limitations
  - Many patients are treatment resistant
  - Slow onset of action
  - Side-effects/withdrawal problems
  - Poor compliance
- Need for a rapid onset, well-tolerated treatment
- Registration trials require large numbers of patients due to placebo effects
- Recent history of costly Phase 3 failures
  - e.g. Neurokinin NK-1 antagonists
- Potential for experimental medicine studies to select best compound(s) for late stage trials
The Neurochemical Story

MAOIs prevent monoamine catabolism

TCAs, SSRIs, NRIs, SNRIs inhibit monoamine re-uptake

Other actions facilitate neurotransmitter function
The Cognitive Psychology Story

Events

- Negative appraisal bias
  - Low mood
  - Negative memories
  - Negative schema

Clinical depression
Cognitive Cycles in Depression

Events

- Negative appraisal bias
- Negative memories

Low mood

Negative schema

Clinical depression
Emotional Test Battery

Background

- Identify semi-discrete components of neuropsychology or physiology that provide insights into pathophysiology and drug action in depression
- Memory, attention and interpretation are biased towards negative information in depression
- Similar biases towards threat-relevant stimuli are found in anxiety and depression
  - Increased recognition of fearful facial expressions in depression
- Cognitive behavioural therapy attempts to remediate the conscious negative biases in the treatment of depression/anxiety
- Do antidepressants work by correcting more automatic negative biases?

A collaboration with Catherine Harmer, Phil Cowen and Guy Goodwin, University of Oxford
Objectives

- To show how experimental studies of emotional processing may directly link drug action to psychology in volunteers

- To provide an Emotional Test Battery (ETB) to detect potential antidepressant efficacy in volunteers
  - Emotional categorisation and emotional memory
  - Facial Emotion Recognition Task (FERT)
  - fMRI Blood Oxygen Level Dependent (BOLD) response in relevant brain regions
Emotional Categorisation

Would you like to be called this personally?

- Obnoxious
- Original
- Ugly
Emotional Categorisation and Emotional Memory Method

- Examine effects of SSRI (citalopram) and NRI (reboxetine) antidepressants in healthy male and female volunteers
- Double-blind independent group design
  - Responses to ETB stimuli altered by previous exposure
- Measures
  - Reaction time to identify positive and negative personality characteristics
  - Recall of positive and negative words
Effect of Citalopram and Reboxetine on Emotional Categorisation

Antidepressants increased speed to identify positive vs. negative personality characteristics

* $P < .05$
Antidepressants facilitated the recall of positive vs negative emotional material.
FERT Method

- Facial expressions associated with six basic emotions
  - Happiness, sadness, fearfulness, anger, surprise and disgust
- Each face 'morphed' between neutral (0%) and each emotional standard (100%) in 10% steps, leading to a range of emotional intensities
- Accuracy of recognition of each emotion, reaction time for correct answers and misclassifications recorded
- Drug studies
  - Acute citalopram (20 mg p.o. or 10 mg i.v.)
  - One week citalopram (20 mg p.o. for 7 days)
  - One week reboxetine (4 mg p.o. b.i.d. 7 days)
- Double-blind independent group design
  - Responses to FERT stimuli altered by previous exposure
FERT Stimuli

FEARFUL

ANGRY

DISGUSTED

Morphed facial expressions (developed by Young et al 1997)
FERT Responses

Angry

Percent correct

0% 25% 50% 75% 100%

10 20 30 40 50 60 70 80 90 100
Acute Citalopram (20 mg p.o.) Increases Accuracy of Recognition of Fearful Faces

Discriminatibility for seven facial expressions: □ Placebo  □ Citalopram 20 mg * p < 0.05.
Citalopram (20 mg p.o. for 7 days) Reduces Accuracy of Recognition of Fearful Faces

Facial expression intensity

Recognition of fear and happiness over different intensity levels of facial expression used in the FERT following citalopram (●) and placebo (■).

Left graph: fear recognition; Right graph: happiness recognition.
Citalopram Reduces Medial Temporal Lobe fMRI Responses to Fearful Faces

Medial temporal lobe BOLD response to fearful facial expressions reduced in volunteers receiving citalopram (20 mg p.o. for 7 days) vs placebo.

Placebo>Citalopram response to fear

Mixed effects analysis, FSL (Oxford), Clusters determined by Z>2.3 and (corrected) cluster significance threshold of p<0.01

![Brain images showing medial temporal lobe activity comparison between placebo and citalopram conditions.](image-url)
Fear: parahippocampal – limbic response suppressed by citalopram

Placebo-citalopram

Extra visual processing too
Reboxetine Reduces Amygdala fMRI Responses to Fearful Faces

Amygdala BOLD response to fearful facial expressions reduced in volunteers receiving reboxetine (4 mg b.i.d. 7 days) vs placebo

Right amygdala response to covert fear: ■ Placebo  □ Reboxetine 4 mg b.i.d. 7 days
*P<0.03.
Conclusions from FERT Studies

- **Acute citalopram (20 mg p.o. or 10 mg i.v.)**
  - Facilitated recognition of fear
  - Acute SSRIs/serotonin promoting drugs have been reported to increase anxiety responses in preclinical models and facilitate conditioned fear in humans

- **Citalopram (20 mg p.o. for 7 days)**
  - Decreased the recognition of negative emotional faces
  - Decreased medial temporal lobe fMRI response to fearful faces

- **Reboxetine (4 mg p.o. b.i.d for 7 days)**
  - Produced a similar effect to citalopram on face recognition
  - Reduced amygdala fMRI responses to fearful faces
Conclusions from ETB Studies and Next Steps

- SSRI and NRI antidepressants given for 7 days
  - Increased speed to identify positive vs. negative personality characteristics
  - Facilitated recall of positive vs negative emotional material
  - Decreased accuracy of recognition of fearful facial expressions
  - Decreased BOLD responses fMRI responses to fearful facial expressions

- Citalopram has differential effects on FERT when given acutely and for 7 days prior to testing
  - Potential to measure bidirectional mood changes
  - Anxiogenic and/or antidepressant actions of novel compounds in Phase 1 clinical studies

- Next steps to establish clinical relevance
  - Examine behavioural and fMRI responses to ETB in an “at risk” population (dysphoric volunteers selected using the BDI)
  - Examine sensitivity of ETB and fMRI measures to antidepressants in dysphoric volunteers

- Emotional Test Battery (ETB) meets the aims of an experimental medicine approach
  - Drug sensitive
  - Predictive value
  - Operationally feasible and portable
  - Has face validity and should be independent of drug-mechanism

- Potential for making early Go/No Go decisions on drug candidates