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

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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 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 truly reflect different or complementary approaches and how they may 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 in order 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 levels of serotonin and noradrenaline, [2] and this action was hypothesised to underpin their antidepressant action. In the decades that have passed since this initial clinical discovery a range of antidepressant drugs have been developed which, 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 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 may underlie this delay, with the hope of finding faster acting antidepressant agents. This review summarises contemporary approaches to understanding the delayed clinical effects of antidepressant drug action and considers how we can use this information to refine future treatments.

Search strategy

References for this review were identified through searchers of PubMed (between 1971 and August 2016) by the use of the terms “antidepressant” “mechanisms” “depression” “Delay” and “emotion” or “Plasticity”. Articles published in English and resulting from these searches and relevant references cited in those articles were reviewed.

Current pharmacological treatment approaches

Following discovery of their antidepressant effect, the tricyclic antidepressants (TCAs) rapidly became the most widely employed 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 (5-HT) and noradrenaline re-uptake and, in particular, to lack the anticholinergic and membrane stabilizing (‘quinidine-like’) effects that make TCAs 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 re-uptake inhibitors are available, for example, reboxetine, a selective noradrenaline reuptake inhibitor (NARI). Reboxetine, however, seems less efficacious than SSRIs in some meta-analyses, though this could be due to its relatively poor tolerance.[6] Another agent, bupropion, is an inhibitor of noradrenaline and dopamine reuptake which gives it a more activating profile than SSRIs. Two drugs, venlafaxine and duloxetine are classified as dual serotonin-noradrenaline reuptake inhibitors (SNRIs), although the efficacy for blockade of noradrenaline reuptake in clinically-used doses is unclear. [7] Clinical guidelines commonly recommend the use of an SNRI in patients who fail to 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-HT receptor subtypes. For example, vilazodone, has partial agonist activity at the 5-HT_{1A} receptor while vortioxetine binds to several other 5-HT receptor subtypes (5-$HT_{1A/1B/1D,}$ 5-HT_3, 5-HT_7). Whether these agents have advantages over SSRI treatment is not fully clear, though vilazodone is claimed to produce less sexual dysfunction and vortioxetine to have particular benefits in depression-related cognitive impairment. [8]

There are also some antidepressant agents that do not act through blockade of noradrenaline and serotonin reuptake. The most widely used is mirtazapine which blocks α_2-adrenoceptors on noradrenaline cell bodies and terminals, thereby facilitating noradrenaline release. It's ability to antagonize 5-$HT_{2A/2C}$ receptors could also increase noradrenaline 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, though whether agomelatine blocks 5-HT_{2C} receptors in humans at clinical doses is questionable.[9] Overall, however, all currently licensed antidepressants are believed to relieve depression by increasing serotonin/and or noradrenaline availability, at least initially.

Explaining the delayed clinical onset of antidepressant drugs

<u>Neurochemical theories</u>

The disjunction in the timescale of monoamine increases vs clinical changes led researchers to study the neuroadaptive changes that evolve in the days and weeks following the initiation of antidepressant treatment. The underlying assumption was that neurobiological adaptive changes which 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 noradrenaline 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 this focused on post-synaptic beta-adrenoceptors that are downregulated by both repeated TCA and MAOI treatment.[10] However, the notion that decreasing beta-adrenoceptor activity, with for example, a beta-adrenoceptor antagonist could be a useful antidepressant strategy was implausible and served a warning that neuroadaptive changes might represent homeostatic mechanisms by which the brain of a normal animal attempts to regulate monoamine neurotransmission in the presence of a monoamine enhancing drug. [11]

As the era of SSRI treatment developed, attention shifted to the role of 5-HT_{1A} autoreceptors that act normally to restrain serotonin release from nerve terminals. Repeated SSRI treatment decreases the functional sensitivity of 5-HT_{1A} autoreceptors both in animals and in humans giving rise to the suggestion that the delay in therapeutic onset of action of SSRIs might represent the time needed for autoreceptor desensitization, which results in greater serotonin availability in the synapse.[12] From this it would be expected that combining an SSRI with drugs that selectively block 5-HT_{1A} autoreceptors should speed the onset therapeutic effect of SSRIs but this approach has not thus far proved clinically useful.[13]

Neuroplasticity theories of stress and antidepressant treatment response

With the elucidation of molecular and cellular pathways that regulate neuronal function, work has moved beyond monoamine neurotransmitter receptors to focus on intracellular signaling cascades, gene expression, and protein translation as central for antidepressant drug action. A major theme of much 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 Ca2+ signaling, trafficking of glutamate AMPA receptor subunits, and increased number and function of synapses.[14] Reviewed here is evidence that synaptic plasticity mechanisms are affected by chronic stress and that antidepressant treatments oppose or reverse these effects.

Stress and depression disrupt synaptic plasticity: intracellular and morphological changes. Repeated stress significantly alters neuronal circuits in the brain, including disruption of intracellular signaling and the number and function of synapses. Rodent studies demonstrate synaptic loss in cortical and limbic areas associated with depression, notably the PFC and hippocampus, regions that control emotion, mood, and cognition in response to chronic physical or psychological stress.[15,16] There is also evidence that stress decreases the birth of new neurons in the adult hippocampus.[17] Brain imaging studies demonstrate that depression is associated with reductions in the volume of PFC and hippocampus, suggesting atrophy and disruption of connectivity.[18,19] In contrast to PFC and hippocampus, chronic stress causes hypertrophy of neurons in the nucleus accumbens and in the amygdala, [20,21] effects that could contribute to disruption of behaviors that are regulated by these regions, including motivation, reward and emotion.

At the molecular level, chronic stress causes alterations of glutamate, intracellular signaling, transcription factors, and gene expression (including epigenetic changes). There is evidence that stress increases extracellular glutamate and that this could contribute to excitotoxic damage.[22] 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 in postmortem brains of depressed subjects. [23,24] Mice with a single nucleotide polymorphism of BDNF, Val66Met, that blocks the processing, trafficking, and release of BDNF, show decreased synapse number in hippocampus and mPFC. [25,26] The Met polymorphism is found in approximately 25% of Caucasians and has been associated with decreased hippocampal volume and executive function and increased susceptibility to depression. [27,28]

BDNF signaling pathways are also decreased by stress and in postmortem brains of depressed subjects. [24,29] In addition, the mechanistic target of rapamycin complex 1 (mTORC1) pathway is decreased by chronic stress via induction of a negative regulator REDD1.[30,31] Expression of REDD1 causes depression-like behaviors and decreases mPFC synapse number in rodent models, while REDD1 null mice are resistant to these effects. REDD1 is also increased in the postmortem PFC of depressed subjects.[30] These findings demonstrate that disruption of BDNF signaling contributes to the synaptic and behavioral deficits of stress, and provide a mechanism for how exposure to stress and genetic factors may modify risk for depression.

Chronic administration of typical antidepressants increases BDNF expression and promotes neuroplasticity. Chronic, but not short-term administration of SSRI or NARI antidepressants can enhance synaptic plasticity and block the synaptic deficits caused by stress .[27,24,32,35,36] However, the actions of SSRI and NARI 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 elegant rodent models , demonstrating 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.[37,38]

BDNF and intracellular signaling. In contrast to stress, chronic antidepressant administration, both SSRI and NARI agents, increases the expression of BDNF and its receptor TrkB in the PFC and hippocampus.[24,29] (Figure 1). Moreover, the behavioral actions of typical antidepressants in animal models are blocked by deletion of BDNF, and infusion of BDNF into the PFC or hippocampus is sufficient to produce antidepressant effects.[23,24,29] In addition, fuoxetine-induced synaptic plasticity in the ocular dominance and fear extinction studies is dependent on BDNF, and BDNF infusions are sufficient to produce these effects.[37,38] These studies demonstrate that antidepressant induction of BDNF expression, over the course of several weeks of treatment, enhances synaptic plasticity that contributes to behavioral response to these agents. Antidepressant treatment also increases downstream signaling, including the cAMP and Ca2+ that increase the expression of BDNF.[39]

If reduction of BDNF in the PFC and hippocampus plays a causal role in vulnerability to depression, then we would expect that BDNF deletion would cause depressive behaviors. But this is not the case in rodent BDNF gene deletion models.[24,29] This could be due to differential effects of BDNF in the mesolimbic DA system, where BDNF produces depressive-like behaviors in social defeat models, [40,21] indicating that BDNF is required for plasticity of different circuits, some of which could be prodepressive while others produce antidepressant actions. Evidence for this possibility is supported by studies demonstrating that region specific deletion of BDNF in hippocampus is sufficient to produce depressive behaviors.[41] BDNF deletion mutant mice are also more vulnerable depressive behaviors upon exposure to mild stress. [27] Additional signaling pathways and brain regions have been implicated in antidepressant drug action, and are described in comprehensive reviews elsewhere.[42,32]

Cognitive neuropsychological approaches

In parallel to the research reviewed above which focuses on molecular and cellular pathway actions there has been recent interest in understanding 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 described above, and there is no

research directly addressing this question. It is possible that these psychological and synaptic plasticity changes simply describe different levels of analysis and the potential for integration of these two approaches is therefore considered in *Future Perspectives*.

Negative affective biases in depression: The incidence of depression is increased following a period of life events or stress,[43] and individual differences in how negative events are experienced, perceived and recalled can exacerbate these effects. Indeed, depression is associated with the tendency to perceive social cues as more negative, to preferentially attend to aversive information and to recall negative over and above positive information concerning themselves. [44,45] This style of focusing on and remembering affective and social information which is negative, while disregarding positive information, is hypothesized to reinforce negative thoughts, feelings and beliefs seen in depression. Negative affective biases during remission are associated with an increased risk of relapse [44] and improved positive emotional processing has been found to precede changes in symptoms of depression. [46] These observations highlight that negative bias may not be just a 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 work has highlighted negative bias as a target for pharmacological and psychological treatments in depression [45,47,48]

Reversal of negative affective bias with antidepressant drug administration: Antidepressant administration increases the relative processing of positive vs negative affective information very early on in treatment in both depressed patients and healthy volunteers. [47] For example, a single dose of reboxetine facilitated the recognition of happy facial expressions and the recall of positive vs negative self-referent memory in depressed patients compared to double blind administration of placebo.[49] Similarly, single, as well as 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[47,50]. Early effects of antidepressants on negative affective bias may act to reduce the influence of this key maintaining factor and set the scene for improved symptoms across time.[51,52] Early changes in affective processing following other treatment modalities for depression and anxiety have been described including transcranial direct current stimulation [53] negative ion treatment [54] and with cognitive behavioral therapy (CBT) in panic disorder. [55] Thus, early effects on the way in which information is processed may be important across treatment modalities.

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 vs positive stimuli, important for the detection and response to emotionally salient stimuli. This limbic over-activity has been coupled with decreased engagement of areas important for regulation and inhibition of such responses, including the dorsolateral and medial PFC. [48] Antidepressant treatment reverses this pattern of neural response to affective information in depressed patients as well as introducing a similar direction of change in healthy people. [56] For example, acute clinical doses of SSRIs decrease amygdala response to negative affective faces [57,58] and this effect is also seen after 7 days administration in healthy participants [59] and depressed patients. [60] These effects tend to occur in the absence of any significant changes in the symptoms of depression suggesting that they may 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 longer term treatment. For instance, 6 weeks SSRI treatment was associated with reduced responses in the amygdala, anterior cingulate and fusiform

face area to negative facial expressions in depressed patients [61,56]. Likewise, responses to happy faces were enhanced across similar regions after 6 weeks treatment.[62,56]

The effects of antidepressants seen in these models after just a single dose highlight that the reversal of negative bias may occur, at least in part, before changes in the measures of neuroplasticity or neurotrophic factors (such as BDNF) with conventional antidepressants examined in animal models in PFC and hippocampus (see section *Neuroplasticity theories of stress and antidepressant treatment response*). Further work is therefore needed to examine the timescale of neuroplasticity markers in relation to these early changes in nonconscious 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 may expect that patients who show the greatest resolution of negative bias early in treatment may 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. [51,52,63] A classification based approach of data from Tranter et al., (2009) [51] study 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 (see Table 1). A similar effect was seen in older adults where a group of depressed patients who did not show an improvement in the recognition of happy faces after one week of citalopram treatment also failed to respond after 8 weeks of treatment.[52] 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.[64] These results suggest the effects on emotional bias may not be restricted to monoamine antidepressant drug action and may be applicable to the development of novel agents. These results 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, we 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.[63] The responder group showed a greater reduction in neural response in these areas during the processing of negative vs 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 above, 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, processes and remembered.

Can these effects help us understand the delays in clinical effects of antidepressants? Given that antidepressants have rapid effects on emotional processing, why 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 *i.e.* 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, experimentally inducing a negative affective bias in healthy volunteers does not affect subjective state directly but impairs mood response after exposure to a stressor [65]. 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.[66]

The translation of change in negative bias into clinical response might therefore involve re-learning a range of emotional associations *i.e.* 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 (see above) could help consolidate early changes in emotional bias and allow these effects to have longer lasting influence.

The requirement for changes in negative affective biases and interaction with the external social environment may help explain some of the variance in clinical response to antidepressant treatment. For example, treatment resistant depressed patients may 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. Indeed, a recent study found that improved accuracy of happy facial expression recognition by perceived level of social support is a significant predictor of change in depressive symptoms[52]. In particular, the increase in emotional bias towards positive information was only associated with a therapeutic response in those patients with a good level of social support. This approach highlights the need for a more integrative perspective in depression and antidepressant drug research, where the psychopharmacology, neurobiology, psychological and environmental influences are explored together. Indeed, Rose (2016) [67] 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, we need to consider multiple factors when understanding antidepressant drug action, its limitations, blocks to successful treatment and methods to facilitate its effects.

Faster acting agents for the treatment of depression

While currently available antidepressants have a delayed clinical onset, is is notable that a single dose of ketamine, a noncompetitive open channel NMDA antagonist, produces rapid antidepressant actions within hours [68] and leads to a rapid resolution of suicidal ideation. Moreover, many of these studies include patients who have failed to respond to two or more typical antidepressants.

Preclinical studies demonstrate that a single dose of ketamine produces rapid antidepressant like effects in rodent models and reverses the depressive behaviors caused by chronic stress. [69,70,71] The results also demonstrate that a single dose of ketamine rapidly increases synapse number and function in mPFC neurons, and reverses the synaptic deficits caused by chronic stress. [70,71] (Figure 1). The synaptic and behavioral actions of ketamine are blocked in BDNF null mice or BDNF Met knockin mice. [72,26] Interestingly, MDD patients carrying the BDNF Met allele show a 50 percent lower response compared to Val carriers, identifying a potential biomarker that may be explored as a predictor of treatment response to ketamine, although further studies are required to confirm this finding. [73] Preclinical studies also demonstrate that the synaptic and behavioral actions of ketamine are dependent on BDNF signaling via the Akt and mTORC1 cascade, leading to increased synthesis of synaptic proteins (Figure 1) [70,71,74] There is also evidence that other rapid acting antidepressants act through a similar mechanism [75,76]

Ketamine produces a paradoxical increase in extracellular glutamate in the mPFC, and the behavioral actions of ketamine are blocked by pretreatment with a glutamate receptor antagonist,[27] which could result in activity dependent release of BDNF and the rapid synaptogenic response. [28, 70] 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[70,74]. Other theories propose that ketamine acts via blockade of NMDA receptors on postsynaptic principle neurons in the mPFC or hippocampus to increase synaptic function via a homeostatic mechanism. [72,74] Studies are being conducted using cell specific NMDA receptor subunit knockdown approaches to address this question.

These findings provide potential molecular mechanisms for fast 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 humans [77] though the nature and timing of these effects have not been directly compared to 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 while conventional antidepressants affect the acquisition of a positive bias they do not affect the retrieval of previously-acquired negative memory associations[78]. By contrast, ketamine did not affect the learning of positive affective information but was able to abolish memory for negative associations where stimuli had been paired with psychosocial stress or administration of an anxiogenic drug via effects within mPFC[78]. It is therefore possible that while conventional antidepressants only change positive processing of incoming information, novel rapid onset drugs may 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 a riluzole and memantine. [79] New forms of ketamine that can be administered more continuously, orally or intranasally, are being developed and are in clinical trials. Here the issue will be to assess whether the antidepressant effects of ketamine can be sustained without the development of therapeutic tolerance or safety concerns (for example, dependence, psychosis, bladder toxicity). A potentially important development, based on animal studies, is the demonstration that the antidepressant effect of ketamine may depend principally on the ability of its active metabolite, hydroxynorketamine, to produce a rapid and sustained stimulation of glutamatergic AMPA receptors, although whether efficacious levels of the metabolite are achieved with the ketamine doses used is questionable. [80] 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 characterize it's actions in other brain regions, notably the mPFC. Nevertheless, hydroxynorketamine could be free of many of the safety problems associated with ketamine and studies of its clinical efficacy in depressed patients 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, while lanicemine is a 'low trapping' nonselective antagonist of the NMDA receptor which 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. [81] 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 currently in phase 3 trials in patients with major depression [82] 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. [83]

Future perspectives: Relationship between changes in neural plasticity and negative bias

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 (see Table 2 for predictions made by these different approaches). Research in humans 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. Further, the observation that emotional bias is typically affected prior to when changes in plasticity would be expected suggests that these may 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 [84] presents a novel opportunity to investigate both cellular and psychological processes in the same animal. This would allow the timescale of specific changes in bias and different aspects of plasticity to be related and also test whether blocking the expression of intracellular signaling 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 may be that transformations in the emotional world might stimulate similar experience-dependence plasticity changes. Exploring these relationships in animal models may therefore provide unique hypotheses for how we conceptualize and speed up antidepressant drug action (Table 2). It is clear that the effects of these two processes would be expected to be mutually synergistic: that is that increased neural plasticity may facilitate the re-learning of new emotional associations to inner and external environmental cues, thereby consolidating and generalising the implicit changes produced by initial doses of medication. Characterization of the neural circuitry and signaling pathways that underlie early changes in emotional processing will further inform our understanding of the relationship with synaptic plasticity.

Conclusions

There has been considerable progress in understanding mechanisms of antidepressant drug action over 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 characterized in animal models but contextualized 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 humans but with recent extension to animal models. These effects occur very early, prior to changes in mood, but are related to later clinical change. The two theories also provide different perspectives on the underlying mechanisms of fast acting agents like ketamine in

the treatment of depression. However, it is possible that these processes are related or may operate synergistically for treatment success. The contrasting perspectives on fast acting agents (disruption of fixed negative memories versus BDNF release) may 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 going forward 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.

Conflicts of interest

Dr. Harmer reports grants from Johnson & Johnson, UCB, Sunovion, personal fees from P1vital Ltd, Lundbeck, outside the submitted work; Dr. Duman reports grants from Taisho, Forest, Naurex, Sunovion, Lilly, Lundbeck, personal fees from Taisho, Naurex, Sunovion, Johnson & Johnson, outside the submitted work; Dr. Cowen reports personal fees from Lundbeck advisory board, outside the submitted work.

Author contributions

All authors contributed to the literature search, creation of figures and writing of the manuscript. All authors approved the final submission.

Table and Figure legends

Table 1: Predicting antidepressant response from early changes in emotional processing (EP). Clinical response: decrease of ≥50% of symptoms on the CORE at week 6. Positive EP test: increase in positive face recognition at 2 weeks vs baseline.[51]

	Response	No Response	Total
Positive EP test	22	15	37
Negative EP test	1	10	11
Total	23	25	

Table 2: Predictions made by the neuroplasticity and cognitive neuropsychological theories. These predictions do not necessarily represent competing views but rather different perspectives, levels of analysis and methods that may be synergistic or overlapping.

	Neuroplasticity	**Neuropsychological**
Target development	Novel agents should target neural plasticity that reverses synaptic deficits in PFC and hippocampus caused by stress	Novel agents should target neural plasticity/transmitter systems in amygdala and cortex that control emotional processing
Speeding up 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	Entrained emotional processing response which is difficult to shift Toxic environment or reduced environmental engagement
Predicting 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
Exploring the relationship between the two theories	Restricting plasticity change should limit the effect of agents on emotional bias in animal models	Blocking the expression of negative bias change should reduce the plasticity changes induced by antidepressant agents
Combination approaches	Agents which 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	

Figure 1: The neurotrophic theory of antidepressant drug action

Figure 2: The cognitive neuropsychological theory of antidepressant drug action showing possible interactions with plasticity changes also induced with antidepressant drug treatments.

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