

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

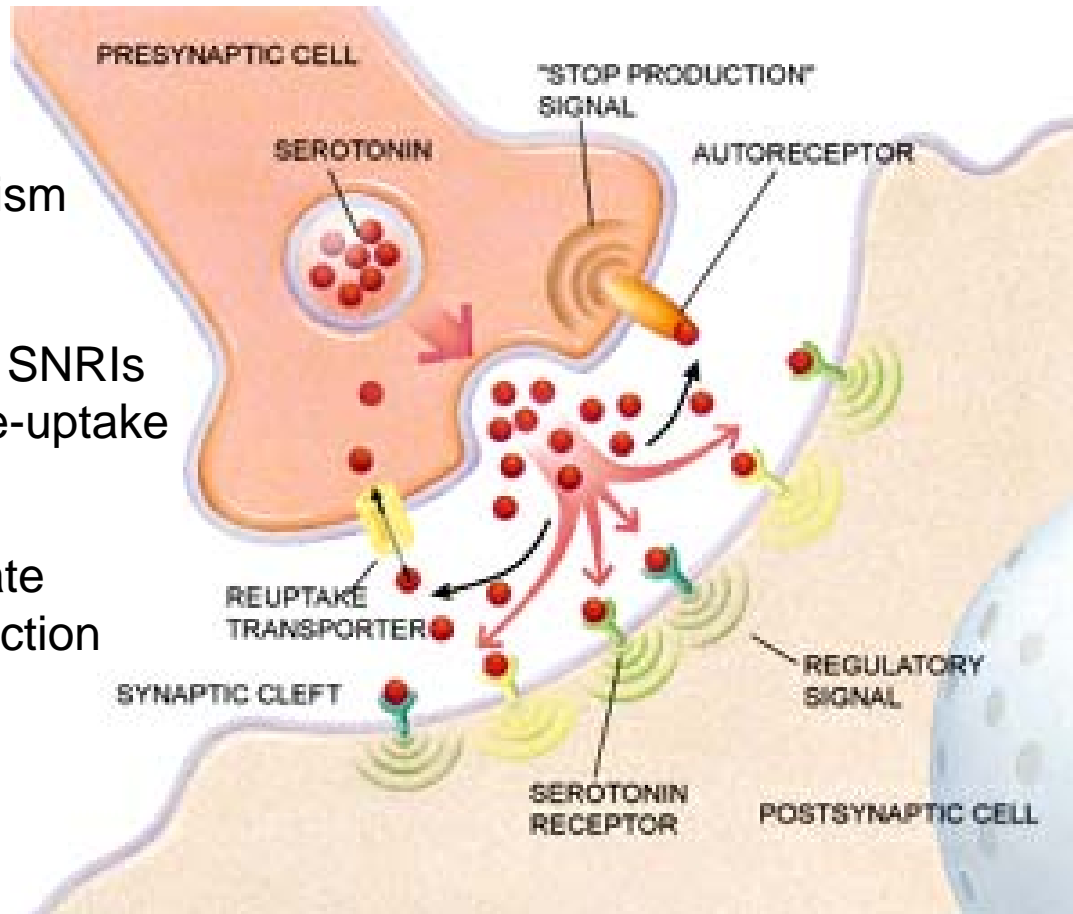
The Neurochemical Story



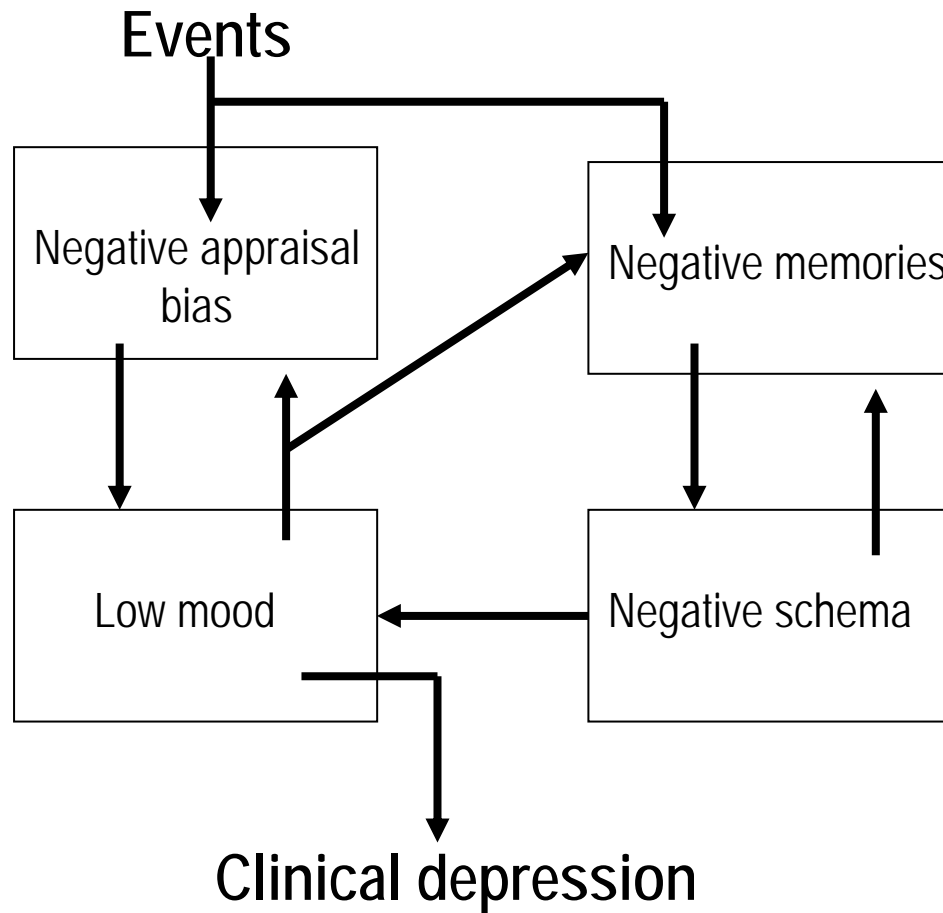
MAOIs prevent monoamine catabolism

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

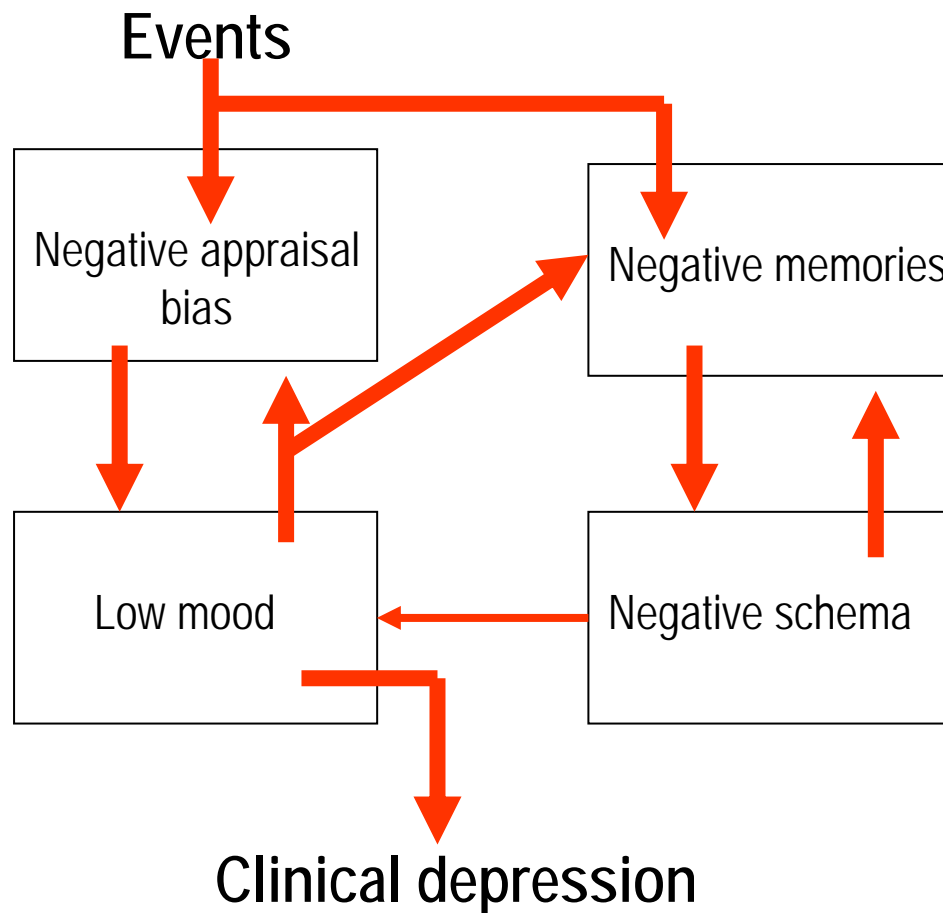
Other actions facilitate neurotransmitter function



The Cognitive Psychology Story



Cognitive Cycles in 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?

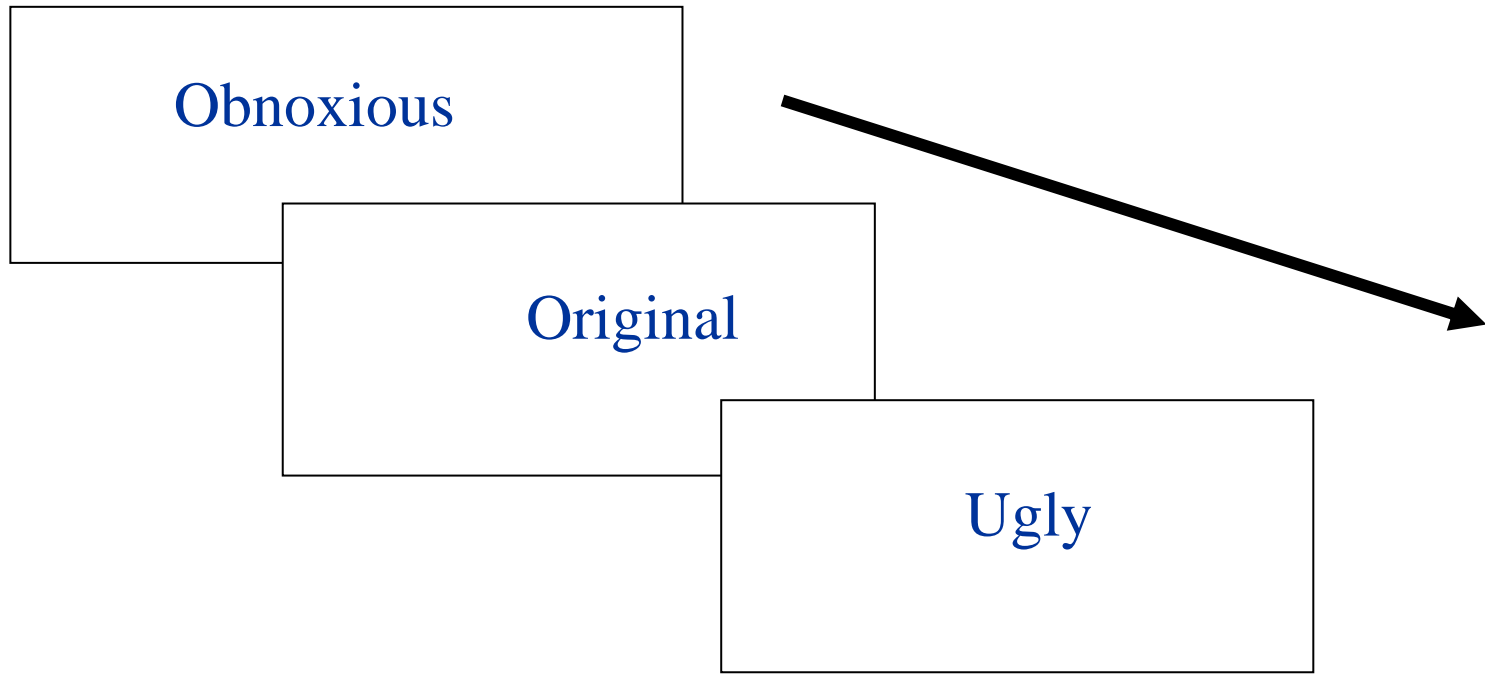
A collaboration with Catherine Harmer, Phil Cowen and Guy Goodwin, University of Oxford

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



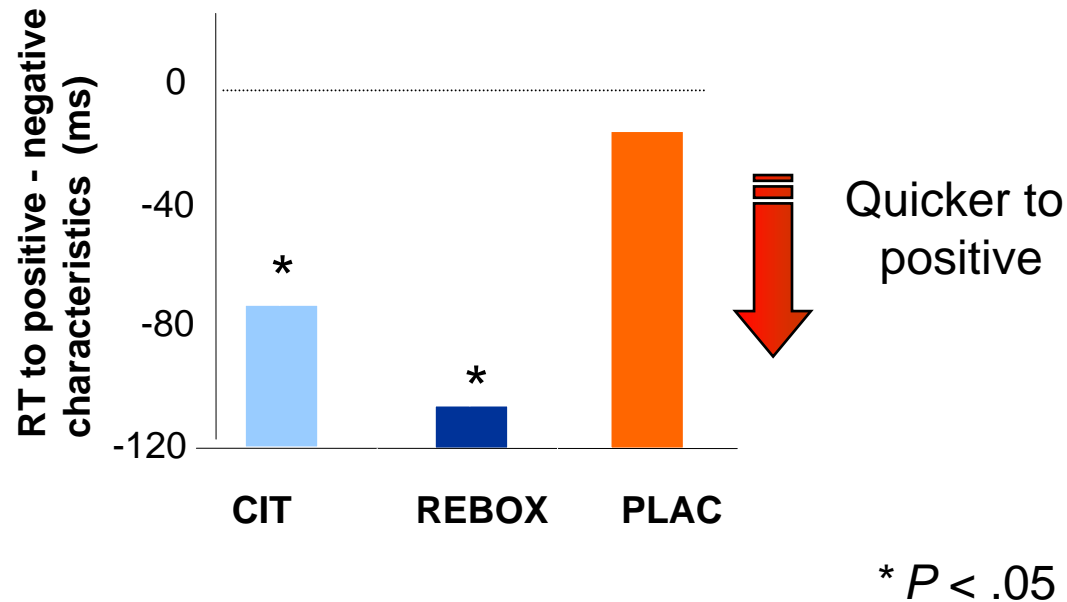
Would you like to be called this personally?

Emotional Categorisation and Emotional Memory Method



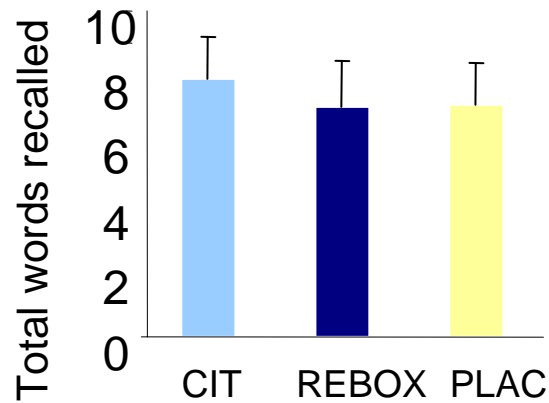
- Examine effects of SSRI (citalopram) and NRI (reboxetine) antidepressants in healthy male and female volunteers
- Double-blind independent group design
 - Responses to ETB stimuli altered by previous exposure
- Measures
 - Reaction time to identify positive and negative personality characteristics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

Effect of Citalopram and Reboxetine on Emotional Categorisation

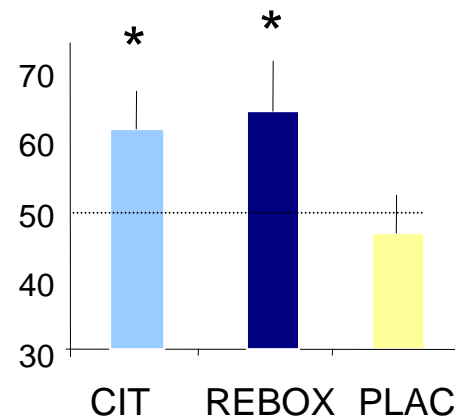


Antidepressants increased speed to identify positive vs. negative personality characteristics

Effect of Citalopram and Reboxetine on Emotional Memory



Positive words recalled
as percent of total



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

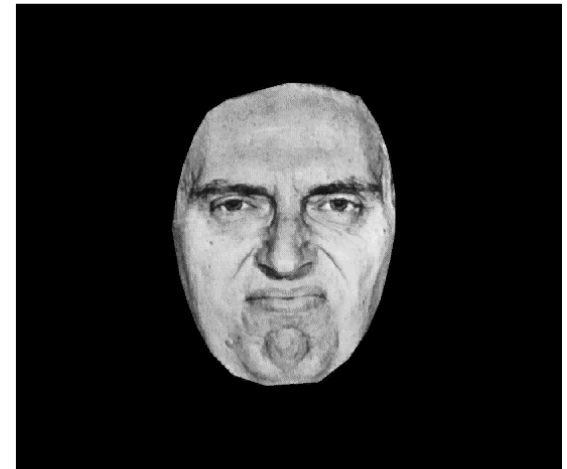
FERT Stimuli



FEARFUL



ANGRY

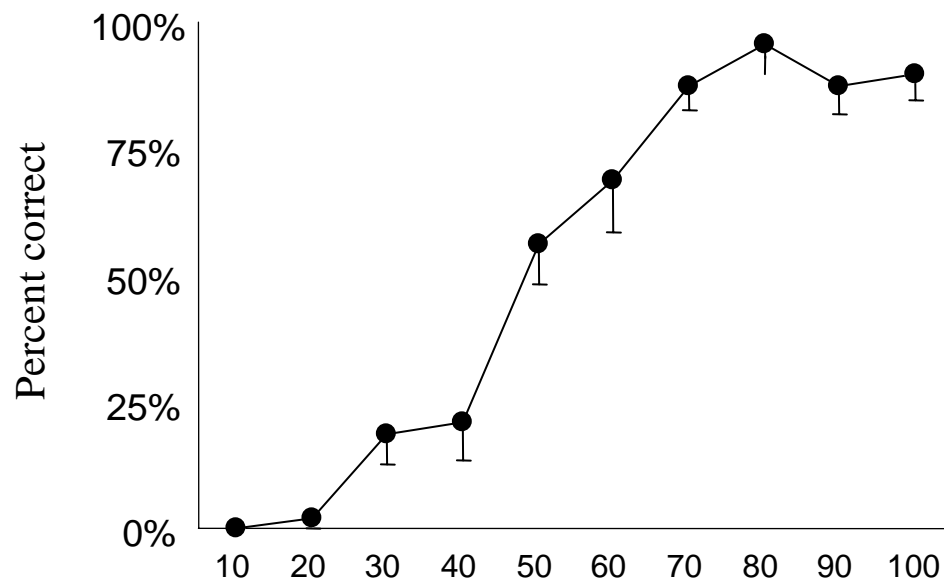


DISGUSTED

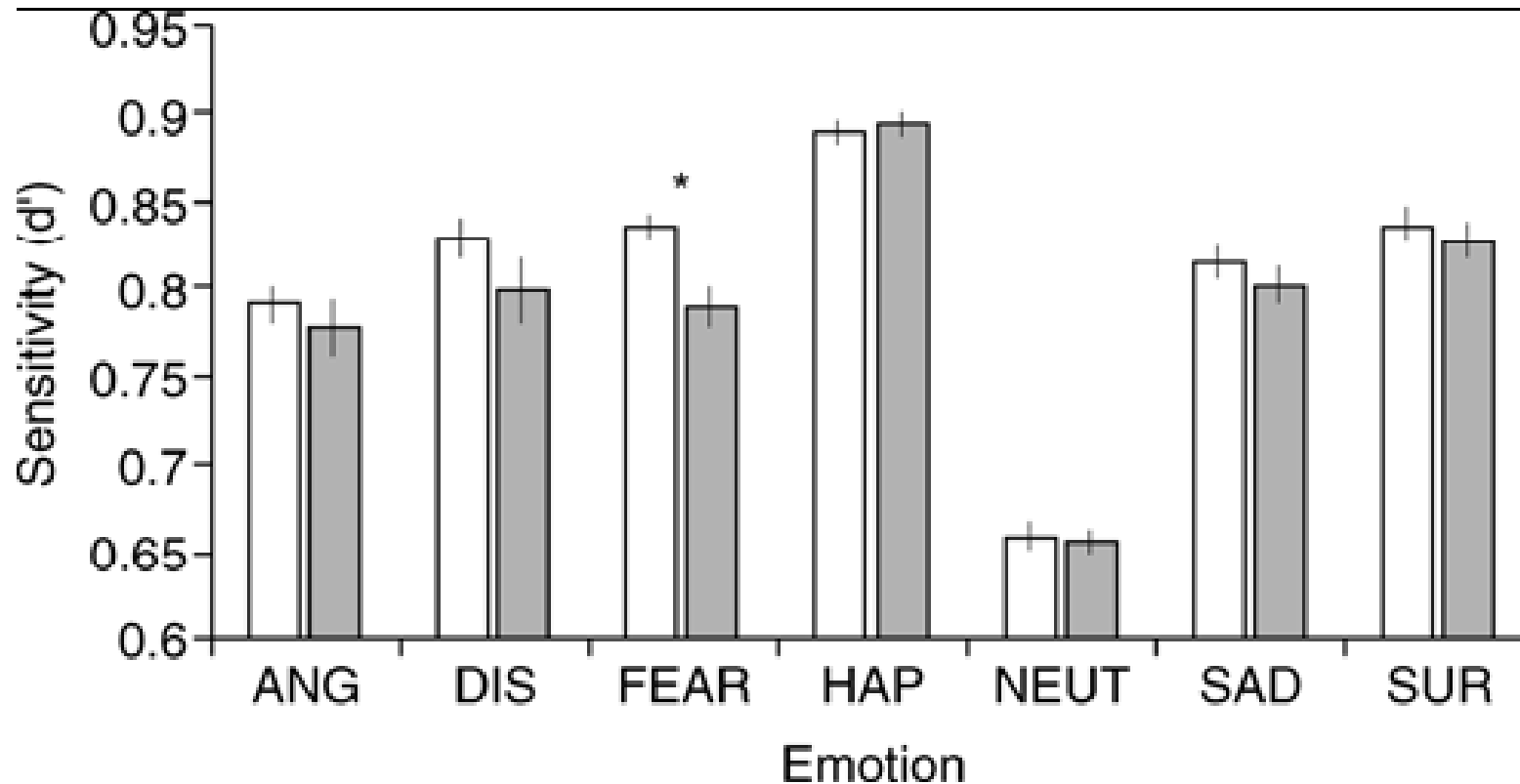


Morphed facial expressions (developed by Young et al 1997)

FERT Responses

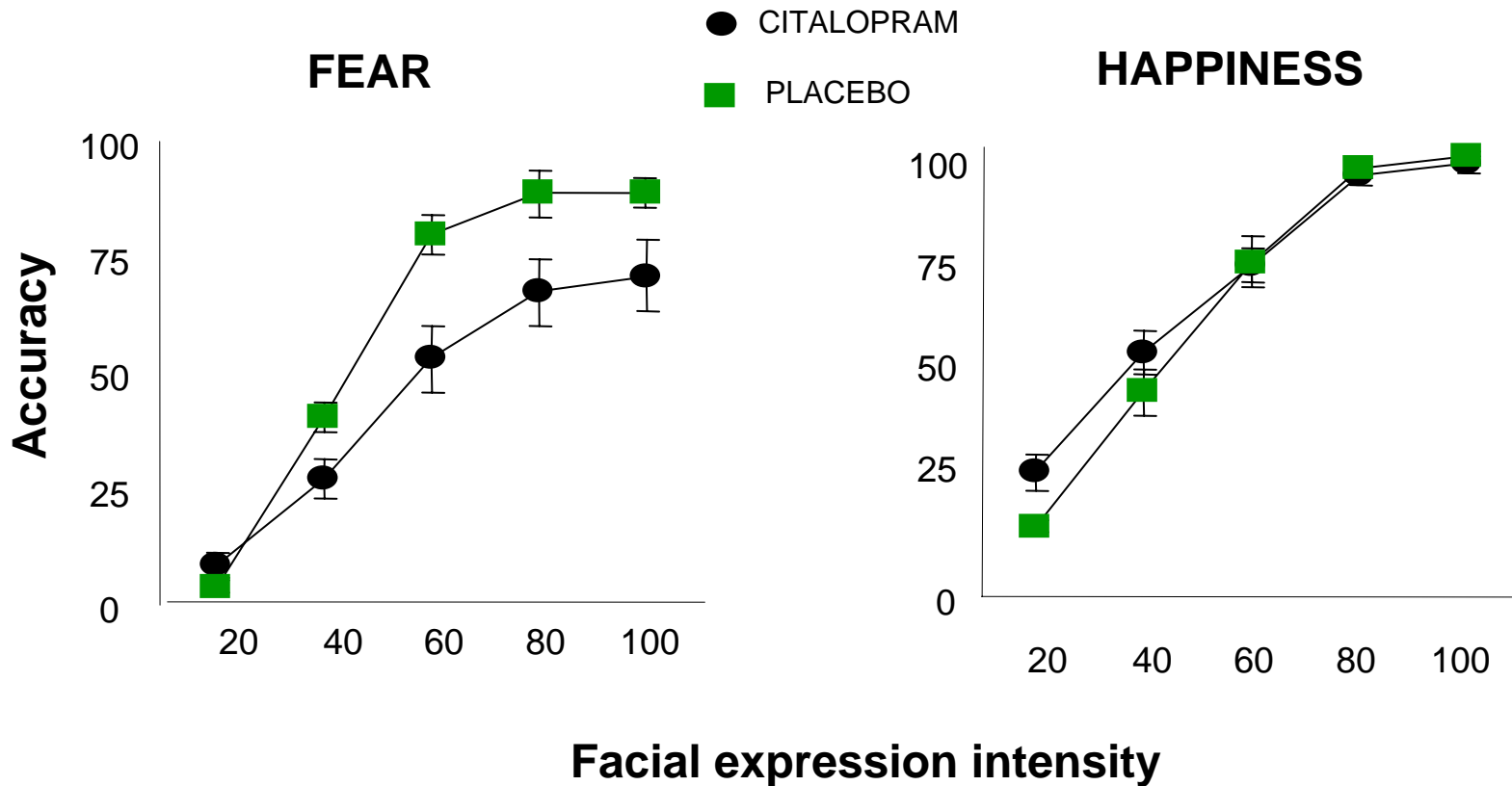


Acute Citalopram (20 mg p.o.) Increases Accuracy of Recognition of Fearful Faces



Discriminability 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



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

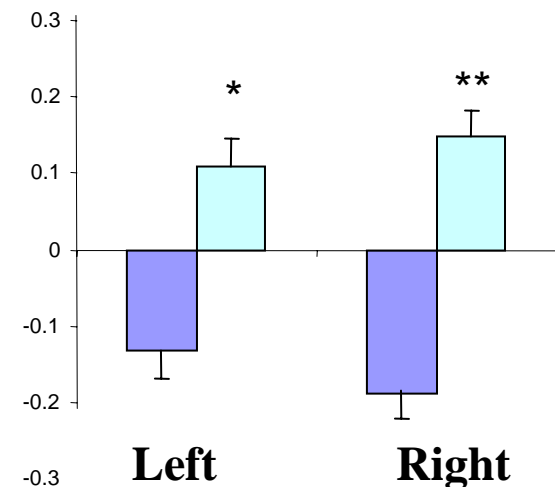
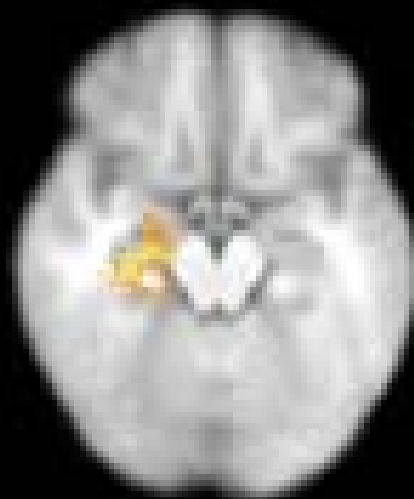


Medial temporal lobe BOLD response to fearful facial expressions reduced in volunteers receiving citalopram (20 mg p.o. for 7 days) vs placebo



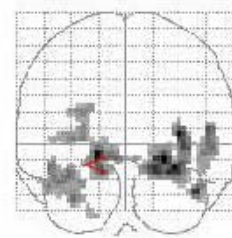
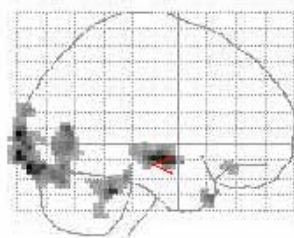
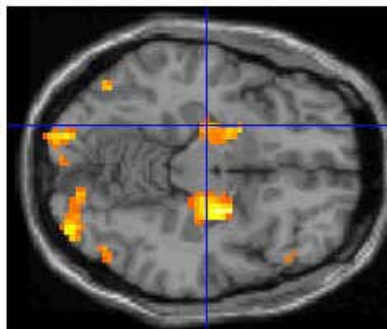
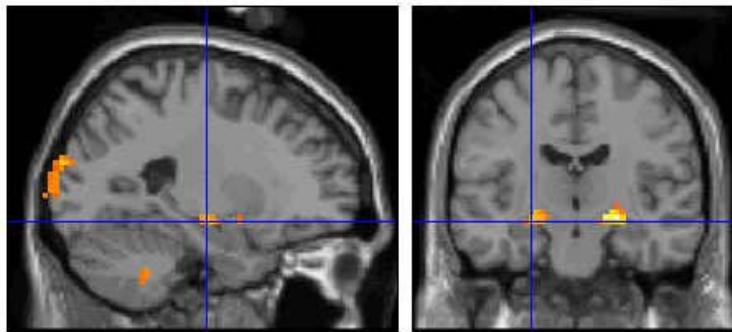
Placebo > Citalopram response to fear

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

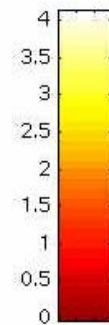
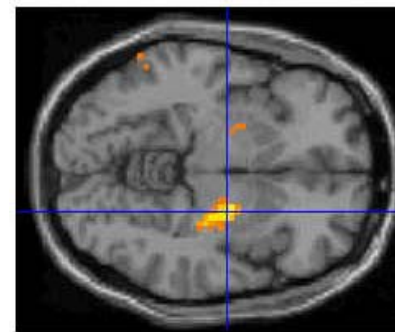
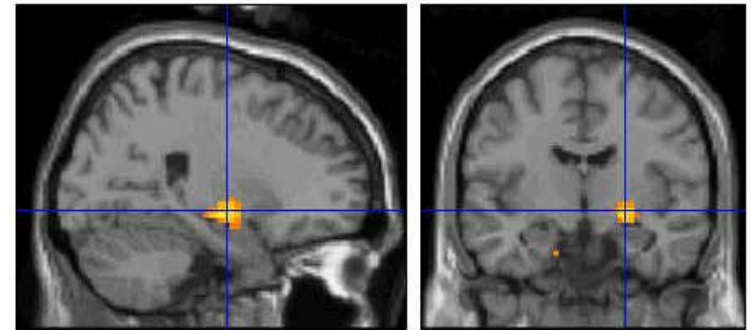


Placebo
Citalopram

Fear: parahippocampal – limbic response suppressed by citalopram



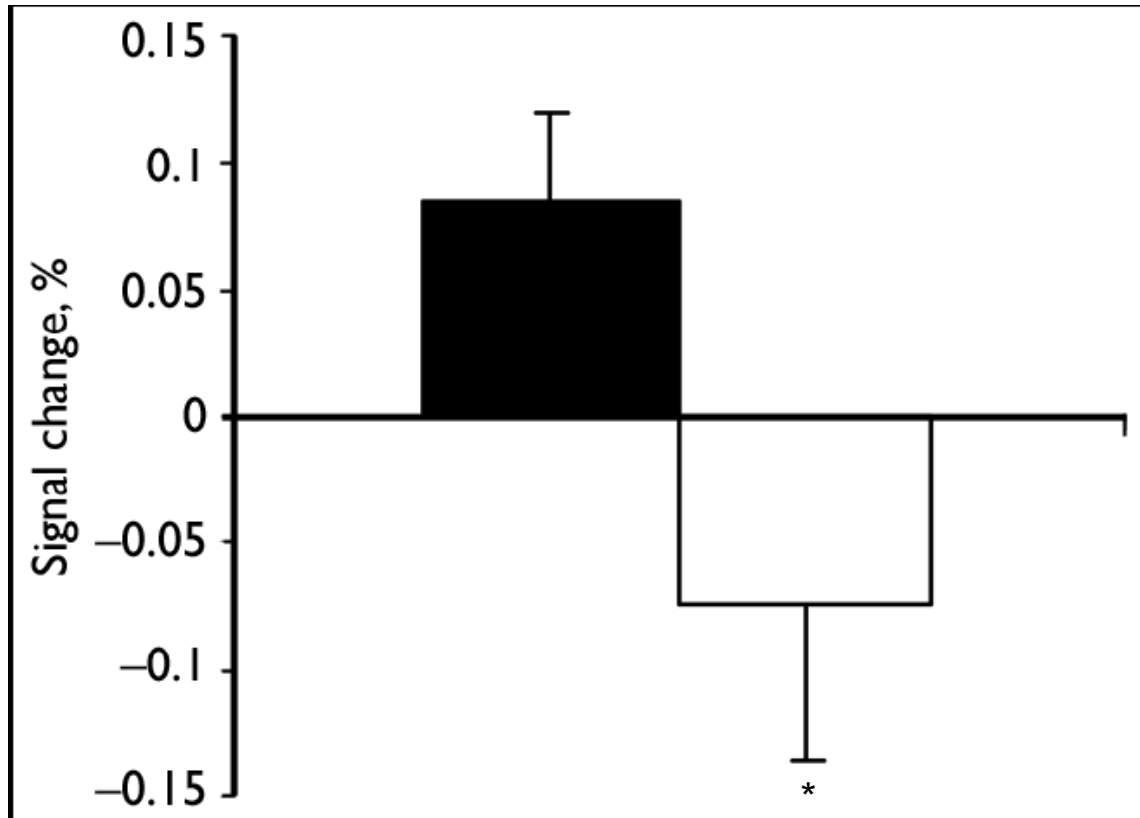
SPM T_{11}



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