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How do antidepressants work? New perspectives for refining future treatment approaches

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Abstract

Most currently available antidepressants target monoamine neurotransmitter function. However, a purely neurotransmitter-based explanation for antidepressant drug action is challenged by the delayed clinical onset of most agents and the need to explain how neurochemical changes reverse the many different symptoms of depression. Novel approaches to understanding of antidepressant drug action include a focus on early changes in emotional and social processing and the role of neural plasticity. In this Review, we discuss the ways in which these two different theories reflect different or complementary approaches, and how they might be integrated to offer novel solutions for people with depression. We consider the predictions made by these mechanistic approaches for the stratification and development of new therapeutics for depression, and the next steps that need to be made to facilitate this translation of science to the clinic.

Introduction

The first clinically useful antidepressant medications were discovered serendipitously about 60 years ago.[1] Subsequently, laboratory studies revealed that these drugs increased synaptic concentrations of serotonin and norepinephrine,[2] and this action was hypothesised to underpin their antidepressant action. Decades later, a range of antidepressant drugs have been developed that, with few exceptions, act to enhance monoamine neurotransmission.

It was realised fairly early that the onset of neurochemical and therapeutic effects of antidepressants had very different time scales, with potentiation of monoamine function occurring within hours of drug administration and clinical improvement often taking days or weeks.[3] This finding led researchers to challenge the central role for acute monoamine potentiation in the mechanism of antidepressant action. Recent approaches, therefore, have sought to target more directly the neurobiological processes that might underlie this delay,

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with the hope of finding rapid-acting antidepressant agents. In this Review, we summarise contemporary approaches to understanding of the delayed clinical effects of antidepressant drug action, and consider how this information can be used to refine future treatments.

Current pharmacological treatment approaches

Following the discovery of their antidepressant effect, the tricyclic antidepressants rapidly became the most widely used agents for the treatment of depression. The efficacy of tricyclic antidepressants such as amitriptyline—particularly in severe melancholic depression—has never been surpassed, but modern agents have been developed to be more selective inhibitors of serotonin and norepinephrine reuptake and, in particular, to reduce the anticholinergic and membrane stabilising (so-called quinidine-like) effects that make tricyclic antidepressants poorly tolerated and dangerous in overdose.[4]

National and international guidelines currently recommend selective serotonin reuptake inhibitors (SSRIs) as first-line treatment for most patients with major depression.[4,5] Other selective monoamine reuptake inhibitors are available—eg, reboxetine, a selective norepinephrine reuptake inhibitor. Reboxetine, however, seems less efficacious than SSRIs in some meta-analyses,[6] although these findings could be due to its relatively poor tolerance.[7] Another agent, bupropion, is an inhibitor of norepinephrine and dopamine reuptake, which gives it a more activating profile than SSRIs. Two drugs, venlafaxine and duloxetine, are classified as dual serotonin– norepinephrine reuptake inhibitors (SNRIs), although the efficacy for blockade of norepinephrine reuptake in clinically used doses is unclear.[8] Clinical guidelines commonly recommend the use of an SNRI in patients who do not respond to SSRIs.[4,5]

More recent developments have led to drugs that block serotonin reuptake while having additional effects on a variety of 5-hydroxytryptamine (5-HT) receptor subtypes. For example, vilazodone has partial agonist activity at the 5-HT_{1A} receptor, whereas vortioxetine binds to several other 5-HT receptor subtypes ($5HT_{1A}$, $5HT_{1B}$, $5HT_{1D}$, $5HT_{3}$, and 5-HT_{7}). Whether these agents have advantages over SSRI treatment is not fully clear, although vilazodone is suggested to produce less sexual dysfunction and vortioxetine to have particular benefits in depression-related cognitive impairment.[9]

Additionally, some antidepressant agents do not act through blockade of norepinephrine and serotonin reuptake. The most widely used is mirtazapine, which blocks α_2-adrenoceptors on norepinephrine cell bodies and terminals, thereby facilitating norepinephrine release. Mirtazapine's ability to antagonise 5-HT_{2A} and 5-HT_{2C} receptors could also increase norepinephrine and dopamine release in cortical regions.[4] A similar antagonist action at 5-HT_{2C} receptors has been suggested to contribute to the antidepressant action of the melatonin agonist agomelatine, although whether agomelatine blocks 5-HT_{2C} receptors in people at clinical doses is questionable.[10] Overall, however, all currently licensed antidepressants are believed to relieve depression by increasing serotonin or norepinephrine availability, or both, at least initially.

Explaining the delayed clinical onset of antidepressant drugs

Neurochemical theories

The disjunction in the timescale of monoamine increases versus clinical changes led researchers to study the neuroadaptive changes that evolve in the days and weeks after the initiation of antidepressant treatment. The underlying assumption was that neurobiological adaptive changes that correlate in time with the onset of the therapeutic response could represent a more direct antidepressant target than the initial action of antidepressants to block serotonin and norepinephrine reuptake.

To some extent the adaptive mechanisms identified have gone hand-in-hand with technical advances in laboratory science. For example, the development of ligand receptor binding led to studies of the effects of antidepressant treatment on monoamine receptor populations. Initially, these studies focused on postsynaptic β-adrenoceptors that are downregulated by both repeated tricyclic antidepressant and monoamine oxidase inhibitor treatment.[11] However, the notion that decreasing β-adrenoceptor activity—with, for example, a β-adrenoceptor antagonist—could be a useful antidepressant strategy was implausible, and served as a warning that neuroadaptive changes might represent homoeostatic mechanisms by which the brain of a healthy animal attempts to regulate monoamine neurotransmission in the presence of a monoamine enhancing drug.[12]

As the era of SSRI treatment developed, attention shifted to the role of 5-HT_{1A} autoreceptors that act normally to inhibit serotonin release from nerve terminals. Repeated SSRI treatment decreases the functional sensitivity of 5-HT_{1A} autoreceptors both in animals and human beings. This finding gave rise to the suggestion that the delay in therapeutic onset of action of SSRIs might represent the time needed for autoreceptor desensitisation, which results in greater serotonin availability in the synapse.[13] It would therefore be expected that combining an SSRI with drugs that selectively block 5-HT_{1A} autoreceptors should speed the onset of therapeutic effect of SSRIs but this approach has not, thus far, proved clinically useful.[14]

Neuroplasticity theories

With the elucidation of molecular and cellular path ways that regulate neuronal function, research has progressed beyond monoamine neurotransmitter receptors to focus on intracellular signalling cascades, gene expression, and protein translation as central for antidepressant drug action. A major theme of this work has been to explore mechanisms of neuroplasticity—a fundamental process that underlies learning and memory, but also the ability of neuronal systems to incorporate and adapt to environmental stimuli and then to make appropriate adaptive responses to future related stimuli. Complex mechanisms mediate neuroplasticity, including regulation of presynaptic mechanisms of neurotransmitter release, postsynaptic Ca^{2+} signalling, trafficking of glutamate AMPA receptor subunits, and increased number and function of synapses.[15] Evidence suggests that synaptic plasticity mechanisms are affected by chronic stress, and that antidepressant treatments oppose or reverse these effects.

Stress and depression: intracellular and morphological changes—Chronic stress substantially alters neuronal circuits in the brain, including disruption of intracellular signalling and the number and function of synapses. Findings from rodent studies show synaptic loss in cortical and limbic areas associated with depression, notably the prefrontal cortex and hippocampus—regions that control emotion, mood, and cognition in response to chronic physical or psychological stress.[16,17] Additionally, evidence suggests that stress decreases the formation of new neurons in the adult hippocampus.[18] Brain imaging studies show that depression is associated with reductions in the volume of the prefrontal cortex and hippocampus, suggesting atrophy and disruption of connectivity.[19,20] By contrast with the prefrontal cortex and hippocampus, chronic stress causes hypertrophy of neurons in the nucleus accumbens and amygdala,[21,22] effects that could contribute to disruption of behaviours that are regulated by these regions, including motivation, reward, and emotion.

At the molecular level, chronic stress causes alterations of glutamate, intracellular signalling, transcription factors, and gene expression (including epigenetic changes). Evidence suggests that stress increases extracellular glutamate, and that this increase could contribute to excitotoxic damage.[23] There have been extensive studies of brain-derived neurotrophic factor (BDNF), a major neurotrophic factor that plays an important role in the formation, guidance, and survival of neurons during development but also in synaptic plasticity and survival in the adult brain (figure 1). BDNF is decreased by chronic stress in rodents and postmortem brains of indviduals with depression.[24,25] Mice with a single nucleotide polymorphism of BDNF—ie, Val66Met, which blocks the processing, trafficking, and release of BDNF—show decreased synapse number in the hippocampus and medial prefrontal cortex.[26,27] The Met polymorphism is found in approximately 25% of people who are white, and has been associated with decreased hippocampal volume and executive function and increased susceptibility to depression.[28,29]

BDNF signalling pathways are also decreased by stress and in post-mortem brains of indviduals with depression.[25,30] Additionally, the mechanistic mammalian target of rapamycin complex 1 (mTORC1) pathway is decreased by chronic stress via induction of a negative regulator REDD1.[31,32] Expression of REDD1 causes depression-like behaviours and decreases the medial prefrontal cortex synapse number in rodent models, whereas REDD1 null mice are resistant to these effects. REDD1 is also increased in the post-mortem prefrontal cortex of indviduals with depression.[31] These findings show that disruption of BDNF signalling contributes to the synaptic and behavioural deficits of stress, and provide a mechanism for how exposure to stress and genetic factors might modify risk for depression.

Chronic administration of typical antidepressants—Chronic, but not short-term administration of SSRI or norepinephrine reuptake inhibitor antidepressants can enhance synaptic plasticity and block the synaptic deficits caused by stress.[25,28,33–35] However, the actions of SSRI and norepinephrine reuptake inhibitor agents on synapse number are subtle and delayed, possibly due to the modulatory actions of serotonin and norepinephrine neurotransmitter systems (figure 1). The ability of typical antidepressants to increase synaptic plasticity has been directly tested in well designed rodent models, showing that chronic fluoxetine administration reinstates ocular dominance neuroplasticity even in adult

rodents and enhances fear extinction training by causing fear circuitry to convert to a more immature and plastic state.[36,37]

BDNF and intracellular signalling—By contrast with stress, chronic antidepressant administration, both SSRI and norepinephrine reuptake inhibitor agents, increases the expression of BDNF and its receptor TrkB in the prefrontal cortex and hippocampus (figure 1).[25,30] Moreover, the behavioural actions of typical antidepressants in animal models are blocked by deletion of BDNF, and infusion of BDNF into the prefrontal cortex or hippocampus is sufficient to produce antidepressant effects.[24,25,30] Additionally, fluoxetine-induced synaptic plasticity in the ocular dominance and fear extinction studies is dependent on BDNF, and BDNF infusions are sufficient to produce these effects.[36,37] These studies show that antidepressant induction of BDNF expression, over the course of several weeks of treatment, enhances synaptic plasticity that contributes to behavioural response to these agents. Antidepressant treatment also increases downstream signalling, including the cAMP and Ca^{2+} that increase the expression of BDNF.[38]

If reduction of BDNF in the prefrontal cortex and hippocampus plays a causal role in vulnerability to depression, then we would expect that BDNF deletion would cause depressive behaviours. But this is not the case in rodent models with BDNF gene deletion.[25,30] This finding could be due to differential effects of BDNF in the mesolimbic dopaminergic system, in which BDNF produces depressive-like behaviours in social defeat models,[22,39] indicating that it is required for plasticity of different circuits—some of which could be prodepressive whereas others produce antidepressant actions. Evidence for this possibility is supported by studies showing that region-specific deletion of BDNF in the hippocampus is sufficient to produce depressive behaviours.[40] Mutant mice with BDNF deletion are also more vulnerable to depressive behaviours upon exposure to mild stress.[28] Additional signalling pathways and brain regions have been implicated in antidepressant drug action.[33,41]

Cognitive neuropsychological approaches

In parallel to the research reviewed, which focuses on molecular and cellular pathway actions, there has been recent interest in understanding of the effects of antidepressant drugs on core psychological processes important in depression (figure 2). It is unclear to what extent these psychological changes relate to the effects on synaptic plasticity, and there is no research directly addressing this question. It is possible that these psychological and synaptic plasticity changes describe different levels of analysis rather than competing theories.

Negative affective biases in depression—The incidence of depression is increased following a period of life events or stress,[42] and individual differences in how negative events are experienced, perceived, and recalled can exacerbate these effects. Depression is associated with the tendency to perceive social cues as more negative, to preferentially attend to aversive information, and to recall negative more than positive information concerning oneself.[43,44] This style of focusing on and remembering affective and social information that is negative, while disregarding positive information, is hypothesised to reinforce negative thoughts, feelings, and beliefs seen in depression. Negative affective

biases during remission are associated with an increased risk of relapse,[43] and improved positive emotional processing has been found to precede changes in symptoms of depression.[45] These observations highlight that negative bias might not be just an epiphenomenon of low mood but play a role in determining response to everyday social and emotional situations, life events and stressors, and the evolution of symptoms of depression over time. Recent studies have highlighted negative bias as a target for pharmacological and psychological treatments in depression.[44,46,47]

Reversal of negative affective bias with antidepressant drug administration— Antidepressant administration increases the relative processing of positive versus negative affective information very early on in treatment in both patients who are depressed and participants who are healthy.[46] For example, a single dose (4 mg) of reboxetine facilitated the recognition of happy facial expressions and the recall of positive versus negative self-referent memory in patients with depression compared with double-blind administration of placebo.[48] Similarly, single and repeated administration of antidepressants across different pharmacological classes has been found to increase the relative recognition of positive over negative social cues in a facial expression recognition task in healthy people.[46,49] Early effects of antidepressants on negative affective bias might act to reduce the influence of this key maintaining factor and set the scene for improved symptoms over time.[50,51] Early changes in affective processing following other treatment types for depression and anxiety have been described, including transcranial direct current stimulation,[52] negative ion treatment,[53] and with cognitive behavioural therapy in panic disorder.[54] Thus, early effects on the way in which information is processed might be important across treatment types.

At a neural level, depression is associated with an increased response in limbic areas of the brain (such as the amygdala, insula, and anterior cingulate) to negative versus positive stimuli, important for the detection and response to emotionally salient stimuli. This limbic overactivity has been coupled with decreased engagement of areas important for regulation and inhibition of such responses, including the dorsolateral and medial prefrontal cortex.[47] Antidepressant treatment reverses this pattern of neural response to affective information in patients with depression, and introduces a similar direction of change in healthy people.[55] For example, acute clinical doses of SSRIs decrease amygdala response to negative affective faces,[56,57] and this effect is also seen after 7 days administration in healthy participants[58] and patients with depression.[59] These effects tend to occur in the absence of any changes in the symptoms of depression, suggesting that they might be an early mechanism of change rather than just a correlate of feeling better during the scan. Nonetheless, these changes in affective processing observed early are maintained during long-term treatment. For instance, 6 weeks of SSRI treatment was associated with reduced responses in the amygdala, anterior cingulate, and fusiform face area to negative facial expressions in patients with depression.[55,60] Likewise, responses to happy faces were enhanced across similar regions after 6 weeks of SSRI treatment.[55,61]

The effects of antidepressants seen in these models after just a single dose highlight that the reversal of negative bias might occur, at least in part, before changes in the measures of neuroplasticity or neurotrophic factors (such as BDNF) with conventional anti-depressants examined in animal models in the prefrontal cortex and hippocampus. Further work is

therefore needed to examine the timescale of neuroplasticity markers in relation to these early changes in non-conscious emotional bias across different mechanisms and neural systems.

Prediction of clinical action—If early changes in negative bias are involved in the evolution of clinical response over time, we might expect that patients who show the greatest resolution of negative bias early in treatment might be more likely to respond to the antidepressant drug with continued administration. In line with this hypothesis, early change in the perception and neural response to positive facial expressions has been associated with subsequent improvement in depression severity.[50,51,62] A classification-based approach of data from Tranter and colleagues' study[50] suggests that if an early change in positive processing is not seen with antidepressant treatment, patients have little chance of responding to this same treatment later (table 1). A similar effect was seen in older adults in which a group of patients with depression who did not show an improvement in the recognition of happy faces after 1 week of citalopram treatment also did not respond after 8 weeks of treatment.[51] A recent study found that early response to happy facial expression predicted later clinical response to novel candidate treatment for depression (a nociception antagonist) but not placebo.[63] These results suggest that the effects on emotional bias might not be restricted to monoamine antidepressant drug action, and might be applicable to the development of novel agents. They also suggest that drug-induced variation in emotional processing is a specific treatment effect rather than being a more general mediator of placebo response or expectation.

The early change in neural response to emotional information has also been associated with later clinical response. In a recent study, Godlewska and colleagues[62] found that clinical response to escitalopram after 6 weeks of treatment was associated with early change during affective processing in the amygdala, thalamus, cingulate, and insula. The responder group showed a greater reduction in neural response in these areas during the processing of negative versus positive facial expressions, consistent with the hypothesis that these early changes are important for the expression of later clinical benefit. These findings, along with the studies reviewed, challenge the view that antidepressants do not have clinically relevant effects until they are administered over weeks of treatment. Rather these results suggest that there are rapid changes in non-conscious mechanisms involved in how stressors, life events, and interactions with others are managed, processed, and remembered.

Can these effects help to elucidate the delays in clinical effects of antidepressants?—Given that antidepressants have rapid effects on emotional processing, why are the clinical effects of drug treatments still delayed? We have argued that such non-conscious changes are only apparent to the patient after interaction with the social environment—ie, the patient is aware of the products of having a more positive bias (more positive feedback) rather than the processing style itself. In line with this argument, experimentally inducing a negative affective bias in healthy volunteers does not affect subjective state directly but impairs mood response after exposure to a stressor.[64] The role of negative bias in mood response is shown by a positive correlation between the effects of SSRI treatment on negative affective bias and resistance to a negative mood induction in

healthy people.[65] The translation of change in negative bias into clinical response might, therefore, involve relearning a range of emotional associations— ie, where ambiguous events or cues are perceived more positively while taking antidepressant drug treatment. The effect of antidepressants on synaptic plasticity, hippocampal neurogenesis, and learning in animal models could help to consolidate early changes in emotional bias and allow these effects to have long-lasting influence.

The requirement for changes in negative affective biases and interaction with the external social environment might help to explain some of the variance in clinical response to antidepressant treatment. For example, patients with treatment-resistant depression might have highly entrenched, long-standing negative affective biases that are resistant to change or highly adverse social environments that cannot support an improvement in mood even with remediation of the negative affective biases. A study from 2014 found that improved accuracy of happy facial expression recognition by perceived level of social support is a significant predictor of change in depressive symptoms.[51] In particular, the increase in emotional bias towards positive information was associated only with a therapeutic response in patients with a good level of social support. This approach highlights the need for a more integrative perspective in depression and antidepressant drug research, for which the psychopharmacology, neurobiology, psychological, and environmental influences are explored together. Rose[66] suggested that depression should be viewed as arising from more than the brain alone, drawing on an understanding of the whole person, in a particular environment, and with a shaping role for social experiences and milieu. In a similar way, multiple factors need to be considered when understanding antidepressant drug action, its limitations, blocks to successful treatment, and methods to facilitate its effects.

Rapid-acting agents for the treatment of depression

Although currently available antidepressants have a delayed clinical onset, a single dose of ketamine, a non-competitive open channel NMDA (N-methyl-D-aspartate) antagonist, produces rapid antidepressant actions within hours[67] and leads to a rapid resolution of suicidal ideation. Moreover, many of these studies include patients who have not responded to two or more typical antidepressants (eg, SSRI or SNRI agents).

Data from preclinical studies show that a single dose of ketamine produces rapid antidepressant-like effects in rodent models and reverses the depressive behaviours caused by chronic stress.[68–70] The results also show that a single dose of ketamine rapidly increases synapse number and function in medial prefrontal cortex neurons, and reverses the synaptic deficits caused by chronic stress (figure 1).[69,70] The synaptic and behavioural actions of ketamine are blocked in BDNF null mice or BDNF Met knock-in mice.[27,71] Patients with major depressive disorder and carrying the BDNF Met allele show a 50% lower response than do Val/Val carriers, identifying a potential biomarker that might be explored as a predictor of treatment response to ketamine, although further studies are required to confirm this finding.[72] Preclinical studies also show that the synaptic and behavioural actions of ketamine are dependent on BDNF signalling via the Akt and mTORC1 signalling cascade, leading to increased synthesis of synaptic proteins (figure 1).[69,70,73] Evidence also suggests that other rapid-acting antidepressants act through a similar mechanism.[74,75]

Ketamine produces a paradoxical increase in extracellular glutamate in the medial prefrontal cortex, and the behavioural actions of ketamine are blocked by pre treatment with a glutamate receptor antagonist,[28] suggesting that ketamine could result in activity-dependent release of BDNF and the rapid synaptogenic response.[29,69] Activity-dependent BDNF release distinguishes ketamine from typical antidepressants that slowly increase BDNF expression, but not BDNF release (figure 1). Increased extracellular glutamate is thought to occur via blockade of tonic firing NMDA receptors on GABA neurons, resulting in disinhibition and increased glutamate transmission.[69,73] Other theories propose that ketamine acts via blockade of NMDA receptors on postsynaptic principal neurons in the medial prefrontal cortex or hippocampus to increase synaptic function via a homoeostatic mechanism.[71,73] Studies are being done using approaches for cell-specific knockdown of NMDA receptor subunits to address this question.

These findings provide potential molecular mechanisms for rapid-acting antidepressant agents, but how can these effects be explained at a psychological level? Neural and behavioural changes in emotional processing are also observed rapidly following ketamine administration in people,[76] although the nature and timing of these effects have not been directly compared with conventional antidepressants to identify possible reasons for its faster onset of action. However, recent work using a rodent model of negative affective bias suggests that although conventional antidepressants affect the acquisition of a positive bias they do not affect the retrieval of previously acquired negative memory associations.[77] By contrast, ketamine did not affect the learning of positive affective information but was able to abolish memory for negative associations for which stimuli had been paired with psychosocial stress or administration of an anxiogenic drug via effects within the medial prefrontal cortex.[77] It is therefore possible that although conventional antidepressants change only positive processing of incoming information, novel rapid-onset drugs might be able to change or reduce memories of already encoded negative information, which would be predicted to have faster effects on mood because there is less dependence on the environment. The role of glutamate in memory and memory consolidation provides an interesting link to this hypothesis.

The antidepressant effect of ketamine can persist for several days but then wanes. Thus far, it has not been possible to sustain the therapeutic effect of ketamine with clinically available glutamatergic agents, such as riluzole and memantine.[78] New forms of ketamine that can be administered more continuously, orally, or intranasally are being developed and are in clinical trials. The issue will be to assess whether the antidepressant effects of ketamine can be sustained without the development of therapeutic tolerance or safety concerns—eg, dependence, psychosis, or bladder toxicity. A potentially important development, based on animal studies, is the finding that the antidepressant effect of ketamine might depend principally on the ability of its active metabolite, hydroxynorketamine, to produce a rapid and sustained stimulation of glutamatergic AMPA receptors, although whether efficacious concentrations of the metabolite are achieved with the ketamine doses used is questionable.[79] Additional studies are required to identify the initial target of hydroxynorketamine, to confirm that the effects are independent of NMDA receptor blockade, and to further characterise its actions in other brain regions, notably the medial prefrontal cortex. Nevertheless, hydroxynorketamine could be free of the many safety

problems associated with ketamine, and studies of its clinical efficacy in patients with depression are, therefore, a priority.

The compelling antidepressant effect of ketamine has led to interest in other agents acting on the glutamate system, particularly the NMDA receptor. For example, traxoprodil and MK-0657 are selective antagonists at the GluN2B subtype of the NMDA receptor, whereas lanicemine is a low trapping non-selective antagonist of the NMDA receptor that should theoretically be associated with fewer psychotomimetic effects than ketamine. All these drugs have shown promise of a rapid antidepressant effect in initial studies but development of traxoprodil and lanicemine for major depression was suspended after disappointing results in phase 2 trials.[80] Another approach has been to develop agents acting at the glycine modulatory site of the NMDA receptor such as the partial agonist GLYX-13 (rapastinel), which is in phase 3 trials in patients with major depression.[81] There are also studies with drugs acting at metabotropic glutamate receptors (mGluR) with a variety of possible targets and promising preliminary clinical results with the mGlu5 receptor antagonist basimglurant.[82]

Future perspectives

This Review has considered two contemporary approaches to understanding the delay in antidepressant drug efficacy in depression focused on neural plasticity and negative affective bias. The extent to which these reflect similar, parallel, or dependent processes requires further investigation; table 2 summarises predictions made by these different approaches. Research in people is limited by the absence of reliable markers of neural plasticity in vivo, which makes it difficult to explore the inter dependence of changes in plasticity and bias in the same individual. Furthermore, the observation that emotional bias is typically affected before changes in plasticity would be expected suggests that these might not be markers of exactly the same underlying mechanism. The development of a rodent model of affective bias, which shows similar effects of antidepressant agents to human models,[83] provides a novel opportunity to investigate both cellular and psychological processes in the same animal. This rodent model would allow the timescale of specific changes in bias and different aspects of plasticity to be related, and test whether blocking the expression of intracellular signalling pathways would prevent the induction of positive affective biases. It is also conceivable, however, that changes in neuroplasticity are a consequence of alterations in emotional processing. That is, in the same way that changes in external environment can lead to alterations in plasticity and neurogenesis in animals, it might be that transformations in the emotional world might stimulate similar experience-dependent plasticity changes. Exploring these relationships in animal models can therefore provide unique hypotheses for how we conceptualise and speed up antidepressant drug action (table 2). The effects of these two processes would be expected to be mutually synergistic—ie, increased neural plasticity might facilitate the relearning of new emotional associations to inner and external environmental cues, thereby consolidating and generalising the implicit changes produced by initial doses of medication. Characterisation of the neural circuitry and signalling pathways that underlie early changes in emotional processing will further inform understanding of the relationship with synaptic plasticity.

Conclusion

Considerable progress has occurred in understanding mechanisms of antidepressant drug action in recent years. Work in this area has moved from an exclusive focus on the neurochemical theories of antidepressant drug action to a broader understanding of the effects of antidepressants on neuroplasticity and emotional and cognitive function. The neurotrophic theory has focused on intracellular mechanisms, largely characterised in animal models but contextualised in human MRI and post-mortem studies. These effects evolve over days to weeks, mirroring the delayed clinical onset of antidepressant drugs. By contrast, the neuropsychological theory has moved into the domain of clinical psychology, exploring the effects of antidepressants on emotional processes at a neural and cognitive level in people but with recent extension to animal models. These effects occur very early, before changes in mood, but are related to later clinical change.

The two theories also provide different perspectives on the underlying mechanisms of rapid-acting agents such as ketamine in the treatment of depression. However, these processes are possibly related or might operate synergistically for treatment success. The contrasting perspectives on rapid-acting agents (disruption of fixed negative memories *vs* BDNF release) might reflect different levels of analysis explaining the psychological experience as opposed to the underlying cellular changes. Both of these approaches offer perspective for the future development, screening, and improvement of treatments in depression. A key challenge is to elucidate and harness the potential synergistic effects of changes in negative bias and plasticity to overcome the widely acknowledged limitations of current treatments.

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Search strategy and selection criteria

We identified references for this Review through searches of PubMed between Aug 1, 1971, and Aug 1, 2016, with the search terms “antidepressant”, “mechanisms”, “depression”, “delay”, AND “emotion” OR “plasticity”. We selected and reviewed articles published in English from these searches and relevant references cited in the identified articles.

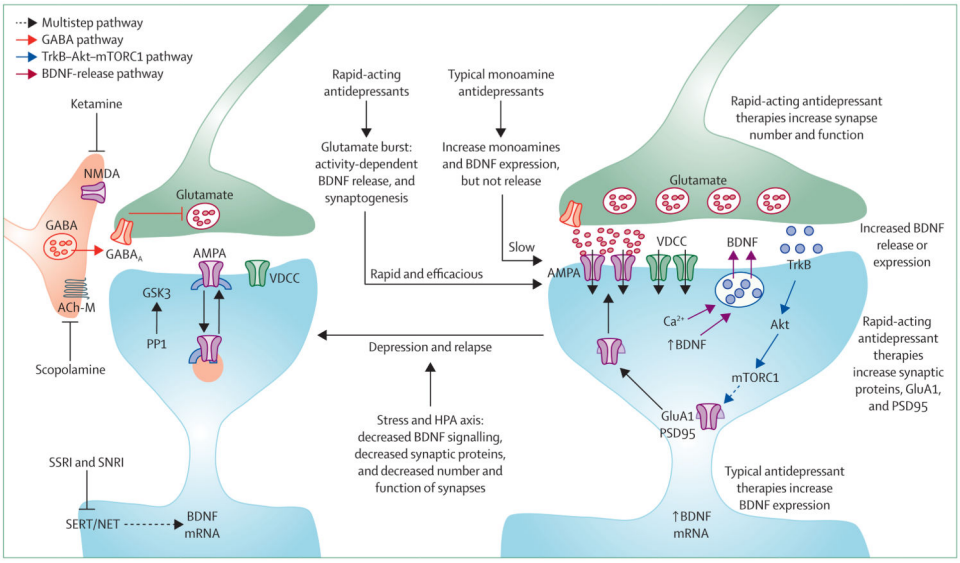

Figure 1. The neurotrophic theory of antidepressant drug action

NMDA=N-methyl-D-aspartate receptor. $GABA_A$=γ-aminobutyric acid receptor. Ach-M=acetylcholine muscarinic receptor. AMPA=α-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid receptor. VDCC=voltage dependent calcium channel. SSRI=selective serotonin reuptake inhibitor. SNRI=serotonin-norepinephrine reuptake inhibitor. SERT=serotonin transporter. NET=norepinephrine transporter. BDNF=brain-derived neurotrophic factor. HPA=hypothalamic-pituitary-adrenal.

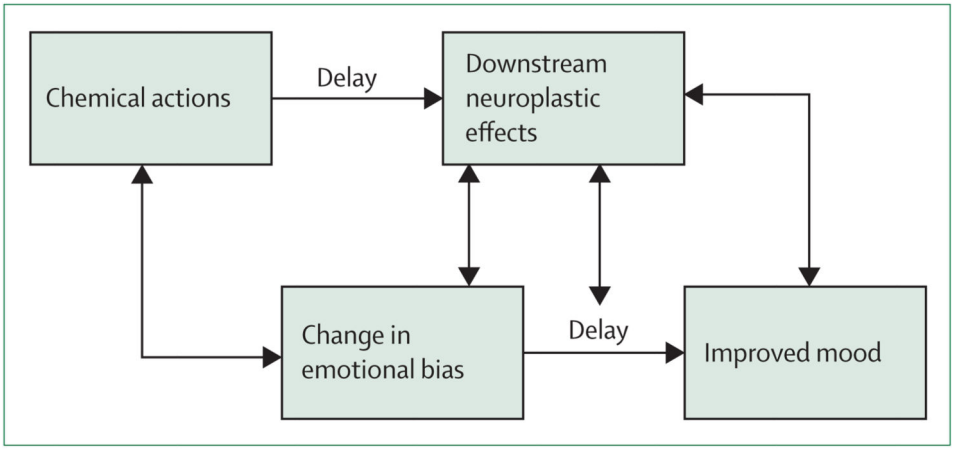

Figure 2. The cognitive neuropsychological theory of antidepressant drug action

Possible interactions with plasticity changes and induced with antidepressant drug treatments are shown.

Table 1
Prediction of antidepressant response from early changes in EP

	Clinical response*	No clinical response	Total
Positive EP test†	22	15	37
Negative EP test	1	10	11
Total	23	25	48

EP=emotional processing. CORE=Clinical Outcomes in Routine Evaluation.

*Decrease of ≥50% of symptoms on the CORE outcome measure at week 6.

†Increase in positive face recognition at 2 weeks *vs* baseline.[50]

Table 2

Predictions made by the neuroplasticity and cognitive neuropsychological theories

	Neuroplasticity theory	Neuropsychological theory
Target development	Novel agents should target neural plasticity that reverses synaptic deficits in prefrontal cortex and hippocampus caused by stress	Novel agents should target neural plasticity or transmitter systems in amygdala and cortex that control emotional processing
Speeding up of antidepressant effects	Faster or more direct actions on neural plasticity; environmental enrichment to facilitate effects of plasticity	Enhance the translation of emotional processing change into clinical change by environmental enhancement and targeted psychological treatments
Example reasons for non-response	Insufficient neural architecture to support plasticity change; insufficient effect of drug on plasticity	Entrenched emotional processing response, which is difficult to shift; toxic environment or reduced environmental engagement
Prediction of individual drug response	Measures of plasticity-induced neurotrophic and synaptic markers should predict treatment success	Early change in emotional processing should predict later clinical change
Exploration of the relationship between the two theories	Restriction of plasticity change should reduce the effect of agents on emotional bias in animal models	Blockade of the expression of negative bias change should reduce the plasticity changes induced by antidepressant agents
Combination approaches	Agents that target neural plasticity combined with emotional processing change will have effects greater than either target in isolation; in particular, effects of ketamine will be sustained when combined with agents that shift negative biases in emotional processing	Agents that target neural plasticity combined with emotional processing change will have effects greater than either target in isolation; in particular, effects of ketamine will be sustained when combined with agents that shift negative biases in emotional processing

These predictions do not necessarily represent competing views but rather different perspectives, levels of analysis, and methods that can be synergistic or overlapping.