The effects of drugs on human models of emotional processing: an account of antidepressant drug treatment

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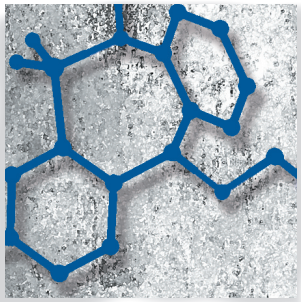

Human models of emotional processing suggest that the direct effect of successful antidepressant drug treatment may be to modify biases in the processing of emotional information. Negative biases in emotional processing are documented in depression, and single or short-term dosing with conventional antidepressant drugs reverses these biases in depressed patients prior to any subjective change in mood. Antidepressant drug treatments also modulate emotional processing in healthy volunteers, which allows the consideration of the psychological effects of these drugs without the confound of changes in mood. As such, human models of emotional processing may prove to be useful for testing the efficacy of novel treatments and for matching treatments to individual patients or subgroups of patients.

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Introduction

Human models of emotional processing provide a bridge between pharmacological and psychological accounts of depression and its treatment. In this review we will consider how such models may be useful in explaining the psychological mechanisms by which successful treatments for depression exert their effects, and their potential applications.

The monoamine hypothesis—does manipulating central mononamine levels *directly* affect mood?

The late 1950s saw the chance discovery of the first psychiatric drugs, and with it a sea-change in psychiatry moving from a largely psychoanalytic to a more biological approach—biochemical changes were now suggested to underlie the etiology of depression. In its simplest formulation, the monoamine hypothesis of depression states that low mood can be attributed to reduced central monoamine neurotransmission whilst antidepressant treatment works by reversing these changes.[1] Evidence for the hypothesis came from data showing that antidepressants potentiated monoamine neurotransmission, that depleting monoamines could cause depressed mood, and that patients with depression might have abnormalities in these systems.[2-4]

The hypothesis has generated much controversy, with a central issue of whether manipulating central

monoamine levels has a direct, causal effect on mood.[5] The clearest evidence for a direct link between monoamine neurotransmission and mood comes from the demonstration that reducing central monoamines can induce low mood. For example, nutritional manipulation acute tryptophan depletion (ATD) lowers central serotonin neurotransmission[6] and lowers mood in some groups of participants.[7] However, the effects of ATD on mood are most reliable in those who have an underlying vulnerability to depression, and the procedure does not reliably reduce mood in healthy volunteers.[7] Moreover, although antidepressant drugs are useful in treating low mood, Alec Coppen (one of the pioneers of antidepressant treatment) himself pointed out a serious problem in the argument that monoamines directly affect mood: "[…] but monoamine deficiency is not the sole cause of the disorder, and although patients do respond to monoamine oxidase inhibitors and tryptophan they do not do so as quickly or effectively as with ECT."[4] This remains true today, despite the development of newer treatments with reduced side-effect profiles, the primary target of the majority of antidepressant remains to increase monoamine neurotransmission, and it typically takes 2 to 6 weeks of treatment before clinically significant decreases in symptoms are seen.[8]

Taking these findings together, it has become increasingly difficult to argue that monoamines have a direct effect on mood, and pharmacological explanations of antidepressant drug action have looked to the downstream neurophysiological effects of the drug to explain their efficacy.

The neurocognitive model of antidepressant drug action: is the direct effect of antidepressant treatment a modification of emotional processing?

Pharmacological accounts have emphasized a possible role for neural plasticity, and perhaps neurogenesis in particular, in explaining the delayed effects of antidepressant drugs on mood; for a review see ref 9. However, understanding how increasing or restoring neurogenesis would contribute to the relief of the psychological symptoms of depression in humans is challenging. Indeed, we and others have argued that, given the great difficulty inherent in modeling the very human symptoms of mood disorders in animals, understanding the direct psychological effects of effective psychological treatment in humans will be key to understanding how these treatments work.[10-12]

To this end, a large body of evidence has now considered the acute and short-term effects of antidepressant treatment in both human healthy volunteers and depressed patients. The key hypothesis underlying this work has been that the direct effect of antidepressant treatment is to modify emotional processing.[10-12] The term "emotional processing" here is used to describe the cognitive processing of emotional information, for example, the recognition of, memory for, and attention to emotional stimuli. The idea that biases in the processing of emotional information plays a role in depression and the relief of its symptoms is not a new one, and has its roots in cognitive theories of depression. Indeed, cognitive theories of depression, for example Beck, Rush, Shaw and Emery,[13] emphasize a key role for cognitive biases in the maintenance of and treatment for depression. A large body of evidence now documents processing biases in memory, attention, recognition, and interpretation away from positive and towards negative stimuli in patients currently unwell with depression.[14] Memory biases have perhaps been best documented, with relatively consistent evidence for increased memory for negative compared with positive information in those currently suffering from depression, with the strongest evidence being for self-relevant information.[15] For example, compared with healthy control subjects, patients with depression remembered more negative than positive self-referent adjectives.[16]

Given that such biases in cognitive processing are mood-congruent, establishing whether they play a causal role in emotional vulnerability or are rather the result of low mood has been important. Probably the clearest evidence comes from studies which demonstrate that modifying processing biases can influence mood. The classic example of such a study is that by MacLeod et al[17] in which attention for emotional stimuli in healthy volunteers was manipulated using a modified dot probe task. Their results showed that following a stress test, those who had been trained to preferentially attend to negative stimuli in the dot probe task reported more anxious symptoms.

The cognitive neuropsychological model of antidepressant drug action[10-12] therefore hypothesizes that the direct action of effective treatment for depression is to modify biases in emotional processing. These changes in the cognitive processing of emotional stimuli are linked

to the direct pharmacological action of the treatment, but they are dissociated in time from changes in mood which appear some weeks later in treatment. This delay between the direct action of the treatment and subsequent mood improvement is suggested to be caused by the need for relearning of emotional associations, which can only be achieved over time as the patient interacts with his or her social environment in the context of the modified processing bias.

An important test of this model, then, is not only whether it is possible to show the existence of processing biases in depression, but whether these can be reversed by antidepressant drug treatment on a timescale similar to the primary pharmacological target of the treatment and prior to any changes in mood. Evidence to support this comes from study in which the effects of a single dose of the selective noradrenaline reuptake inhibitor (SNRI) reboxetine were compared with placebo in both depressed and healthy volunteers.[18] In that study, compared with placebo-treated controls, depressed patients who received placebo showed a bias away from positive emotional information in tasks measuring the recognition of facial expressions of emotion and the categorization of, and subsequent memory for, self-referent adjectives. These negative biases in emotional processing were reversed in depressed patients who received the reboxetine treatment, and importantly in the absence of any changes in subjective mood or anxiety, suggesting that they are a direct effect of the manipulation rather than an epiphenomenon of changes in mood.

A number of studies have now examined whether such changes predict subsequent clinical improvements. Behaviorally, an increase in the recognition of happy faces following 2 weeks' treatment with reboxetine or the selective serotonin reuptake inhibitor (SSRI) citalopram has been shown to be correlated with clinical improvement in mood 4 weeks later.[19] It has also been possible to demonstrate that neural changes following 2 weeks of treatment with escitalopram are predictive of whether or not patients show a clinical response to the treatment 4 weeks later.[20] In older adults with depression, the recognition of happy facial expressions was marginally predictive of improvement following an 8-week open-label treatment with citalopram.[21] Interestingly, this relationship became statistically significant when perceived level of social support was included in the model; this fits well with the cognitive neuropsychological explanation of antidepressant drug action which emphasizes the need for social interaction for subsequent remission following bias change.

Thus, the cognitive neuropsychological model of antidepressant drug action hypotheses that the direct effect of effective antidepressant treatment is to remediate biased emotional processing, and that this subsequently, and in interaction with the social environment, leads to later changes in mood. Data from patients with depression support the existence of processing biases, and that these remit following even a single dose of an antidepressant, prior to any clinically significant changes in mood. Moreover, early changes in emotional processing following treatment may be predictive of subsequent clinical improvement.

Behavioral effects of antidepressant drug treatments on emotional processing in healthy volunteers

A key prediction of the cognitive neuropsychological model is that it should be possible to employ behavioral and neural models of emotional processing to investigate the effects of antidepressant treatment in healthy volunteers. This is useful for a number of reasons. For example, modeling depression in rodents is challenging, and the validity of such models has been questioned.[22] Moreover, healthy volunteers by definition do not have low mood, and so this approach allows the consideration of the psychological and neural effects of treatment free from the confound of altered mood or changes in mood state. Finally, healthy volunteer models might be a viable means of considering the potential efficacy of a putative antidepressant prior to taking it through to expensive and time-consuming phase 2 and 3 trials.

Healthy volunteer models of emotional processing use a number of behavioral tasks to measure bias; in this section we specifically consider evidence from tasks assessing emotional memory and the recognition of facial expressions of emotion.

Emotional memory

Biases in emotional memory are perhaps the best documented of the emotional processing biases in depression, based on the early work by Bower[23] on mood and memory. There is relatively consistent evidence for biases in explicit memory in depression; for a review see ref 24.

In line with the prediction of the cognitive neuropsychological model, conventional antidepressant treatments such as SSRIs and SNRIs can modulate emotional memory in healthy volunteers. For example, 7 days' treatment with either an SSRI or SNRI increased positive relative to negative emotional recall,[25] and in a separate study citalopram increased positive emotional recognition memory.[26] Following a single dose, the SNRI reboxetine positively modulated recall,[27] but this was not seen in a study in which healthy volunteers were given a single dose of the SSRI citalopram.[28]

Facial emotional expression recognition

Being able to recognize the emotion portrayed in a facial expression is fundamental to social interaction. In depression, it has been suggested that interpersonal difficulties may contribute to vulnerability and maintenance of the disorder,[29] and moreover that impairments in the ability to recognize emotion in faces may lead to these difficulties.[30] The prevalent view has been that depressed patients have negative biases in this skill; a recent meta-analysis, however, suggested rather a general deficit in facial expression recognition, with some moderate evidence to suggest that the recognition of sadness is uniquely preserved, with large sample sizes being necessary to reliably detect this effect.[31] Insufficient data in that meta-analysis meant that response bias could not be measured; moreover, both medicated and unmedicated patients were included, both of which may have limited the power of the meta-analysis to detect specific bias.

Seven days' treatment with the SSRI citalopram reduced the recognition of the negative expressions of anger, fear, and disgust as well as surprise, in the absence of any changes in subjective mood. Moreover, it is possible to detect such positive changes within hours of just a single dose of an antidepressant, so that a single dose of the SNRI reboxetine increased the recognition of happy facial expressions.[27] Studies considering the effects of a single dose of citalopram give more complex results, since they appear to show not only increases in happy recognition,[32] but also increases in the processing of fearful expressions.[28,32] Clinically certain antidepressant treatments, including citalopram, have been associated with early increases in anxiety; see for example ref 33. We have therefore suggested that these early increases in fear processing reflect this and that, as in the clinic, longer-term dosing shows a reversal of this early bias towards threat.[28] The pharmacological mechanism underlying this early increase in anxiogenic responding and subsequent reversal remains unclear, though candidate mechanisms involve desensitization of serotonin $(5\text{-HT})_{2a/c}$ postsynaptic receptors[34] or region-specific differences in net serotonin efflux following acute administration. Nonetheless, the dissociation between improved positive processing (occurring immediately and being sustained) and threat processing (often enhanced in the early stages of treatment and reversing) suggest these may rely at least to some extent on separate mechanisms.

Recent work using eye tracking suggests that antidepressant drug treatment may modify the pattern of the visual scanning of facial expressions.[35,36] This may be one low-level perceptual mechanism underlying changes in facial expression recognition following antidepressant drug treatment.

Can changes in emotional processing following antidepressant drug treatment be explained simply in terms of changes in arousal or other nonspecific effects of the drug?

As reviewed above, evidence from healthy volunteer models of emotional processing suggest that both 7-day and single doses of common antidepressant drugs have positive effects on both emotional memory and the recognition of emotion in facial expressions. Unlike depressed patients, however, healthy volunteers generally show positive biases in emotional processing at baseline.[37] This raises the possibility that changes in emotional processing in healthy volunteers might simply reflect nonspecific changes in factors such as arousal, which amplify already present positive bias. The data, however, do not support this interpretation. Subjective effects of treatment are usually measured in such studies, and there is no evidence to suggest that changes in emotional processing are correlated with any change in subjective feelings of, for example, arousal. Indeed, where subjective effects have been reported, these have usually been negative effects associated with the drug's side effects and thus there is, in fact, a clear dissociation between positive effects on emotional processing and the negative subjective effects of the drug. For example, in a single-dose study in healthy volunteers, the dual

5-HT and NA reuptake inhibitor duloxetine produced high levels of negative subjective effects, including increases in nausea and dizziness.[38] Although the drug did improve the recognition of one negative emotion (disgust, an effect which may be associated with the negative side effects), in common with selective serotonin and noradrenaline treatments, positive effects on emotional memory and the recognition of happy faces were also seen.

Neural correlates of depression and antidepressant treatment

Understanding the neural bases for negative biases in depression and their reversal following antidepressant treatment is important both to further corroborate the cognitive neuropsychological model, but also to begin to unpack the neural mechanisms underlying these changes. At the functional level, depression is conceived of as a network level disorder, meaning that multiple brain regions including frontal, striatal, and limbic areas in interaction account for the symptoms of the disorder.[11,12,39-41]

Although a network level disorder, for the purposes of this review we focus on the effects of antidepressant drugs on the amygdala as one example of the possible underlying mechanisms of these drugs. A large body of work has considered amygdala function in relation to depression and antidepressant treatment. This is not least because this area is innervated by 5-HT inputs from dorsal raphe, but also because it has been suggested to be an important region in modulated responses to threat[42] and appears to be hyperactive in depression; see for example ref 43. Facial expressions of emotion, and especially fearful expressions, have frequently been used to probe the function of this brain region, both in depression and following treatment, and several studies report increased amygdala responses to negative faces in depression.[44,45] Antidepressant treatment modifies this, and hyperactive responses in the amygdala are normalised following 7 days'[46] or longer[44,45] treatment with an SSRI. At shorter dosing regimens, the normalization of amygdala responses precedes changes in clinical status.[46] In healthy volunteers, SSRIs and SNRIs at dosing regimens of between 7 and 21 days show similar effects of reducing amygdala activity to threatening facial expressions[47-50] or increasing amygdala responses to positive facial expressions.[51]

A natural prediction from behavioral studies showing that single doses of SSRI drugs can bias towards negative facial stimuli would be that amygdala responses could be increased by acute citalopram treatment. In reality, however, the evidence following single-dose treatment is rather mixed, and both increases in amygdala reactivity[52] and decreases[53] have been reported; see for example the recent review in ref 54 and meta-analysis in ref 55. Reconciling these disparate findings is an ongoing area of research, but it will be important to take into account the nonspecific effects of the drug on brain function and individual differences in serotonergic tone. For example, a recent study found that amygdala activity was modulated following a single dose of citalopram in men homozygous for the long allele of the common polymorphism in the promotor region of the serotonin transporter gene *(5HTTLPR),* but not those who were homozygous for the short allele.[56] The reliability of the amygdala response to fearful faces over time may also need consideration. Over a 90-day period, this response was showed to be only moderate reliable, the implication of which is that longer scan periods and large sample sizes may be necessary to adequately power studies of this kind.[57]

How can we separate anxiolytic and antidepressant effects in healthy volunteer models of emotional processing?

The symptoms of low mood and anxiety are highly comorbid, and clinically some antidepressants, for example SSRIs, are useful in treating anxious symptoms. Any useful model for assessing the effects of psychoactive drugs must therefore be able to distinguish between those treatments which affect primarily anxious symptoms and those which affect the symptoms of low mood. The emotion-potentiated startle may be a behavioral assay that is useful for making this distinction, and of all the behavioral assays of emotional processing, this task perhaps most closely parallels an animal model. Clinically, the benzodiazepine diazepam is useful for treating anxious symptoms but not low mood and in healthy volunteers a single dose of diazepam reduced overall startle responses.[58] A comparison between the SSRI citalopram and the SNRI reboxetine is also useful here, since the former, but not the latter, is useful in treating anxious symptoms. Seven days' treatment with citalopram, but not reboxetine, reduced the emotion-

potentiated startle,[25] and in line with clinical experience and effects on fearful face recognition, a single dose of citalopram potentiates this startle response.[59] Measures of emotional attention towards threat may also be especially relevant to anxious symptoms, perhaps particularly with short duration of stimulus presentation.[60,61] In line with this, a single dose of diazepam modulated emotional attention away from fearful faces at very short stimulus durations, as measured by a dot probe task.[58] As would be expected, 7 days treatment with citalopram but not reboxetine was shown to reduce attentional vigilance for fearful faces, also using a dot probe task.[62] By contrast, a single dose of the anxiolytic diazepam did not result in changed facial expression recognition or emotion memory that would be consistent with those seen following treatment with conventional antidepressant medication.[57,63] Taken together, this suggests that dot probe measures of emotional attention and the emotion potentiated startle may be particularly sensitive to anxiolytic drugs, and that healthy volunteer models of emotional processing can be used to distinguish between drug efficacy for low mood and anxious symptoms.

Are human models of emotional processing just models of monoamine effects?

Although the majority of effective antidepressant drugs prescribed today still upregulate monoamine neurotransmission as their primary pharmacological action, their efficacy is imperfect, and there is continued effort to finding new and more effective treatments. Given that the evidence reviewed so far considers the effects of drugs that block the reuptake of serotonin and/or noradrenaline, one criticism of this healthy volunteer model of antidepressant drug action could be that the measures of emotional processing are rather a measure of monoaminergic receptor blockade. If this were the case, then such models would not be useful assays of putative antidepressant treatments with alternative pharmacological mechanisms, being a model of monoamine potentiation as opposed to one of antidepressant action.

Considering the effects of antidepressant treatments with diverse mechanisms of action in this human model is one way of addressing this issue. Mirtazapine is classified as a tetracyclic antidepressant having multiple receptor targets with effects at both dopamine and histamine receptors in addition to complex actions at multiple 5-HT receptors and adrenergic receptors. In healthy volunteers, a single dose of this drug modulated measures of emotional processing reducing the recognition of fearful faces, attenuating the emotion-potentiated startle, speeding up the categorization of positive words and inducing positive biases in emotional recall.[64] At the neural level, a single dose of mirtazapine reduced right amygdala responses to fearful faces in a gender discrimination task.[65] Similarly, agomelatine, which is both an agonist at the melatonergic receptors (M1 and M2) and a 5-HT2C receptor antagonist, had positive effects in the emotional processing model, reducing the recognition of sad faces, increasing positive affective memory, and reducing the emotion-potentiated startle.[66]

Can human models of emotional processing be used to discriminate between effective and noneffective putative antidepressant treatments?

A clear implication of this model of antidepressant drug action is that it should be possible to employ healthy volunteer models of emotional processing as an assay for putative novel treatments.[10] Emotional processing models in healthy volunteers may be more relevant to the human psychological disorder than animal models which have questionable validity,[22] and as such could be a useful step in the drug discovery process prior to engaging in expensive phase II and III clinical trials.

Proof of concept experimental studies using the neurokinin (NK)1 receptor antagonist aprepitant[67,68] and the *N*-methyl D-aspartate (NMDA) receptor antagonist memantine[69] support the utility of this approach. The NK1 receptor antagonists such as aprepitant were suggested as potential antidepressant agents on the basis of demonstrating antidepressant like effects in several animal models of depression[70] and performed well in early, small-scale clinical trials.[71,72] In large phase III trials, however, aprepitant failed to replicate positive effects in depression.[73] Consistent with this, in healthy volunteer models following both a single dose[67] and 7-day repeated dosing[68] aprepitant showed some limited effects on emotion processing, but these effects were more restricted and less consistent than the effects seen on emotional processing following conventional antidepressant treat-

ment. Following this, a study with the combined NK1 receptor antagonist and serotonin reuptake inhibition agent GSK424887 was the first to use this healthy volunteer model of emotional processing in a phase I clinical trial.[74] Here, a single dose of GSK424887 was compared with both citalopram and placebo, with negligible effects on emotional processing.

Following both single doses of citalopram (reflecting possible early anxiogenic responses)[28,59] and acute tryptophan depletion[75] negative changes in emotional processing can be measured in healthy volunteer models (although it is important to note that following a single dose of citalopram positive shifts in emotional processing on some measures are seen in addition to these effects on threat relevant processing). This suggests the intriguing possibility that these models might also allow the screening of novel drugs for potential unwanted depressogenic effects. Further evidence to corroborate this possibility comes from studies considering the effects of the cannabinoid antiobesity agent rimonabant, which found that both single and repeated (7 days) dosing with this agent resulted in negative biases emotional memory.[76,77] In line with these findings, in 2009 rimonabant was withdrawn from the market because of concerns about depressogenic side effects.

Together these results suggest that healthy volunteer models of emotional processing may be useful in phase I screening of drugs, both to look for antidepressant efficacy and unwanted depressogenic side effects. Further work will be required to optimize the study design and to determine parameters that could be used for go/no-go decisions for drug development pathways. In addition, although more novel antidepressant treatments such as agomelatine and mirtazapine have been tested in this model, all of the drug treatments that have been studied within this emotional processing model include at least some effects on serotonin and/or noradrenaline. Further studies to consider treatments with alternative neurochemical mechanisms of action will be necessary to validate the emotional processing model as a useful screening tool. Evidence from studies showing effects on emotional processing following nonpharmacological treatments for depression such as vagus nerve stimulation[78] and negative ion treatment[79] provide some preliminary evidence for the utility of the model in testing treatments with diverse mechanisms of action.

Is it possible to use human models of emotional processing to stratify treatment for depression?

A clear prediction of the model is that early, direct effects of treatment underlie subsequent mood improvement.[10] Amongst the many problems inherent in treating depression is the issue of how to match individual patients or subgroups of patients to the appropriate pharmacological intervention. Many patients do not respond to first-line treatment, and the delay between starting treatment and measurable clinical effects on mood means that being able to predict treatment efficacy early in treatment therefore has the potential to significantly expedite and improve treatment outcomes. Since there is evidence that models of emotional processing predict treatment response, it might be possible to use changes in performance on these tasks following a single dose of a drug to predict its suitability for particular patient. Whilst theoretically possible, this individualized approach to the use of antidepressant drug treatments would require further work to quantify the amount of change on a particular measure or measures of emotional processing that is needed in the short term to provide a fair prediction of longer-range mood improvement.[40] Current work is focusing on using mathematical approaches to develop algorithms for estimating the amount of variance explained by differences in performance on emotional processing measures.

We have also previously suggested that models of emotional processing might facilitate stratified medicine by matching subgroups of patients with similar clusters of symptoms to drugs which may be particularly effective for these particular symptom clusters.[80] As an example of this, it has previously been suggested that abnormalities in NA neurotransmission might primarily underlie symptoms of anhedonia and a loss of positive affect, whilst abnormalities in 5-HT neurotransmission might be more closely related to increases in negative affect such as sadness.[81] Preliminary evidence from existing data on the effects of drugs which primarily potentiate NA and those that primarily potentiate 5-HT suggest that broad patterns of effects in emotional processing may be associated with these two different classes of drugs, and in particular, that drugs which potentiate noradrenaline may have more prominent effects in upregulating positive aspects of emotional processing.[80] Whilst further studies will be needed to direct-

ly test this hypothesis, this does provide support for the idea that emotional processing models may be useful for determining differential effects of different classes of antidepressant drugs with implications for stratified treatment. Imaging measures taken at baseline prior to treatment may also be useful in differentiating between treatment responses to specific antidepressants. In a study comparing the SSRIs escitalopram and sertraline and the dual 5-HT and NA reuptake inhibitor venlafaxine-XR, amygdala hyporeactivity to happy and fearful faces at baseline predicted clinical responses across treatments, but amygdala hyperreactivity to sad faces specifically predicted a nonresponse to venlafaxine-XR.[82] More research will be needed to determine whether these results are related to treatment effects on NA.

Why do some antidepressant drugs work so quickly?

Until very recently the question most frequently asked about antidepressant drugs has been: why do they take so long to work? The cognitive neuropsychological model of antidepressant drug treatment can account for this delay before clinically significant effects on mood, suggesting that the primary psychological target of these treatments is to modify emotional processing and that it takes time and interaction with the social environment for this modulated processing to subsequently affect mood. It has been suggested that the modification of emotional bias may be the final common pathway by which all antidepressant drug treatments exert their positive effects on mood,[10-12] and we have reviewed evidence from drugs with diverse pharmacological actions to support this. If this is correct, then how can newly discovered fast-acting antidepressant treatments such as ketamine[83] and scopolamine,[84] which produce effects on mood within hours or days of treatment, be accommodated within the model?

There is evidence that in humans ketamine produces positive biases in emotional processing,[85] but if the hypothesis that time and interaction with the social environment are necessary is correct, then it is difficult to explain how this psychological change could be so quickly translated into changes in mood. Back translation to animal models may provide an answer to this conundrum. Recent work suggests that it is possible to measure affective biases in rodents using simple learning and subsequent preference tasks.[86] Using this approach, it was possible to differentiate between the effects of the serotonin and noradrenaline reuptake inhibitor venlafaxine (delayed onset) and the NMDA receptor antagonist ketamine (rapid onset). Venlafaxine, but not ketamine, induced positive bias in this model when administered prior to the learning phase. However, only ketamine, and not venlafaxine, could reverse a negative bias acquired during learning in a subsequent preference test. These novel findings suggest that fast-acting antidepressant treatments may be able to retrogradely interfere with existing memories, effectively recoding existing associations, which would be expected to result in much faster changes in mood. These data are corroborated by human emotional processing models in which ketamine has been shown to increase positive false memory.[85]

Conclusions and future directions

Drug effects on human models of emotional processing support the cognitive neuropsychological model of antidepressant drug action, whereby the direct effect of these treatments is to bias the processing of affective information. In between-group comparisons in healthy volunteer models, different effects for effective vs non-effective treatments have been revealed, and as such may be a useful step between preclinical animal trials of putative novel treatments and large and expensive phase 2 and 3 trials. Human models of emotional processing may also prove an effective means of predicting treatment response very early in treatment. Studies to quantify the amount of change in emotional processing necessary early in treatment to see subsequent clinical improvement will be necessary to both of the above uses of these models. Novel, fast-acting antidepressants have been a challenge to this model of antidepressant drug action, but the use of measures of affective biases in rodent models provides a possible explanation for how these drugs might work so quickly, and underscores the utility of back-translation to animal models. ❑

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Los efectos de fármacos en modelos humanos de procesamiento emocional: una consideración del tratamiento con antidepresivos

Los modelos humanos de procesamiento emocional sugieren que el efecto directo de un tratamiento antidepresivo exitoso puede consistir en la modificación de las distorsiones en el procesamiento de la información emocional. Las distorsiones negativas en el procesamiento emocional están documentados en la depresión, y el empleo de antidepresivos convencionales en dosis única o por corto tiempo revierte estas distorsiones en los pacientes depresivos previo a cualquier cambio subjetivo en el ánimo. Los tratamientos con antidepresivos también modulan el procesamiento emocional en voluntaries sanos, por lo que hay que tener en cuenta los efectos psicológicos de estos fármacos y no confundirlos con los cambios en el ánimo. Asimismo los modelos humanos de procesamiento emocional pueden resultar útiles para probar la eficacia de nuevos tratamientos y para adaptar las terapias a pacientes individuales o subgrupos de ellos.

Les effets des médicaments sur les modèles humains de traitement de l'information émotionnelle : décryptage du traitement antidépresseur

D'après les modèles humains du traitement des émotions, un antidépresseur efficace agirait directement en en modifiant les distorsions de traitement de l'information émotionnelle. Ces dernières sont documentées dans la dépression et inversées avant toute modification subjective de l'humeur, chez des patients déprimés, lors de traitement court ou à dose unique par des antidépresseurs classiques. Les antidépresseurs modulent également le traitement de l'information émotionnelle chez les volontaires sains, ce qui permet d'envisager les effets psychologiques de ces médicaments sans les confondre avec les changements d'humeur. Ainsi, des modèles humains de traitement de l'information émotionnelle pourraient être utilisés pour tester l'efficacité de nouveaux médicaments et les adapter individuellement ou à des sous-groupes de patients.

REFERENCES

1. Schildkraut JJ. The catecholamine hypothesis of affective disorders: a review of supporting evidence. *Am J Psychiatry.* 1965;122(5):509-522.
2. Marshall EF, Stirling GS, Tait AC, Todrick A. The effect of iproniazid and imipramine on the blood platelet 5-hydroxytrptamine level in man. *Br J Pharmacol Chemother*. 1960;15:35-41.
3. Glowinski J, Axelrod J. Inhibition of uptake of tritiated-noradrenaline in the intact rate brain by imipramine and structurally related compounds. *Nature.* 1964;204:1318-1319.
4. Coppen A. The biochemistry of affective disorders. *Brit J Psychiatry.* 1967;113(504):1237-1264.
5. Sharp T, Cowen PJ. 5-HT and depression: is the glass half-full? *Curr Opin Pharmacol.* 2011;11(1):45-51.
6. Crockett MJ, Clark L, Roiser JP, et al. Converging evidence for central 5-HT effects in acute tryptophan depletion. *Mol Psychiatry.* 2012;17(2):121-123.
7. Ruhé HG, Mason NS, Schene AH. Mood is indirectly related to serotonin, norepinephrine and dopamine levels in humans: a meta-analysis of monoamine depletion studies. *Mol Psychiatry.* 2007;12(4):331-359.
8. Frazer A, Benmansour S. Delayed pharmacological effects of antidepressants. *Mol Psychiatry.* 2002(7):S23-S28.
9. Castrén E, Hen R. Neuronal plasticity and antidepressant actions. *Trends Neurosci.* 2013;36(5):259-267.
10. Harmer C, Goodwin G, Cowen P. Why do antidepressants take so long to work? A cognitive neuropsychological model of antidepressant drug action. *Br J Psychiatry.* 2009;195(2):102-108.
11. Roiser J, Elliott R, Sahakian B. Cognitive mechanisms of treatment in depression. *Neuropsychopharmacology.* 2012;37(1):117-136.
12. Elliott R, Zahn R, Deakin W, Anderson I. Affective cognition and its disruption in mood disorders. *Neuropsychopharmacology.* 2011;36(1):153-182.
13. Beck AT, Rush AJ, Shaw BF, Emery G. *Cognitive Therapy of Depression*. New York, NY: Guilford; 1979.
14. Mathews A, MacLeod C. Cognitive vulnerability to emotional disorders. *Annu Rev Clin Psychol.* 2005;1:167-195.
15. Williams JMG, Watts FN, MacLeod C, Mathews A. *Cognitive Psychology and Emotional Disorders*. Oxford, UK: John Wiley and Sons; 1988.
16. Bradley BP, Mathews A. Negative self-schemata in clinical depression. *Br J Clin Psychol.* 1983;22:173-181.
17. MacLeod C, Rutherford E, Campbell L, Ebsworthy G, Holker L. Selective attention and emotional vulnerability: assessing the causal basis of their association through the experimental manipulation of attentional bias. *J Abnorm Psychol.* 2002;111:107-123.
18. Harmer C, O'Sullivan U, Favaron E, et al. Effect of acute antidepressant administration on negative affective bias in depressed patients. *Am J Psychiatry.* 2009;166(10):1178-1184.
19. Tranter R, Bell D, Gutting P, Harmer C, Healy D, Anderson I. The effect of serotonergic and noradrenergic antidepressants on face emotion processing in depressed patients. *J Affect Disord.* 2009;118(1-3):87-93.
20. Godlewska BR, Browning M, Norbury R, Cowen PJ, Harmer CJ. Early changes in neural response to emotional stimuli predict clincial reponse to ssri treatment in depression. *J Psychopharmacol.* 2014;28(8 Abstract Supplement):Abstract.
21. Shiroma PR, Thuras P, Johns B, Lim KO. Emotion recognition processing as an early predictor of response to 8-week citalopram treatment in late-life depression. *Int J Geriatr Psychiatry*. 2014;29(11):1132-1139.
22. Berton O, Hahn C-G, Thase ME. Are we getting closer to valid translational models for major depression? *Science.* 2012;338(6103):75-79.
23. Bower GH. Mood and memory. *Am Psychol.* 1981;36(2):129-148.
24. Gotlib IH, Joormann J. Cognition and depression: current status and future directions. *Annu Rev Clin Psychol.* 2010;6:285-312.
25. Harmer C, Shelley N, Cowen P, Goodwin G. Increased positive versus negative affective perception and memory in healthy volunteers following selective serotonin and norepinephrine reuptake inhibition. *Am J Psychiatry.* 2004;161(7):1256-1263.
26. Browning M, Grol M, Ly V, Goodwin G, Holmes E, Harmer C. Using an experimental medicine model to explore combination effects of pharmacological and cognitive interventions for depression and anxiety. *Neuropsychopharmacology.* 2011;36(13):2689-2697.

27. Harmer C, Hill S, Taylor M, Cowen P, Goodwin G. Toward a neuropsychological theory of antidepressant drug action: increase in positive emotional bias after potentiation of norepinephrine activity. *Am J Psychiatry.* 2003;160(5):990-992.

28. Browning M, Reid C, Cowen PJ, Goodwin GM, Harmer CJ. A single dose of citalopram increases fear recognition in healthy subjects. *J Psychopharmacol.* 2007;21(7):684-690.

29. Brown GW, Harris T. *Social Origins of Depression*. London, UK: Tavistock Publications; 1978.

30. Gotlib IH, Asarnow RF. Interpersonal and impersonal problem-solving skills in midly and clincially depressed university students. *J Consult Clin Psychol.* 1979;47(1):86-95.

31. Dalili MN, Penton-Voak IS, Harmer CJ, Munafo MR. Meta-analysis of emotion recognition deficites in major depressive disorder. *Psychol Med.* 2015;45(6):1135-1144.

32. Harmer CJ, Bhagwagar Z, Perrett DI, Völlm BA, Cowen PJ, Goodwin GM. Acute SSRI administration affects the processing of social cues in healthy volunteers. *Neuropsychopharmacology.* 2003;28(1):148-152.

33. Kent JM, Coplan JD, Gorman JM. Clinical utility of the selective serotonin reuptake inhibitors in the spectrum of anxiety. *Biol Psychiatry.* 1998;44(9):812-824.

34. Graeff FG, Guimaraes FS, De Andrade TGCS, Deakin JFW. Role of 5-HT in stress, anxiety, and depression. *Pharmacol Biochem Behav.* 1996;54(1):129-141.

35. Di Simplicio M, Doallo S, Costoloni G, Rohenkohl G, Nobre AC, Harmer CJ. 'Can you look me in the face?' Short-term SSRI administration reverts avoidant ocular face exploration in subjects at risk for psychopathology. *Neuropsychopharmacology.* 2014;39(13):3059-3066.

36. Jonassen R, Chelnokova O, Harmer CJ, Leknes S, Landro NI. A single dose of antidepressant alters eye-gaze patterns across face stimuli in healthy women. *Psychopharmacology.* 2015;232(5):953-958.

37. Heine SJ, Lehman DR, Markus HR, Kitayama S. Is there a universal need for positive self-regard? *Psychol Rev.* 1999;106(4):766-794.

38. Harmer CJ, Heinzen J, O'Sullivan U, Ayres RA, Cowen PJ. Dissociable effects of acute antidepressant drug administration on subjective and emotional processing measures in healthy volunteers. *Psychopharmacology.* 2008;199(4):495-502.

39. Drevets WC, Price JL, Furey ML. Brain structural and functional abnormalities in mood disorders: implications for neurocircuitry models of depression. *Brain Struct Funct.* 2008;213(1-2):93-118.

40. Harmer C, Cowen P, Goodwin G. Efficacy markers in depression. *J Psychopharmacol.* 2011;25(9):1148-1158.

41. Disner SG, Beevers CG, Haigh EA, Beck AT. Neural mechanisms of the cognitive model of depression. *Nat Rev Neurosci.* 2011;12(8):467-477.

42. Adolphs R. Social cognition and the human brain. *Trends Cogn Sci.* 1999;3(12):469-479.

43. Drevets WC, Raichle ME. Neuroanatomical circuits in depression: implications for treatment mechanisms. *Psychopharmacol Bull.* 1992;28(3):261-274.

44. Fu C, Williams S, Cleare A, et al. Attenuation of the neural response to sad faces in major depression by antidepressant treatment: a prospective, event-related functional magnetic resonance imaging study. *Arch Gen Psychiatry.* 2004;61(9):877-889.

45. Victor TA, Furey ML, Fromm SJ, Ohman A, WC. D. Relationship between amygdala responses to masked faces and mood state and treatment in major depressive disorder. *Arch Gen Psychiatry.* 2010;67(11):1128-1134.

46. Godlewska BR, Norbury R, Selvaraj S, Cowen PJ, Harmer CJ. Short-term SSRI treatment normalises amygdala hyperactivity in depressed patients. *Psychol Med.* 2012;41(12):2609-2017.

47. Harmer C, Mackay C, Reid C, Cowen P, Goodwin G. Antidepressant drug treatment modifies the neural processing of nonconscious threat cues. *Biol Psychiatry.* 2006;59(9):816-820.

48. Norbury R, Mackay C, Cowen P, Goodwin G, Harmer C. Short-term antidepressant treatment and facial processing. Functional magnetic resonance imaging study. *Br J Psychiatry.* 2007;190(6):531-532.

49. Arce E, Simmons A, Lovero K, Stein M, Paulus M. Escitalopram effects on insula and amygdala BOLD activation during emotional processing. *Psychopharmacology.* 2008;196:661-672.

50. Windischberger C, Lanzenberger R, Holik A, et al. Area-specific modulation of neural activation comparing escitalopram and citalopram revealed by pharmaco-fMRI: a randomized cross-over study. *NeuroImage.* 2010;49(2):1161-1170.

51. Norbury R, Taylor M, Selvaraj S, Murphy S, Harmer C, Cowen P. Short-term antidepressant treatment modulates amygdala response to happy faces. *Psychopharmacology.* 2009;206(2):197-204.

52. Bigos KL, Pollock BG, Aizenstein HJ, Fisher PM, Bies RR, Hariri AR. Acute 5-HT reuptake blockade potentiates human amygdala reactivity. *Neuropsychopharmacology.* 2008;33(13):3221-3225.

53. Murphy S, Norbury R, O'Sullivan U, Cowen P, Harmer C. Effect of a single dose of citalopram on amygdala response to emotional faces. *Br J Psychiatry.* 2009;194(6):535-540.

54. Murphy S. Using functional neuroimaging to investigate the mechanisms of action of selective serotonin reuptake inhibitors (SSRIs). *Curr Pharm Des.* 2010;16(18):1990-1997.

55. Ma Y. Neuropsychological mechanism underlying antidepressant effect: a systematic meta-analysis. *Mol Psychiatry.* 2014;20(3):311-317.

56. Ma Y, Li B, Wang C, Zhang W, Rao Y, Han S. Allelic varation in 5-HTTLPR and the effects of citalopram on the emotional neural network. *Br J Psychiatry.* 2015;206(5):385-382.

57. Ruhé HG, Koster M, Booij J, van Herk M, Veltman DJ, Schene AH. Occupancy of serotonin transporters in the amygdala by paroxetine in association with attenuation of left amygdala activation by negative faces in major depressive disorder. *Psychiatry Res.* 2014;221(2):155-161.

58. Murphy SE, Downham C, Cowen PJ, Harmer CJ. Direct effects of diazepam on emotional processing in healthy volunteers. *Psychopharmacology.* 2008;199(4):503-513.

59. Grillon C, Levenson J, Pine D. A single dose of the selective serotonin reuptake inhibitor citalopram exacerbates anxiety in humans: a fear-potentiated startle study. *Neuropsychopharmacology.* 2007;32(1):225-231.

60. Browning M, Holmes EA, Harmer CJ. The modification of attentional bias to emotional information: A review of the techniques, mechanisms, and relevance to emotional disorders. *Cogn Affect Behav Neurosci.* 2010;10(1):8-20.

61. Gotlib IH, Kasch KL, Traill SK, Joormann J, Arnow BA, Johnson SL. Coherence and specificity of information processing biases in depression and social phobia. *J Abnorm Psychol.* 2004;113:386-398.

62. Murphy S, Yiend J, Lester K, Cowen P, Harmer C. Short-term serotonergic but not noradrenergic antidepressant administration reduces attentional vigilance to threat in healthy volunteers. *Int J Neuropsychopharmacol.* 2009;12(2):169-179.

63. Coupland NJ, Singh AJ, Sustrik RA, Ting P, Blair RJ. Effects of diazepam on facial emotion recognition. *J Psychiatry Neurosci.* 2003;28(6):452-463.

64. Arnone D, Horder J, Cowen PJ, Harmer CJ. Early effects of mirtazapine on emotional processing. *Psychopharmacology.* 2009;203(4):685-691.

65. Rawlings N, Norbury R, Cowen P, Harmer C. A single dose of mirtazapine modulates neural responses to emotional faces in healthy people. *Psychopharmacology.* 2010;212(4):625-634.

66. Harmer C, de Bodinat C, Dawson G, et al. Agomelatine facilitates positive versus negative affective processing in healthy volunteer models. *J Psychopharmacol.* 2011;25(9):1159-1167.

67. Chandra P, Hafizi S, Massey-Chase RM, Goodwin GM, Cowen PJ, Harmer CJ. NK1 receptor antagonism and emotional processing in healthy volunteers. *J Psychopharmacol.* 2010;24(4):481-487.

68. Pringle A, McTavish S, Williams C, Smith R, Cowen P, Harmer C. Short-term NK1 receptor antagonism and emotional processing in healthy volunteers. *Psychopharmacology.* 2011;215(2):239-246.

69. Pringle A, Parsons L, Cowen L, McTavish S, Cowen P, Harmer C. Using an experimental medicine model to understand the antidepressant potential of the N-Methyl-D-aspartic acid (NMDA) receptor antagonist memantine. *J Psychopharmacol.* 2012;26(11):1417-1423.

70. Ebner K, Singewald N. The role of substance P in stress and anxiety responses. *Amino Acids.* 2006;31(3):251-272.

71. Kramer MS, Winokur A, Kelsey J, et al. Demonstration of the efficacy and safety of a novel substance P (NK1) receptor antagonist in major depression. *Neuropsychopharmacology.* 2004;29(2):385-392.

72. Kramer MS, Cutler N, Feighner J, et al. Distinct mechanism for antidepressant activity by blockade of central substance P receptors. *Science.* 1998;281(5383):1640-1645.
73. Keller M, Montgomery S, Ball W, et al. Lack of efficacy of the substance p (neurokinin1 receptor) antagonist aprepitant in the treatment of major depressive disorder. *Biol Psychiatry.* 2006;59(3):216-223.
74. Harmer CJ, Dawson GR, Dourish CT, et al. Combined NK1 antagonism and serotonin reuptake inhibition: effects on emotional processing in humans. *J Psychopharmacol.* 2013;27(5):435-443.
75. Hayward G, Goodwin GM, Cowen PJ, Harmer CJ. Low-dose tryptophan depletion in recovered depressed patients induces changes in cognitive processing without depressive symptoms. *Biol Psychiatry.* 2005;57(5):517-524.
76. Horder J, Browning M, Di Simplicio M, Cowen P, Harmer C. Effects of 7 days of treatment with the cannabinoid type 1 receptor antagonist, rimonabant, on emotional processing. *J Psychopharmacol.* 2012;26(1):125-132.
77. Horder J, Cowen P, Di Simplicio M, Browning M, Harmer C. Acute administration of the cannabinoid CB1 antagonist rimonabant impairs positive affective memory in healthy volunteers. *Psychopharmacology.* 2009;205(1):85-91.
78. Critchley HD, Lewis PA, Orth M, et al. Vagus nerve stimulation for treatment-resistant depression: behavioral and neural effects on encoding negative material. *Psychosom Med.* 2007;69(2):17-22.
79. Malcolm CP, Cowen PJ, Harmer CJ. High-density negative ion treatment increases positive affective memory. *Psychol Med.* 2009;39(11):1930-1932.
80. Pringle A, McCabe C, Cowen PJ, Harmer CJ. Antidepressant treatment and emotional processing: can we dissociate the roles of serotonin and noradrenaline? *J Psychopharmacol.* 2013;27(8):719-731.
81. Nutt D, Demyttenaere K, Janka Z, et al. The other face of depression, reduced positive affect: the role of catecholamines in causation and cure. *J Psychopharmacol.* 2007;21(5):461-471.
82. Williams LM, Korgaonkar MS, Song YC, et al. Amygdala reactivity to emotional faces in the prediction of general and medication-specific responses to antidepressant treatment in the randomized iSPOT-D trial. *Neuropsychopharmacology.* 2015;40(10):2398-2408.
83. Murrough JW. Ketamine as a novel antidepressant: from synapse to behavior. *Clin Pharmacol Ther.* 2012;91(2):303-309.
84. Drevets WC, Furey ML. Replication of scopolamine's antidepressant efficacy in major depressive disorder: a randomized, placebo-controlled clinical trial. *Biol Psychiatry.* 2010;67(5):432-438.
85. Deakin JW, Williams S, Downey D, et al. PharmacoMRI and cognitive effects of the low-trapping NMDA channel blocker AZD6765 compared with ketamine in untreated major depressive disorder. Abstract presented at: 28th CINP World Congress of Neuropsychopharmacology. Stockholm, Sweden, 2012.
86. Stuart SA, Butler P, Munafo MR, Nutt DJ, Robinson E. Distinct neuropsychological mechanisms may explain delayed- versus rapid-onset antidepressant efficacy. *Neuropsychopharmacology*. 2015;40(9):2165-2174.