

OPINION

Is mood chemistry?

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Abstract | The chemical hypothesis of depression suggests that mood disorders are caused by a chemical imbalance in the brain, which can be corrected by antidepressant drugs. However, recent evidence indicates that problems in information processing within neural networks, rather than changes in chemical balance, might underlie depression, and that antidepressant drugs induce plastic changes in neuronal connectivity, which gradually lead to improvements in neuronal information processing and recovery of mood.

The first antidepressants were discovered by chance almost 50 years ago, when drugs that had been developed for other disorders were found to elevate the mood of psychiatric patients. Soon after this, drugs with antidepressant activity were shown to increase the extracellular concentrations of two important monoamine neurotransmitters in the brain — serotonin (5-hydroxytryptamine or 5-HT) and noradrenaline — by inhibiting their catabolism or reuptake to nerve endings. These findings were the basis for the monoamine hypothesis of depression, which proposes that mood disorders are caused by a deficiency in serotonin or noradrenaline at functionally important receptor sites in the brain^{1–4} (FIG. 1).

It soon became evident that the monoamine hypothesis in its original form could not explain all of the effects of antidepressants⁵. Therefore, the focus of research was directed towards the receptors and intracellular signal transduction molecules that are regulated by antidepressant treatment^{6,7}. Furthermore, because mood disorders often run in families, genetic studies have been

searching for the genes that might be associated with these familial disorders, and researchers hope to uncover a molecule that is malfunctioning in people with depression⁸. These research strategies seem to be based on an extension of the monoamine hypothesis, the chemical hypothesis of depression (FIG. 2), which proposes that mood disorders are caused by structural or functional changes in particular molecules in the brain, and that antidepressants function by counteracting these molecular changes. Over the last few decades, the view that depression is produced by a chemical imbalance in the brain has become widely accepted among scientists, clinicians and the public.

However, during the past decade, several observations indicated that there might be an alternative hypothesis to the chemical view of depression. This network hypothesis proposes that mood disorders reflect problems in information processing within particular neural networks in the brain and that antidepressant drugs and other treatments that alleviate depression function by gradually improving information processing within these networks (FIG. 3). This review discusses the evidence supporting and contradicting the network hypothesis and the implications of the network view on drug development and the treatment of mood disorders.

The chemical hypothesis

We will soon be celebrating the fiftieth anniversary of the discovery of antidepressants, although the exact date and place of the discovery is a matter of dispute (for the history of the discovery of antidepressants, see

REF. 9). Iproniazid, a drug registered for the treatment of tuberculosis, was found to elevate the mood of patients that received it, and subsequent studies in patients who were depressed but did not have tuberculosis showed its effect as an antidepressant⁹. Simultaneously and independently, imipramine, an experimental antihistamine with a tricyclic structure, was found to have antidepressant effects. These discoveries revolutionized the recognition and treatment of mood disorders. In retrospect, it seems unbelievable that imipramine was introduced to the market only several years after its antidepressant effects were discovered, mainly because the company producing it was unsure that the number of patients who would benefit from antidepressant treatment was sufficiently high⁹. This now sounds incredible given the current estimate that major depression is the single most expensive disorder faced by Western societies and that, overall, antidepressants are among the best selling drugs.

Soon after this discovery, imipramine and iproniazid were found to increase the extracellular concentrations of two important neurotransmitters — serotonin and noradrenaline — in the brain, by blocking their re-uptake back to nerve endings or by inhibiting the main metabolizing enzyme, monoamine oxidase, respectively. As drugs that alleviate depression increase extracellular monoamine concentrations, it was proposed that depression might be produced by a serotonin or noradrenaline deficiency at functionally important receptor sites in the brain^{1–4} (FIG. 1), a proposal that is now known as the monoamine hypothesis of depression. Initially, the idea that a complex psychiatric disorder such as depression could be produced by biochemical changes was met with widespread scepticism among psychiatrists and laymen. Nevertheless, during the last few decades this hypothesis has strongly influenced views about the pathophysiology of mood disorders, among not only pharmacologists, but also clinicians, other scientists and the public⁴.

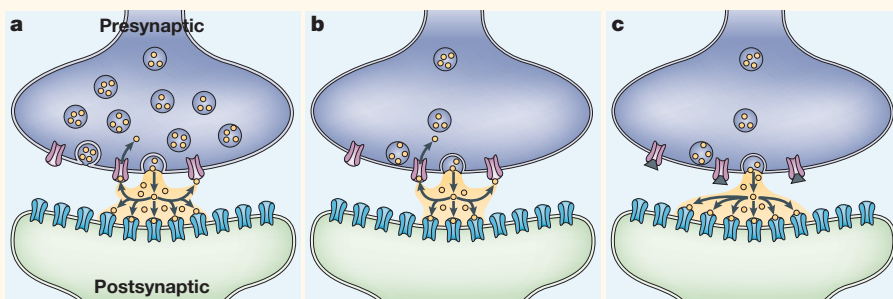


Figure 1 | Monoamine hypothesis of mood disorders. a | In the normal brain, monoamine neurotransmitters (yellow) are released and bind to receptors on the postsynaptic neuron. Transmission is terminated by re-uptake of the transmitter. **b** | In depression, the decreased concentration of monoamine at synaptic sites produces a mood disorder. **c** | Blockade of the re-uptake sites (grey) increases the concentration of monoamine neurotransmitters available at receptor sites and restores mood.

The monoamine hypothesis focused the interest of the pharmaceutical industry on monoamine metabolism for decades. Imipramine, which inhibits the re-uptake of both serotonin and noradrenaline (and various other receptors and enzymes), has now been largely replaced by a host of molecules that inhibit the uptake of either serotonin or noradrenaline more selectively, and iproniazid, which inhibits monoamine oxidase, the main metabolizing enzyme for monoamines, has given way to subtype-selective monoamine oxidase inhibitors. Although this focused drug development effort has clearly been successful from the point of view of safety, it has been less successful in terms of efficacy. Modern antidepressants are no more effective than the first generation of drugs that were discovered several decades ago, and electroconvulsive shock treatment remains the most effective treatment for depression^{5,10,11}.

It was recognized early on that several observations conflict with a simple link between monoamine concentrations in the brain and depression¹¹. For example, depletion of dietary tryptophan, which significantly decreases the concentration of serotonin in the brain, produces either no effects or only a mild dysphoria in healthy volunteers and does not influence the mood of untreated patients with depression^{12,13}. More importantly, although the effects of antidepressants on monoamine metabolism can be seen soon after administration, it typically takes several weeks of continued treatment for the clinical antidepressant response to appear¹¹. The discovery that long-term antidepressant treatment produces adaptive changes in monoamine receptors and in their coupling to intracellular signal transduction¹⁴ caused the research focus to shift towards the effects that long-term antidepressant treatments have on the concentrations of neuropeptides,

growth factors and their receptors, and intracellular signalling molecules^{4,6,7,15} (FIG. 2). As a result of this development, the monoamine hypothesis has evolved to what could be called a chemical or molecular hypothesis of depression. This hypothesis presumes that mood disorders are produced by long-term changes in the production or activity of molecules in the brain and that antidepressants function by counteracting these molecular changes. Motivated by this hypothesis, researchers are using large-scale DNA microarray searches to look for genes that are up- or downregulated in depression or by antidepressant treatments, in the hope that the molecules that are encoded by these genes might be used as targets in the development of new antidepressant drugs^{4,16,17}.

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The network hypothesis

But is this view correct? Is mood chemistry? Observations that have been made during the last few years indicate that there might be an alternative to the chemical view of depression and the action of antidepressants⁵. This new hypothesis, the network hypothesis, proposes that problems in activity-dependent neuronal communication might underlie depression, and that antidepressants might work by improving information processing in the affected neural networks (FIG. 3). A key aspect of the network view is the recognition that the

principal role of the nervous system is not to handle chemicals but to store and process information. Arvid Carlsson, one of the main architects of the concept of chemical neurotransmission in the brain, stated in his Nobel lecture, 'However, it must be recognized that the brain is not a chemical factory but an extremely complicated survival machine'¹⁸. Although chemical neurotransmitters are crucial for the transfer of information between neurons, information in the brain is not stored in a chemical form but is thought to be processed by the complex interactions of neurons in neural networks^{19,20}. These networks develop through interactions with the environment, and the neuronal structure of, and neurotransmission in these networks are constantly being refined through activity-dependent synaptic plasticity to optimally process and store relevant information²¹ (BOX 1). So, disorders of the nervous system, including depression, might represent disturbances in the activity-dependent information processing of the brain, rather than in the chemical balance of signalling molecules.

It should be noted that the chemical and network hypotheses are not mutually exclusive, but are complementary. As the synthesis and release of several important signalling molecules are regulated by neuronal activity, changes in the activity of neural networks produce changes in the concentration of these signalling molecules. Therefore, although the initial effects of antidepressants are obviously chemical and are, in most cases, directed towards the metabolism of monoamines, the ensuing adaptive changes in the concentrations of those signalling molecules are tightly linked to the structure of the neural network, and might be a consequence of the altered information processing rather than its cause. According to this view, antidepressants initiate a 'self-repair' process, whereby plasticity in neural networks and chemical neurotransmission indivisibly cooperate and gradually bring about mood elevation.

Evidence for the network hypothesis

The evidence that supports the network hypothesis of depression and antidepressant action is limited and mostly indirect. Part of the problem is the lack of appropriate experimental models of depression. In particular, there are no relevant and widely accepted *in vitro* models of what might be going on in the brain during depression. Furthermore, methods for direct measurement of changes in neural networks *in vivo* are only now being developed and have not yet been applied to neuropharmacological research^{19,22}.

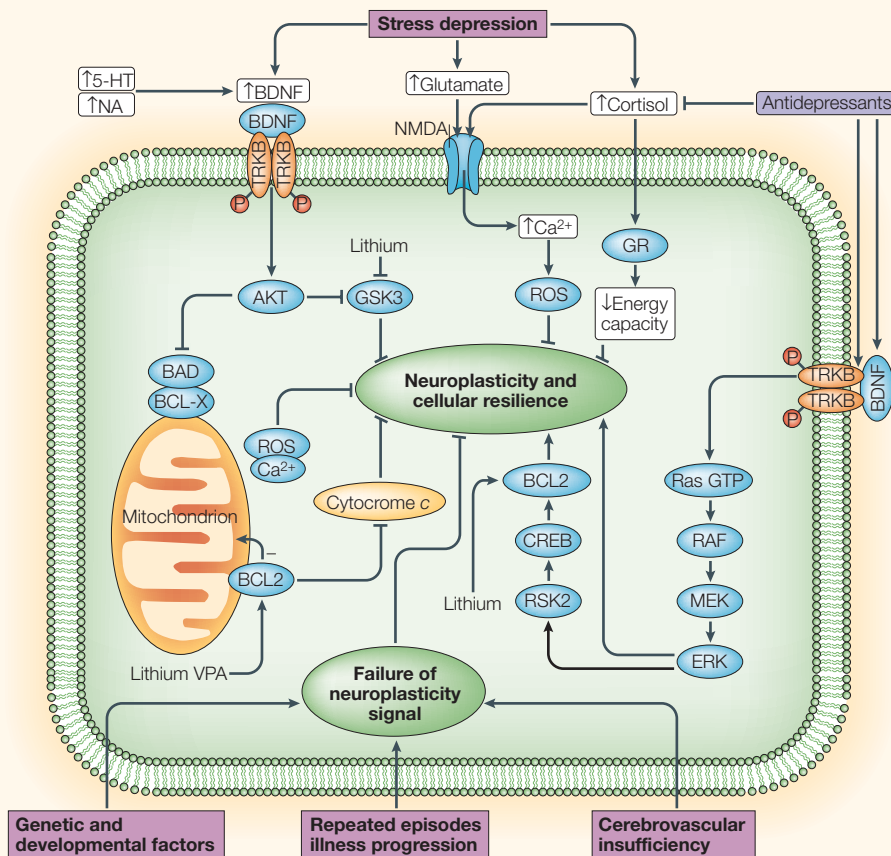


Figure 2 | The chemical hypothesis of depression. The intracellular pathways that are affected by mood disorders and antidepressants. AKT, protein kinase B; BAD, BCL-associated death promoter; BCL2, B-cell leukaemia/lymphoma 2; BCL-X, BCL2-like protein 1; BDNF, brain-derived neurotrophic factor; CREB, cyclic AMP responsive element binding protein; ERK, mitogen activated protein kinase 1; GR, glucocorticoid receptor; GSK3, glycogen synthase kinase 3; MEK, ERK kinase; VPA, valproate; NA, noradrenaline; P, phosphate; RAF, RAF proto-oncogene; ROS, reactive oxygen species; Ras GTP, Ras GTPase-activating protein; RSK2, ribosomal protein S6 kinase polypeptide 3; TRKB, neurotrophic tyrosine kinase receptor type B; 5-HT, 5-hydroxytryptamine (serotonin). Adapted, with permission, from REF. 6 © (2001) Macmillan Magazines Ltd.

Monoamines, particularly serotonin, have a significant role during brain development²³. Genetic elimination of the **5-HT1A** receptor produces anxiety-type behaviour in adult mice, but only when the receptor was absent during early postnatal development — its absence in adulthood produces no behavioural effects²⁴. Furthermore, mutations in monoamine oxidase A produce behavioural alterations in both men and mice^{25,26}, and disrupt the developmental organization of thalamocortical inputs and cortical modules in the brains of rodents^{23,27}. A similar disruption in thalamocortical organization has also been produced with the administration of antidepressants and monoamine oxidase inhibitors during early postnatal development^{27,28}. Furthermore, antidepressant treatment during early postnatal life can produce permanent behavioural disturbances in adult animals^{29,30}.

It is well known that the plasticity of neural connectivity in the brain is greater and more extensive during critical periods of postnatal development than in adults, and that functional structures that are formed during critical periods remain relatively stable in adulthood³¹ (BOX 1). These data highlight the effects that serotonin and antidepressant treatments have on the plasticity of neural networks, and link the effects of antidepressants with the environmental manipulations that are known to modulate neural network formation during development³¹. Moreover, they indicate that the effects of the drugs might be more robust in the brain during early postnatal development and qualitatively different when compared with the effects seen in the adult brain, which could have significant implications for the prescription of antidepressants to children and pregnant mothers.

Imaging studies in patients with depression have revealed reduced grey matter volume in the prefrontal cortex^{32–34} and the hippocampus^{35–39}. Morphological changes in the hippocampus are associated with, and might be preceded by, functional deficits, such as memory impairment³⁵. As the neuronal processes and synapses take up most of the space in the grey matter, reduced volume might mean reduced neuronal complexity and connectivity. To at least some degree, these morphological alterations seem to be reversible by antidepressant therapies^{34,40}. The results of a recent study show that reduced hippocampal volume is particularly common in patients with depression who suffered a childhood trauma⁴¹, which indicates that severe stress during a critical developmental period might have lasting effects on the morphology of the brain. These data support the hypothesis that mood disorders are associated with compromised information processing in crucial neural networks, and that the action of antidepressants might result in morphological and physiological reorganization of specific neuronal connections in the brain. Furthermore, imaging and genetic studies are beginning to elucidate which neural structures are involved in different mental health disorders and which circuits might be important targets for successful medications⁶.

Perhaps the most important evidence for the network hypothesis is the recent observation that antidepressants increase the production of new neurons in the rodent hippocampus⁴². Importantly, the increased neurogenesis that is brought about by chronic antidepressant treatment correlates with the behavioural effects produced by antidepressants⁴³. Newly generated neurons differentiate over time, and are only mature enough to participate in information processing several weeks after their birth⁴⁴. The fact that this time course correlates with the delayed onset of the clinical effects of antidepressants has created a lot of excitement among neuropharmacologists. In the hippocampi of rodents that have received antidepressant treatment, the elimination of neurons through apoptotic cell death increases simultaneously with increased neurogenesis, which indicates that antidepressants might increase neuronal turnover rather than neurogenesis *per se*⁴⁵. This effect might be functionally analogous to the overproduction of neurons that occurs during the development of the peripheral nervous system (BOX 1), and indicates that antidepressants might facilitate optimization of neuronal connectivity by increasing

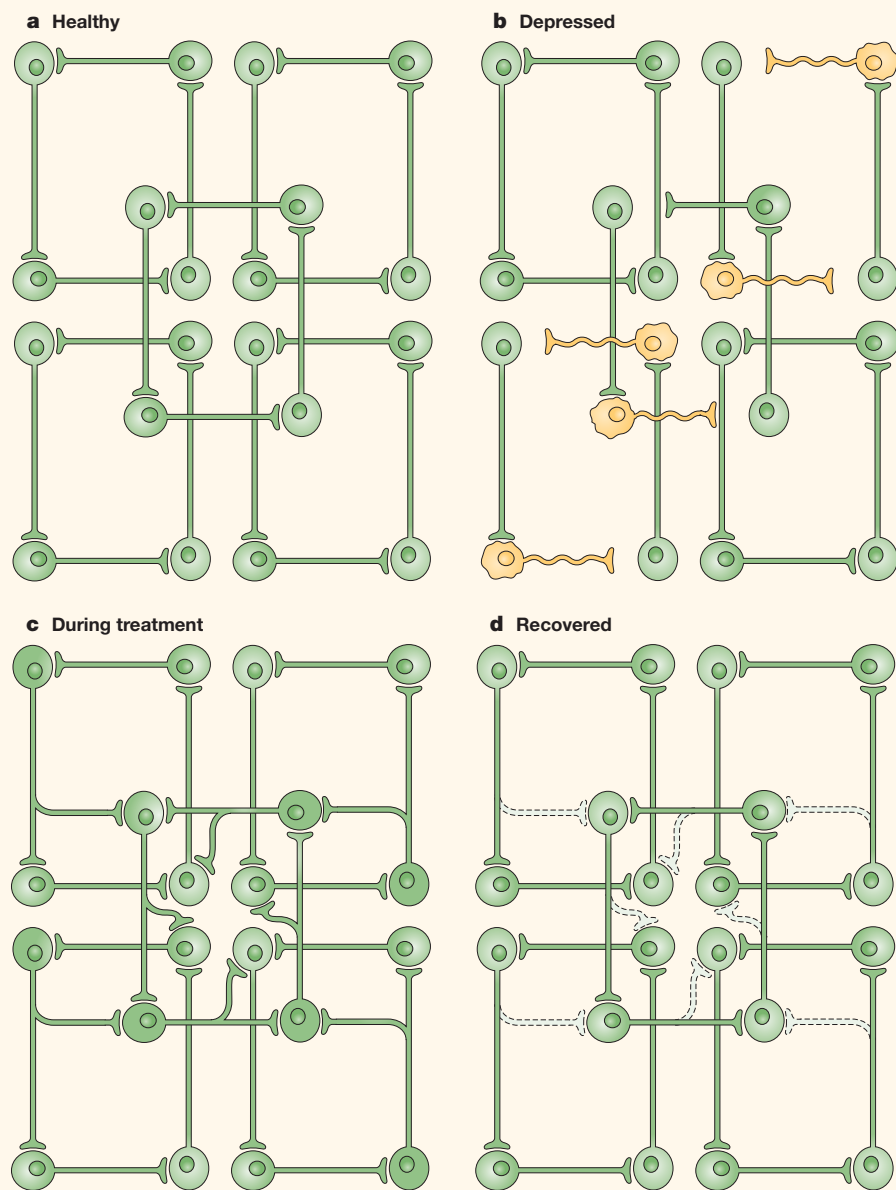


Figure 3 | The network hypothesis of depression. **a** | In the healthy brain, information is processed in partially overlapping neural networks. **b** | In depression, information processing in some networks does not function properly. **c** | Antidepressant treatment enhances connectivity in neural networks. **d** | Activity-dependent pruning of synapses selects out and stabilizes the active synapses and networks.

the choice of neurons available for selection through activity-dependent mechanisms. At a more subtle level, antidepressant drugs can enhance the sprouting of axons⁴⁶ and dendrites⁴⁷, and support the morphological maturation of the newborn neurons⁴⁷. These data indicate that, in addition to their established function in elevating neuronal turnover in the dentate gyrus, antidepressants might also stimulate the turnover of axonal branches and synaptic contacts, thereby providing more material for activity-dependent selection. It should be noted that increased synaptic turnover might lead to significant reorganization of neuronal

connectivity without any net change in synaptic number²⁰. Unfortunately, it is difficult to quantify synaptic turnover *in vivo*.

One possible mechanism through which antidepressants might enhance the plasticity of neuronal connections in the hippocampus and cerebral cortex is the activation of neurotrophin signalling^{48,49}. Brain-derived neurotrophic factor (BDNF), which is produced and released by neurons in an activity-dependent manner⁵⁰, has been proposed to be a crucial factor in the selection and stabilization of active synaptic contacts⁵¹ (BOX 1). Both antidepressants and electroconvulsive shocks increase the expression and signalling

of BDNF in the hippocampus and cortex^{52–54}, and the injection of BDNF into the brain or overexpression of its receptor in transgenic mice produces similar behavioural responses to those typically observed after treatment with antidepressant drugs^{55,56}. Consistent with the importance of BDNF in the effects of antidepressants, transgenic mice with reduced BDNF expression or signalling fail to show these characteristic behavioural responses after the administration of antidepressants⁵⁴, which indicates that normal BDNF signalling might be both necessary and sufficient for a normal antidepressant effect. It should be emphasized that the crucial point is not the increased molecular concentrations of BDNF as such, but the importance of this neurotrophin as a mediator of activity-dependent neuronal plasticity (BOX 1).

In conclusion, the data that are summarized above provide some evidence that antidepressants, through their acute effects on monoamine metabolism, activate processes of plasticity, which are thought to gradually lead to improved information processing in the neural networks that are involved in mood regulation. These processes, which include neurogenesis and selective neural elimination, arborization and retraction of axons and dendrites, and synaptic formation and pruning, are expected to take time to develop and mature, which is consistent with the delayed appearance of the clinical effects of antidepressants.

However, observations have also been made that seem to be incompatible with the network hypothesis. Although depletion of tryptophan — the rate-limiting factor of serotonin synthesis — does not influence the mood of healthy volunteers and untreated patients with depression^{12,13,57}, it does produce a rapid relapse of depressive symptoms in about 50% of remitted patients who are being, or have recently been treated with serotonin selective antidepressants^{12,13}. Furthermore, there is a circadian variation in mood, and sleep deprivation rapidly improves the mood of patients with depression, albeit temporarily⁵⁸. These relatively rapid effects on mood are difficult to reconcile with the view of their production by a gradual change in the structure of mood-elevating neural networks. It is obvious that more experimental work will be necessary to test the new model, but the rapid development of neurophysiological methods and the imaging of neural networks will help us to gain further insights into the relationship between the effects of antidepressants and neural plasticity, which might become a fruitful area of further research.

Box 1 | Activity-dependent refinement of neural networks

During the development of the peripheral nervous system, neurons are produced in excess and compete to innervate the target tissues⁶¹. Neurotrophic factors, which are secreted by the target tissues (for example, muscles) in limited quantities, and which are required by innervating neurons for their survival, select from the competing neurons those that best innervate the target, and the defeated neurons are eliminated by apoptosis. This competitive process matches the number of neurons and targets and ensures optimal innervation of the target cells^{61–63}. In the CNS, neurons target other neurons and competitive selection takes place at several levels: among neurons (as in the peripheral nervous system), among axon branches and among synaptic contacts⁶⁴. In the brain, the release of target-derived trophic factors is activity dependent: the innervating neuron must sufficiently stimulate the target neuron in order to induce the production and release of the trophic factor^{50,51}. Neurons can also cooperate to increase the release of trophic factors: simultaneously active neurons that innervate the same target neuron can induce the release of trophic factors through a much lower level of activity than is required for a single innervating neuron⁵¹. This activity-dependent cooperative selection of simultaneously active neurons and the elimination of inactive and incoherent contacts is considered to be crucial in the development of large, coherently active neural networks: ‘the neurons that fire together, wire together’²¹. Through these mechanisms, neuronal structure and neurotransmission are optimized to best store and process relevant information. During critical periods in early postnatal development, much larger changes in the connectivity and organization of neural networks take place than is possible in the adult brain³¹. Nevertheless, even the adult brain still shows significant plasticity. The crucial event in activity-dependent plasticity is not the formation of neuronal contacts (which might occur stochastically and in excess) but the activity-dependent selection and stabilization of those synapses that mediate useful signals, together with the selective pruning and elimination of those that produce random noise²⁰. Therefore, neurogenesis and synaptogenesis cannot simply be considered beneficial, and neuronal death and synapse elimination harmful; what matters is the optimization of the signal-to-noise ratio in the network. Neurotrophins are important in this process through their selective release from active connections; indiscriminate increases in the levels of neurotrophic factors or their signalling (as, for example, would be produced by a neurotrophic factor receptor agonist) is not expected to be beneficial to the network, as both active and inactive connections would be similarly supported.

be expected to be more beneficial than either treatment alone, and there is evidence that this might be the case⁵⁹. As the network hypothesis emphasizes the importance of environmental information in the process of activity-dependent selection of neurons and synapses (BOX 1), it predicts that full recovery would not even be possible with drug treatment alone, but that external stimuli, such as social communication, would be required to provide environmental input for the selection of the appropriate network connections (FIG. 3). The role of environmental stimulation might also be related to the fact that major depression is typically cyclical and often self-limiting, and many patients improve with time even in the absence of active treatment.

Finally, the effects of antidepressant drugs on network plasticity in the brain might explain why they are effective for many neuropsychiatric disorders, including anxiety, obsessive-compulsive disorder, eating disorders, chronic pain and tinnitus. It has been proposed that some of these disorders, particularly chronic pain, might be produced by aberrant neuronal connectivity⁶⁰.

The hypothesis that mood represents a functional state of neural networks might sound incompatible with the efforts of rational drug development. However, the data reviewed above indicate that the antidepressant drugs that have been used successfully for several decades might function by initiating such plastic processes, apparently indirectly, by influencing monoamine metabolism. It is possible that a similar process could also be initiated through other pharmacological mechanisms, which might become the targets of new antidepressants that could help patients who are resistant to current drugs and only respond to electroconvulsive shock treatment.

Future perspectives

The view of mood disorders as problems of information processing in the brain has several important implications. As developmental neurobiologists have been investigating activity-dependent plastic processes for decades, collaboration between neuropharmacologists, developmental neuroscientists and behavioural geneticists should be encouraged. Recent studies clearly show that genetic manipulation of neural circuits and assessment of the consequences through *in vivo* recording techniques and behavioural assays might provide an incredible potential for beginning to define the relationship between circuit properties, behavioural deficits and potential therapeutics^{23,24}.

During development and in adults, training and rehabilitation produce functional and anatomical changes in neural networks, which are reflected in the gradual improvement of the rehearsed action. Analogously, psychotherapy, cognitive behavioural therapy and other forms of psychological rehabilitation could also have therapeutic effects on mood disorders through use-dependent neuronal

plasticity. Therefore, psychological and pharmacological therapies, electroconvulsive shock treatment and placebo effects might all lead to improved information processing and mood recovery through mechanisms that initiate similar processes of plasticity (FIG. 4). In this scenario, a combination of drug treatment and psychological rehabilitation would

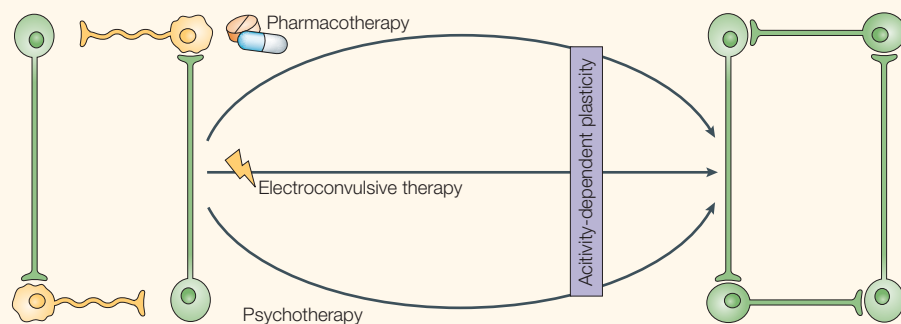


Figure 4 | A combinatorial approach for treating depression based on the network hypothesis. Depression might reflect disturbed information processing in neural networks (left panel). Antidepressant drugs, electroconvulsive shock and psychotherapy can all induce activity-dependent plasticity, which gradually leads to the recovery of connectivity in the affected neural networks (right panel).

Our view of mood disorders and the action of antidepressants is beginning to change from a chemical view towards a network hypothesis, in which problems in information processing and neuronal connectivity in the brain are the central questions. However, several important issues have yet to be addressed. How are neural networks formed and sustained during development and in adults? Which neuronal connections are involved, and are the same networks affected in all patients? How do antidepressants initiate and support the process of plasticity? Does the delayed appearance of clinical antidepressant effects reflect slow maturation of neuronal connections, and could these processes be accelerated? In any case, it is increasingly evident that the activity-dependent plasticity and connectivity of neural networks must be considered when designing future strategies of antidepressant treatment, whether they are pharmacological, psychological or combinatorial.

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Competing interests statement

The author declares no competing financial interests.

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DATABASES

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