

Emotional cognition in depression: Is it relevant for Clinical practice?

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Introduction

Our cognitive function is influenced by emotion, from what we attend to, the decisions we make and the memories we form. This kind of emotional processing can itself be influenced by affective disorders such as depression and anxiety and can play a role in the maintenance of symptoms by prioritising negative information and reinforcing negative thoughts and self-beliefs (Roiser and Sahakian 2013). Negative biases in emotional processing can be measured with both questionnaires (such as the dysfunctional attitude scale) and performance on tasks which tap into attention, interpretation and memory for emotionally-charged stimuli. These kind of negative biases are believed to precede depression and depressive relapse and represent a vulnerability marker for the disorder (Disner et al 2011). Typically the remit of psychologists and a target for psychological treatment, recent research has revealed an effect of antidepressant drug treatment on emotional processing which has been implicated in their mechanism of action (Harmer et al. 2017).

Early effects of antidepressants on negative affective bias

SSRIs and similar antidepressants rapidly change negative affective bias often within hours of the first dose. For example, a single dose of the antidepressant reboxetine increased the recognition of happy facial expressions and memory for self-referent positive stimuli (Harmer et al. 2009). At a neural level, negative affective bias has been associated with an imbalance in corticolimbic circuitry including an increased response in subcortical areas such as the amygdala response to negative stimuli and/or reduced engagement of prefrontal regulatory responses (Disner et al 2011). A recent meta-analysis suggests that, while antidepressants particularly modulate the amygdala which is involved in vigilance and fast responses to salient stimuli, psychotherapy may affect higher order neural systems including medial PFC which is involved in regulation and contextualisation of emotion (Nord et al 2021). Early effects of antidepressants on amygdala responses can be seen prior to changes in symptoms and are associated with later clinical response i.e. responders tend to show larger reductions in amygdala responses to negative vs positive stimuli after 7 days of treatment compared to later non-responders (Godlewska et al. 2016).

These results suggest that antidepressants may not directly target mechanisms directly underpinning mood but rather work by changing the balance of positive vs negative emotional processing which, over time and in interaction with social and emotional experiences, leads to their antidepressant effects. This framework has a number of potential clinical applications.

A framework for discussing mechanisms of action with patients

Understanding how antidepressants are working at a psychological level goes beyond a narrow focus on neurochemistry or brain function and can help demystify their mechanism of action. This can be a powerful message for patients and clinicians. It suggests that treatments are not inert for the first few weeks (as previously believed) but have positive effects which can be detected and built upon for greater clinical response. This approach has been integrated in training programmes and workshops for Psychiatrists and trainees (e.g. National Neuroscience Curriculum Initiative NNCI: <https://www.nncionline.org/course/what-to-say-changing-the-way-we-think-about-and-with-antidepressants/>).

Considering antidepressant drug action in combination with other approaches

Different interventions for depression are often considered within different frameworks, with different terms and levels of analysis. An understanding of the psychological effects of

antidepressants provides a common mechanism of action for pharmacological and psychological treatments, and is thus likely to be of value given that these types of treatment are often used in combination (Nord et al 2021). More broadly, social and environmental factors may moderate the effects of antidepressants (Chiarotti et al 2017). By describing how antidepressants alter the processing of social and environmental information this work provides an opportunity to consider, at a mechanistic level, how antidepressant treatment may most effectively be combined with social and/or psychological interventions.

Use in human experimental medicine models for new treatment innovation

Current screens of novel antidepressant treatments for potential efficacy are largely based on preclinical animal models which have relatively low predictive validity for what happens in the clinic. We have worked together with the pharmaceutical industry to explore the utility of using human based emotion models to screen and understand novel treatments in development (Post et al., 2018). This approach may speed up decision making during novel treatment development and facilitate successful translation into patient care. It allows novel treatments to be understood in more detail, in humans, before large scale and costly randomised controlled trials (RCTs). The information gained during this experimental medicine phase can then be used to inform and optimise subsequent RCT design. It is important to assess whether these same models are sensitive to the effects of fast-acting antidepressants such as ketamine.

Providing an earlier marker of nonresponse to SSRIs

The rapid influence of antidepressants on emotional processing suggests that measures of bias might be useful in predicting whether an individual is likely to respond or not to their treatment. Using of the facial expression measure of affective bias, we found that it was possible to predict, after one week of antidepressant treatment, whether depressed patients would respond to a full six week course (Browning et al., 2019). Building on this work, we then demonstrated in a large randomised controlled trial that using the same predictive algorithm to guide antidepressant treatment led to improved symptoms of anxiety and functional outcomes in patients, when compared to non-guided treatment, though there was no difference in terms of depression response (Browning et al 2021). This highlights a potential role for assessments of emotional cognition in the clinic to provide objective measures of response earlier in treatment than typically possible. Further testing and optimisation of this application is urgently called for.

Conclusions

In summary, understanding how antidepressants influence emotional cognition is useful in terms of how psychiatric treatments are conceptualised, developed and deployed. By providing a common mechanistic language across different forms of treatment it allows us to consider how they may best be combined. When deployed in the clinic, these approaches may help in explaining treatment mechanisms to patients and potentially to help guide treatment selection for depression and other conditions involving emotional processing changes

References

- Browning, M., Bilderbeck, AC., Dias, R., Dourish, CT., Kingslake, J., Deckert, J., Goodwin, GM., Gorwood, P., Guo, B., Harmer, CJ., Morriss, R., Reif, A., Ruhe, HG., van Schaik, A., Simon, J., Sola, VP., Veltman, DJ., Elices, M., Lever, AG., Menke, A., Scanferla, E., Stäblein, M., Dawson, GR., 2021 The clinical effectiveness of using a predictive algorithm to guide antidepressant treatment in primary care (PReDiCT): an open-label, randomised controlled trial. *Neuropsychopharmacology* 46, 1307-1314.
- Browning, M., Kingslake, J., Dourish, CT., Goodwin, GM., Harmer, CJ., Dawson, GR., 2019. Predicting treatment response to antidepressant medication using early changes in emotional processing. *Eur Neuropsychopharmacol.* 29, 66-75.
- Chiarotti, F., Viglione, A., Giuliani, A., Branchi, I 2017 Citalopram amplifies the influence of living conditions on mood in depressed patients enrolled in the STAR*D study. *Transl Psychiatry.* 7, e1066.
- Disner, SG., Beevers, CG., Haigh, EA., Beck, AT., 2011 Neural mechanisms of the cognitive model of depression. *Nat Rev Neurosci.* 12,467-77.
- Godlewska, BR., Browning, M., Norbury, R., Cowen, PJ., Harmer CJ, 2016 Early changes in emotional processing as a marker of clinical response to SSRI treatment in depression. *Transl Psychiatry*, 6, e957.
- Harmer, CJ., O'Sullivan, U., Favaron, E., Massey-Chase, R., Ayres, R., Reinecke, A., Goodwin, GM., Cowen PJ., 2009 Effect of acute antidepressant administration on negative affective bias in depressed patients. *Am J Psychiatry* 166, 1178-84.
- Harmer, CJ., Duman, RS., Cowen, PJ., 2017 How do antidepressants work? New perspectives for refining future treatment approaches. *Lancet Psychiatry* 4, 409-418.
- Nord, CL., Barrett, LF., Lindquist, KA., Ma, Y., Marwood, L., Satpute, AB., Dalglish, T., 2021 Neural effects of antidepressant medication and psychological treatments: a quantitative synthesis across three meta-analyses. *Br J Psychiatry* 25, 1-5.
- Post, A., Smart, TS., Krikke-Workel, J., Dawson, GR., Harmer, CJ., Browning, M., Jackson, K., Kakar, R., Mohs, R., Statnick, M., Wafford, K., McCarthy, A., Barth, V., Witkin, JM., 2016 A Selective Nociceptin Receptor Antagonist to Treat Depression: Evidence from Preclinical and Clinical Studies. *Neuropsychopharmacology* 41, 1803-12.
- Roiser, JP., Sahakian, BJ., 2013 Hot and cold cognition in depression. *CNS Spectr.* 18,139-49.