HOW DO ANTIDEPRESSANT DRUGS WORK?

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WHY DO SSRIS TAKE SO LONG TO WORK?

There is a long delay between the start of antidepressant treatment and the expected response.

This gap slows down finding the right treatment for each individual.

Research has focused on the changes which occur in the brain with a delay i.e. brain change = mood improvement.
ANTIDEPRESSANTS

Drugs

Neurochemicals & the brain

Serotonin

Psychiatrists

THERAPY

Talking

Challenging thoughts & beliefs

How we deal with emotion

Psychologists
Negative Bias in information processing
Negative affective bias is a key psychological factor in the maintenance of depression.

Antidepressant drugs affect emotional processing very early in treatment.

Early effects of antidepressants on emotional processing

Improvement in symptoms takes time
Can we see a change in processing emotional information within hours of the first dose of an antidepressant?
HAPPINESS RECOGNITION

Effects of depression

- Healthy controls
- Depressed patients

Effects of one antidepressant dose

- Depressed: placebo
- Depressed: drug

EMOTIONAL MEMORY

**Effects of depression**

- **DOMINEERING**
- **CHEERFUL**
- **MEAN**
- **UNTIDY**
- **POISED**
- **HOSTILE**
- **ORIGINAL**
- **OPTIMISTIC**

*Effects of depression*

<table>
<thead>
<tr>
<th></th>
<th>Healthy</th>
<th>Depressed</th>
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</thead>
<tbody>
<tr>
<td><strong>Negative</strong></td>
<td><img src="0-4" alt="Blue Bar" /></td>
<td><img src="2-4" alt="Gray Bar" /></td>
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<tr>
<td><strong>Positive</strong></td>
<td><img src="4-5" alt="Blue Bar" /></td>
<td><img src="3-4" alt="Gray Bar" /></td>
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*p<0.05; **p<0.01

EMOTIONAL MEMORY

Effects of one antidepressant dose

* p<0.05; ** p<0.01; Dep, depressed patients

Are early changes in emotional processing associated with clinical response?
EMOTIONAL PROCESSING AS EARLY PREDICTOR OF RESPONSE TO 8-WEEK CITALOPRAM TREATMENT IN LATE-LIFE DEPRESSION

Change in recognition of happy facial expression by Day 7 predicted later clinical improvement in late-life depression

Also see:
Tranter et al. 2009 increase in happy recognition associated with later clinical benefit
Browning et al. 2019 emotional processing change at week 1 to identifies likely non responders (82% correct).

HAM-D17, Hamilton Depression Rating Scale 17-item version

MODEL FOR PREDICTION: A ROLE FOR THE ENVIRONMENT

- Increased serotonin
- Change in emotional bias
- Improved mood

Isolation
Difficult environment
A change in emotional processing with antidepressant drug treatment may be more effective when combined with good interpersonal support / function.

ISEL, Interpersonal Support Evaluation List

SUMMARY

1. Antidepressants affect the processing of emotional information in depressed patients.

2. These effects occur early in treatment and independently from changes in mood.

3. Changes in emotional bias predict later clinical changes in symptoms (in interaction with the environment).
Using emotional processing to understand neural effects of antidepressant treatment
FRONTO-LIMBIC CIRCUITRY IS IMPORTANT FOR NEGATIVE BIAS IN DEPRESSION

• Exaggerated responses in amygdala to negative stimuli

• Under engagement of areas involved in regulation (DLPFC/mPFC) to emotional stimuli

Mah et al., 2015
EFFECTS OF ANTIDEPRESSANTS VS PSYCHOTHERAPY

Role for amygdala response: antidepressants

Role for medial PFC response: psychotherapy

Meta analysis synthesis by Nord et al., 2021

Antidepressants reduce amygdala reactivity; psychotherapy increases mPFC response

(caveat, very different types of studies between treatments)

Nord et al., 2021
NEURAL EFFECTS CAN BE SEEN VERY EARLY IN TREATMENT

Healthy controls

Depressed: Placebo

Depressed: Escitalopram

fMRI Positive vs negative faces

7 days

HAMD; BDI

Godlewska et al 2011
Effect of depression

• The depressed patients showed an increased amygdala response to negative facial expressions

Godlewska et al 2011
Early effect of treatment

- A 7 day antidepressant treatment normalised this amygdala response

Godlewska et al 2011
ARE NEURAL EFFECTS OF SSRIS DIFFERENT IN RESPONDERS VS NON-RESPONDERS?

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

fMRI, functional magnetic resonance imaging

Godlewska et al 2016
SSRI RESPONDERS SHOW EARLY CHANGES IN NEURAL RESPONSE TO EMOTIONAL STIMULI
Do psychological treatments have similar effects on emotional processing?
BEHAVIORAL ACTIVATION

– focused on daily behaviour and finding right balance of routine, pleasurable and necessary activities.

Is BA effective given remotely and during lockdown?

Is BA able to target emotional processing biases?

Susannah Murphy
Co-supervisor

Tereza Ruzickova
DPhil student

Clinical assessments 😊 Facial expression recognition

Ruzickova et al in press
BA REDUCES DEPRESSION, ANXIETY AND ANHEDONIA DURING THE COVID-19 PANDEMIC
BA DECREASES NEGATIVE BIAS IN EMOTIONAL PROCESSING

Recognition of negative faces

Misclassifications of negative to more positive

Early change in facial expression recognition (week 2) was also associated with change in BDI at week 4.
Clinical Implications

A way of understanding and communicating how treatments may be working together with patients

Use as a human model to characterize and predict novel treatments in development (e.g. Post et al 2016)

Early predictor of nonresponse in patients starting SSRI treatment (Browning et al., 2021)
The PREDICT Trial

Patients prescribed SSRI medication for depression

Predicted (treatment change guided by early markers of non-response)

Treatment as usual

Primary outcome: % responders on depression measures at week 8

Other outcomes: anxiety at week 8; function at week 8 and 24

N=913
UK
Germany
France
Holland
Spain

CI: Mike Browning

Browning et al 2021

Co-funded by the Horizon 2020 Framework Programme of the European Union
Lewis et al 2019: SSRI’s in primary care have more robust effects on anxiety than depression
# PREDICT TRIAL OUTCOMES

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<tr>
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<th>Predict</th>
<th>TAU</th>
<th>P-value</th>
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<tbody>
<tr>
<td>QIDS-SR-16</td>
<td>55.9% responder</td>
<td>51.8% responders</td>
<td>0.25</td>
</tr>
<tr>
<td>Primary (week 8)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>GAD-7 (week 8)</td>
<td>-6.12</td>
<td>-5.44</td>
<td>0.04 *</td>
</tr>
<tr>
<td>SAS-SR (week 8)</td>
<td>-7.60</td>
<td>-6.51</td>
<td>0.1</td>
</tr>
<tr>
<td>SAS-SR (week 24)</td>
<td>-9.70</td>
<td>-7.48</td>
<td>0.004 **</td>
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- The Predict group (early ‘non-responders’ identified and treatment adjusted) did better in terms of anxiety and function but not depression
- Change in anxiety at week 8 mediated later change in function

QIDS_SR – Quick Inventory of Depressive Symptoms, self report, 16 items
GAD-7 Generalised Anxiety Disorder Assessment, 7-item version,
SAS-SR Social Adjustment Scale

Browning et al 2021
Early changes in emotional processing are meaningful even at an individual level.

Early resolution of symptoms may be useful for return to and maintaining function.

More work is needed to optimize clinical translation and prediction.
CONCLUSIONS

- Focusing on psychological effects of drug treatments may help us understand how these drugs are working and why the effects are sometimes delayed or incomplete.

- This approach suggests that there are early changes with antidepressant treatment – relevant for patients and clinicians.
- Pharmacological and psychological treatments may best be considered within the same framework and may be synergistic.

- Using these as cognitive biomarkers can be used for the early screening and selection of novel drugs (Harmer et al. 2017).
- These cognitive biomarkers may lead to earlier identification of individuals not responding to antidepressant drug treatment (tested in the PReDicT trial: Kingslake et al., 2017; Browning et al. 2021).
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