Neuropsychological Mechanisms of Antidepressant Drug Action

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How do antidepressant treatments work?

- **Pharmacological focus:** “We think that antidepressants work by increasing the activity of key neurotransmitters. The chemicals most involved are thought to be serotonin and noradrenaline.”

- **Clinical Psychology focus:** “We need to identify and correct patterns of dysfunctional thinking, behaviour and emotional responses, which are supported by negative processing biases.”
Example
Hey, Joe!
Joe ignored me. Why doesn’t he like me?
No one likes me.
An alternative interpretation
Hey, Joe!
Joe was in a hurry! I wonder where he was going…
This always happens to me. It’s not fair.
An alternative interpretation
SQUELCH
At least I wasn’t wearing flip flops!
Increased serotonin → Downstream neuroadaptive effects → Improved mood → Resolution of negative bias

Traditional

Cognitive Neuropsychological

Increased serotonin → Delay → Downstream neuroadaptive effects → Change in emotional bias → Improved mood

Delay

Delay
Do antidepressants affect negative biases early in treatment of depressed patients?

Healthy volunteers and acutely depressed patients randomised to receive placebo or antidepressant (reboxetine) in a double blind design. Emotional processing assessed 2h later.
Facial expression recognition

ANGRY
DISGUSTED
FEARFUL
HAPPY
SAD
SURPRISED
NEUTRAL
Harmer et al. 2009

Effects of depression

Healthy controls
Depressed patients

Effects of acute reboxetine

Depressed: placebo
Depressed: reboxetine

Happiness recognition

Recognition of happiness

30 35 40 45 50

* **
Emotional Categorisation
Emotional Memory

Effects of depression

Effects of acute reboxetine

Number of items recalled

- Negative
- Positive

Healthy
Depressed

Healthy
Depressed

Dep, Placebo
Dep, Reboxetine

* P < 0.05
** P < 0.01
Predicting clinical response?
Association with later clinical response

- Improvement in happy recognition following two weeks antidepressant treatment predicted clinical outcome at week 6

FERT: facial expression recognition task;

Tranter et al., 2009
Can we classify likely responders?

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<td>10</td>
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</tr>
<tr>
<td>Total</td>
<td>23</td>
<td>25</td>
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</tbody>
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- 91% of those patients who did not respond on emotional processing measure did not respond to their antidepressant treatment.
- 60% of patients who responded to emotional processing also responded to the antidepressant treatment.
Emotion recognition processing as early predictor of response to 8-week citalopram treatment in late-life depression

Week 1 recognition of happy facial expression predicted later clinical improvement in late life depression (Shiroma et al., 2014)
Prediction of therapeutic gain from emotional processing bias interacted with levels of interpersonal support

- A change in emotional processing with antidepressant drug treatment may be more effective when combined with good interpersonal support/function (Shiroma et al., 2014)
Antidepressants affect the processing of emotional information in depressed patients.

These effects occur early in treatment.

Changes in emotional bias predict later clinical changes in symptoms (in interaction with the environment).
Neural Correlates
Modulating dysfunctional limbic-cortical circuits in depression: towards development of brain-based algorithms for diagnosis and optimised treatment

Helen S Mayberg

Neurobiology of Emotion Perception II: Implications for Major Depressive Disorder

Mary L. Phillips

Review

Localization of Dysfunction in Major Depressive Disorder: Prefrontal Cortex and Amygdala

Elisabeth A. Murray, Steven P. Wise, and Wayne C. Drevets

Despite considerable hypothesis about its deficit in the valuation system, dysfunction of the amygdala and corticomedial prefrontal cortex contributes to MDD

Neurocognitive Mechanisms in Depression: Implications for Treatment

Luke Clark,1 Samuel R. Chamberlain,1,2 and Barbara J. Sahakian1,2
The depressed patients showed the expected increased amygdala response to negative facial expressions.
A 7 day treatment with 10mg escitalopram normalised this amygdala response.
A clinical predictor?
Study design

• Acutely depressed patients: escitalopram (10mg) for 6 weeks

Godlewska et al. *submitted*
Early change in neural processing of fear predicts antidepressant response
Summary

- Antidepressant treatments decrease amygdala responses to fear early in treatment and independently from changes in mood.

- These effects precede and predict clinical changes in mood.

- A parallel series of studies showed these effects are apparent in healthy volunteer models, with a variety of different antidepressants and within hours of the very first dose (Harmer et al., 2009).
Drug development
A drug development biomarker?

- Pre-clinical animal models of depression: poor prediction of eventual therapeutic success in depression

- Can an experimental medicine approach with healthy volunteers improve on preclinical screening of new compounds?
Glutamate and depression

- Ketamine (NMDA antagonist): early improvements in depression in treatment-resistant patients (Zarate et al 2006)

- Biomarker study: effects of ketamine and novel NMDA antagonist (AZD6765) on emotional processing 24 hours after drug infusion in depressed patients. Manchester and Oxford, in collaboration with P1vital Ltd.

Zarate Arch Gen Psychiatry. 2006;63:856.
AZD6765 decreased amygdala responses during negative facial expression processing.

Fear faces

Sad Faces

% signal change

AZ   Plac   Ket

AZ    Plac   Ket

AZD6765
Placebo
Ketamine

Brain scan images with color scale indicating signal change.
AZD6765 and ketamine increased positive memory intrusions
Summary

- AZD6765 had an antidepressant profile in these emotional processing models.

- Experimental medicine models may provide a way of improving prediction and characterisation of effective treatments for depression.

- Understanding the early psychological effects of antidepressant drug treatments may improve our understanding of how these treatments work.
Do psychological interventions have similar effects?

- CBT for depression and anxiety tends to reduce negative processing biases, measured at the end of treatment (Fu et al 2008; Tobon et al 2011)

- But can we see early effects of CBT before therapeutic change as we do with drug treatment?

- 28 patients with DSM-IV panic disorder and agoraphobia, unmedicated during last 6 months, given single session CBT or equivalent experimenter contact
Single-session CBT
Panic disorder and agoraphobia (N=28)

Baseline

Post-Treatment Day

4-Weeks Follow-up
Attentional bias measurement

Attentional bias: faster responses to detect probe when in same (vs opposite) location to threat face

Reinecke et al., 2012
Symptom changes with single session CBT are expressed with a delay

Agoraphobia
(Mobility Inventory)

Score

Waiting Group

CBT Group

Baseline
Post-Treatment Day
4-Weeks Follow-up

Reinecke et al (2013)
Early changes in emotional bias predict later clinical changes

Threat bias one day after treatment

Prediction of symptom change during 4-weeks follow-up

$R^2 = .44, p = .01$
Summary

- Bias changes early during CBT, before therapeutic effects become apparent
- Emotional processing change might drive symptom change
- Involves a similar mechanism to that proposed for pharmacological treatments.
What underlies antidepressant response and what this means for treatment

- Growing awareness that we need to look beyond simple neurochemical explanations of action
- Changing psychological processes important in depression and anxiety appears to occur with both drugs and psychological treatments before changes in clinical state
- Future treatments may optimise these effects
  - Drug development screening
  - Experimental medicine model for proof of principle
  - Explicit hypothesis and framework for approaches to speed up translation into therapeutic action.
Acknowledgements

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