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Review

Brain-Derived Neurotrophic Factor Signaling in Depression and Antidepressant Action

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ABSTRACT

Neurotrophic factors, particularly BDNF (brain-derived neurotrophic factor), have been associated with depression and antidepressant drug action. A variety of preclinical and clinical studies have implicated impaired BDNF signaling through its receptor TrkB (neurotrophic receptor tyrosine kinase 2) in the pathophysiology of mood disorders, but many of the initial findings have not been fully supported by more recent meta-analyses, and more both basic and clinical research is needed. In contrast, increased expression and signaling of BDNF has been repeatedly implicated in the mechanisms of both typical and rapid-acting antidepressant drugs, and recent findings have started to elucidate the mechanisms through which antidepressants regulate BDNF signaling. BDNF is a critical regulator of various types of neuronal plasticities in the brain, and plasticity has increasingly been connected with antidepressant action. Although some equivocal data exist, the hypothesis of a connection between neurotrophic factors and neuronal plasticity with mood disorders and antidepressant action has recently been further strengthened by converging evidence from a variety of more recent data reviewed here.

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Several lines of evidence link BDNF (brain-derived neurotrophic factor) and its receptor TrkB (neurotrophic receptor tyrosine kinase 2) with mood disorders and antidepressant effects [reviewed in (1–4)]. Duman's group (5,6) was the first to discover a connection between BDNF, depression, and antidepressant action. They first showed that BDNF levels are increased by electroconvulsive treatment in rats and that antidepressants also increase BDNF expression in the hippocampus and cortex (5), a finding that has subsequently been confirmed by several groups (1). The work of the Duman laboratory has been a major contributor to the field ever since (1,7). We review here the role of BDNF signaling in mood disorders and the antidepressant effects. While there is a large amount of convergent evidence suggesting reduced BDNF signaling in mood disorders, not all evidence supports this conclusion, and a reduction in BDNF signaling is not specific to mood disorders. On the other hand, the evidence for the critical role for BDNF signaling in the antidepressant responses is convincing and has recently been further strengthened.

BDNF is a critical mediator of activity-dependent neuronal plasticity in the brain (8,9). It has a major impact on neuronal morphology and physiology, increasing neurite sprouting and synapse stabilization and promoting long-term potentiation (9). Synthesis and release of BDNF are regulated by neuronal activity, which is consistent with the role of BDNF as a major mediator of activity-dependent neuronal plasticity. Recent data suggest that BDNF may also be linked to spontaneous, activity-independent transmission. The blockade of postsynaptic NMDA receptors involved in spontaneous transmission can rapidly increase BDNF protein translation, which can produce an increase in synaptic potentiation that resembles homeostatic scaling. This connection between spontaneous transmission and BDNF that triggers a novel form of plasticity has been linked to the rapid antidepressant action of ketamine (10–13).

BDNF-TrkB SIGNALING IN MOOD DISORDERS

BDNF signaling has been implicated in the pathophysiology of mood disorders in humans. Levels of BDNF messenger RNA (mRNA) and protein have been found to be reduced in postmortem samples taken from brains of depressed patients (14), in particular in the hippocampus (15–17) and amygdala (18). BDNF levels have also consistently been found to be reduced in brain samples of people who died as a result of suicide (19–24). Conversely, antidepressant treatment increases BDNF expression in brains of depressed patients (21). However, the numbers of examined cases are generally low, and reduction in BDNF is not specific to mood disorders, as similar reductions have been observed in other neuropsychiatric disorders, such as schizophrenia and dementia (25,26).

DNA methylation of BDNF gene promoters has been shown to be increased in peripheral blood mononuclear cells of depressed patients (27–29), which is consistent with a reduction in BDNF expression. A similar increase in BDNF promoter methylation has also been observed in brain samples from people who died by suicide (30), suggesting dysregulation of BDNF expression. This suggests that the findings in blood cells may perhaps be extrapolated to neuronal tissue, although this requires further investigation.

In addition to BDNF, levels of TrkB and TrkB mRNA have also been found to be decreased in postmortem samples of

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depressed patients (19,31), and genetic variants in the TrkB gene *NTRK2* are associated with suicide attempts (32). Furthermore, the activated, phosphorylated forms of TrkB have been found to be decreased in brain samples from depressed patients (20).

Genetic Association Between BDNF and Depression

Valine is the predominant amino acid at position 66 of BNDF, but 25% to 50% of individuals in different populations have methionine at this position (Val66Met) (33,34). Mechanistically, this polymorphism influences intracellular BDNF trafficking and activity-dependent BDNF release (33,35), and the Met allele has been shown to impair dendritic transportation of BDNF mRNA (36). As the activity-dependent synaptic release of BDNF is critical for its action on certain types of neuronal plasticity, Met66BDNF might impede plasticity. Early studies suggested that the Met allele might be a risk factor for a number of neuropsychiatric disorders (37). However, subsequent larger studies failed to replicate these effects, and the latest meta-analyses do not support the role of BDNF Val66-Met polymorphism in mood disorders (38,39) [reviewed in (4)], with perhaps an exception of increased risk of depression in male Met-carriers (40). In addition to Val66Met, several other single nucleotide polymorphisms have been detected in the human *BDNF* gene, and initial studies associated some of them with depression (4,41–43). However, also here, meta-analyses have not supported the initial findings (4,38).

There is evidence that Val66Met polymorphism might modulate the effects of early life adversity (44–47) or chronic stress on depression in adulthood (48). Indeed, a recent meta-analysis that examined the interaction between the Val66Met polymorphism and stressful life events or childhood adversity in more than 20,000 participants in 31 independent studies concluded that Met carriers have significantly higher risk of developing depression when exposed to stress either during childhood or in adulthood (49).

Activity-dependent BDNF release is suggested to be important for the antidepressant response. Consistently, behavioral as well as plasticity-related responses to antidepressants were lost in a mouse model of Val66Met polymorphism (35,50). Furthermore, increased spine formation in responses to ketamine and its metabolite (2*R*,6*R*)-hydroxynorketamine were lost in these mice (51,52). However, similar loss has not been observed in human studies, and the Met allele, if anything, improves the response to antidepressants (53–56), and patients heterozygous for Val66Met appear to show a better response to antidepressants than patients homozygous for either the Val or the Met allele (57).

Serum BDNF and Mood Disorders

Levels of BDNF are high in human serum; however, levels in plasma and cerebrospinal fluid are orders of magnitude lower (58–61). More than 90% of BDNF found in blood is contained in platelets (58,59,62–64). Although it has been suggested that circulating BDNF could be derived from brain (65), it is by now clear that serum BDNF is derived from blood platelets that release it on platelet activation (58,59,62). Within platelets, BDNF is contained within the alpha granules and in the cytoplasm (60,66), and on stimulation, less than half of BDNF within platelets is released, probably representing the alpha-granule pool. Platelet BDNF is derived from megakaryocytes that transport BDNF into newly formed platelets (67,68). Whether platelets also take up BDNF from plasma is unclear; platelets do not express BDNF receptors, but uptake of labeled BDNF into platelets has been reported (64). Interestingly, mouse megakaryocytes do not synthesize BDNF, and, consequently, BDNF levels in mouse serum and plasma are very low, below detection limit (68), which speaks against uptake from plasma as a significant source of platelet BDNF.

Several studies have observed that serum or plasma BDNF levels are abnormally low in depressed patients (69) and that the levels increase back to baseline after successful treatment with antidepressants (70–79) or electroconvulsive treatment (80,81), but not after repetitive transcranial magnetic stimulation or vagus nerve stimulation (82). Although a recent meta-analysis found reduced effect sizes in more recent studies, reduction in serum BDNF remained highly significant in untreated depressed patients compared with successfully treated patients or healthy individuals (83). Unfortunately, high interindividual and intraindividual variation in serum BDNF levels (84) prevents its use as a diagnostic marker for depression. However, as serum levels of proBDNF are not reduced in depressed patients while those of mature BDNF are (85), a ratio between mature BDNF and proBDNF has been suggested as a biomarker for bipolar disorder (86) and for discriminating between bipolar and major depressive disorder with reasonable sensitivity (87). Notably, a decrease in serum BDNF levels is not specific to depression: serum BDNF levels have been reported to be decreased also in schizophrenia (88–90) and in autism (91,92).

While serum BDNF levels were low in patients with depression and schizophrenia, whole-blood BDNF levels were not different between patients and control subjects (72,88). Therefore, the difference between patients and control subjects is not in the amount of BDNF in platelets, but in the ability of platelets to release it. Authors have proposed that instead of serum BDNF levels, a ratio between BDNF in serum and whole blood, which represents BDNF release from platelets, should be reported (72). Interestingly, serotonin is concentrated into platelets through the serotonin transporter, the target of serotonin-selective antidepressants (selective serotonin reuptake inhibitors), and, as is the case for BDNF, serotonin release is reduced in depressed patients (60,93), suggesting a link between BDNF and serotonin release. Molecular pathways that regulate vesicular release in the brain and in platelets share many components (94). It is therefore possible that reduced release from platelets could reflect compromised BDNF release also in the brain.

Susceptibility to depression can be influenced by genetic, epigenetic, and environmental risk factors. Stressful life events may contribute to an individual's developing depression, while some individuals display resilience. In preclinical models, stress paradigms are often used to model depression-related behavior. However, the type and duration of stress can produce a range of effects on the hypothalamic-pituitary-adrenal axis, metabolism, and epigenetic and genetic effects as well as behavior. Stress has been shown to decrease BDNF expression in many brain regions, but increased expression

has also been observed in certain brain regions depending on the type and duration of stress. Given the complexity of the relationship between stress and neurotrophins, the reader is referred to articles in this special issue focusing on stress and its role in the transcriptome by Girgenti *et al.* (95) and the neurobiology of stress by Ploski and Vaidya (96).

Taken together, while several studies indicate abnormal expression and function of BDNF in depressed patients and a return to normal on recovery, many other studies, including genetic association studies, have failed to show a consistent relationship between BDNF and mood disorders. Therefore, a causal role for BDNF in depression remains equivocal.

BDNF EXPRESSION AND TrkB SIGNALING ARE REQUIRED FOR ANTIDEPRESSANT DRUG ACTION

Given the evidence that BDNF signaling may be reduced in depression, the finding that antidepressant drugs increase BDNF levels has generated interest. Duman's laboratory was the first to find that electroconvulsive treatment as well as tricyclic and selective serotonin reuptake inhibitor antidepressants increase BDNF expression in rodent brain (5,6), which has been confirmed in numerous studies [reviewed in (1,3,97)]. Antidepressant-induced increase in BDNF levels has also been observed in human postmortem brain samples (21) as well as in serum of depressed patients (see above).

BDNF levels are increased quickly after electroconvulsive treatment, but only after several days of continuous antidepressant treatment (1,5). However, antidepressants activated TrkB autophosphorylation and downstream signaling within an hour after treatment in mice (98,99), indicating that antidepressants may initially promote BDNF release and TrkB signaling and that the increase in BDNF expression takes place only later, but it has been unclear how antidepressants activate TrkB. A recent study demonstrated that antidepressants belonging to different classes, such as fluoxetine, imipramine, and ketamine, directly bind to TrkB (100). Dimerized TrkB transmembrane domains cross each other in the transmembrane domain and create a pocket for antidepressants. Antidepressant binding stabilizes TrkB in synaptic membranes and promotes BDNF-mediated TrkB signaling (Figure 1) (100). The affinity of antidepressants to TrkB is much lower than their affinity to the serotonin transporter, but antidepressants accumulate in brain, and concentrations needed for TrkB binding are achieved in human brain after several weeks of treatment (101), which might contribute to the slow action onset of typical antidepressants. These findings suggest a provocative hypothesis that the primary site of action of antidepressants is direct binding to TrkB instead of monoamine transporters and other classical targets.

BDNF signaling through TrkB is required for the behavioral effects of antidepressants (98,102), and several studies have investigated the brain regions and cell types where BDNF-TrkB signaling mediates antidepressant effects. Adachi *et al.* (103) found that deletion of BDNF from the dentate gyrus cells of mice inhibits the effects of antidepressants in behavioral paradigms. Similarly, deletion of TrkB from the progenitor cells of dentate granule neurons, but not from the mature granule neurons, prevents the effects of antidepressants on the forced swim test as well as on induced neurogenesis (104), suggesting that TrkB in the progenitor cells is the target of BDNF released from the dentate granule neurons. Cortical interneurons have been implicated as the target for both typical (105) and fast-acting (106–108) antidepressants, especially parvalbumin-containing interneurons and perineuronal nets that encase them (109–115), but somatostatin-containing neurons have also been implicated in the antidepressant action (106,116). Finally, BDNF infused into the midbrain produced an antidepressant effect in rats (117), suggesting that this effect may be mediated through monoaminergic neurons. In a recent study using an adeno-associated virus approach to inject Cre recombinase into the dorsal raphe, either BDNF or TrkB was deleted in adult mice. The deletion of BDNF did not impact antidepressant responses in behavioral paradigms, but the loss of TrkB resulted in an attenuated response to antidepressants (118), revealing a critical role for TrkB in the dorsal

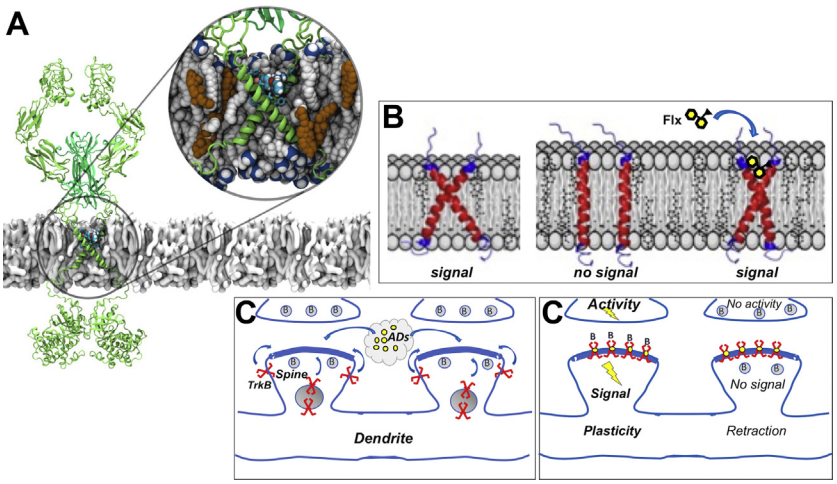

Figure 1. Direct binding of antidepressants to TrkB (neurotrophic receptor tyrosine kinase 2). **(A)** Two TrkB receptors cross each other within the transmembrane region, creating a binding site for fluoxetine (inset, blue) at the outer opening of the crossed dimer of TrkB. Image courtesy of M. Girych and G. Enkavi. **(B)** The configuration of TrkB dimers is dependent on membrane thickness, which is regulated by cholesterol concentration. (Left panel) In moderate cholesterol concentrations, the configuration is favorable for signaling. (Right panel) At high cholesterol concentrations, such as in synaptic membranes, the crossed dimers assume a more parallel orientation, which is not compatible with signaling, and the residence time of TrkB in these membranes is short. Binding of fluoxetine (Flx) acts as a wedge that maintains the crossed transmembrane domain orientation that is compatible with signaling, which increases a probability of BDNF (brain-derived neurotrophic factor) binding and signaling. **(C)** Allosteric activation of BDNF signaling by antidepressants. (Left panel) Antidepressants (ADs) promote TrkB translocation to and retention at the plasma membrane. (Right panel) BDNF (B) released from presynaptic and postsynaptic sites of active synapses efficiently signal through TrkB at the cell surface, but TrkB receptors in inactive synapses remain silent because no BDNF is released.

raphe in conventional antidepressant action and suggesting a noncell autonomous role for BDNF in the dorsal raphe in conventional antidepressant action. However, direct deletion of TrkB in serotonergic neurons did not prevent the antidepressant-like effects of fluoxetine (119), suggesting that the target for BDNF may be nonserotonergic neurons in the raphe nuclei. Taken together, these data suggest that BDNF-TrkB signaling through several different neuronal systems can mediate different effects of antidepressant drugs.

Typical Antidepressants Increase Other Growth Factors

While numerous studies have linked BDNF to antidepressant action, VEGF (vascular endothelial growth factor) and its tyrosine kinase receptor, Flk1 (fetal liver kinase 1), have also been suggested to play a critical role, although with more limited findings. VEGF is a growth factor that is important in hippocampal neurogenesis (120), although it is unclear if this is how it contributes to antidepressant action. Similar to BDNF, VEGF expression is increased by electroconvulsive and conventional antidepressant treatment (121). Conversely, pharmacological approaches that block VEGF-Flk1 signaling block the behavioral effects of conventional antidepressants, suggesting a crucial role in antidepressant-like action (121–123). Curiously, the antidepressant-like effects of BDNF and VEGF appear mutually dependent on each other (124). While additional studies are necessary to delineate the mechanistic role of VEGF in antidepressant drug action, nevertheless these data further strengthen the importance of neurotrophic factors in antidepressant action.

Rapid Antidepressants Require BDNF

The rather unexpected finding that ketamine, an NMDA receptor antagonist, produces rapid antidepressant action provides an opportunity to delineate intracellular signaling involved in the behavioral effects. Three main hypotheses have been put forth to explain the mechanism of action of ketamine. The first is often referred to as the disinhibition hypothesis. In this model, ketamine is postulated to block NMDA receptors on inhibitory neurons, which increases extracellular glutamate levels and activates AMPA receptors. This in turn causes the release of BDNF, which triggers downstream effects, such as activation of mTOR (mechanistic target of rapamycin), and ultimately synaptogenesis (106,125–128). In support of this hypothesis, it was shown that blocking mTOR with an infusion of rapamycin, an mTOR inhibitor, in the cortex blocked ketamine's antidepressant-like effects and synaptogenesis (129). These studies suggested that mTOR was required for rapid antidepressant action and that compounds that promote mTOR activation may have therapeutic potential as rapid antidepressants. However, a separate group demonstrated that administration of rapamycin via intraperitoneal injection, to better mimic potential clinical approaches, did not prevent ketamine's rapid antidepressant action (10). More recently, a small clinical study administered rapamycin intravenously to patients and found that it did not block ketamine's rapid antidepressant action but rather may augment the long-term effects (130). These clinical data call into question the necessity of mTOR in the rapid antidepressant action of ketamine.

The second hypothesis focuses on how ketamine works through intracellular signaling to produce the antidepressant effects and identifies a novel form of synaptic plasticity strongly correlated with the behavioral action. Ketamine, via blockade of NMDA receptors, blocks calcium entry through these receptors, which results in the inhibition of the calcium/calmodulin-dependent kinase eEF2K (eukaryotic elongation factor 2 kinase), dephosphorylation of its sole target, eEF2 (eukaryotic elongation factor 2), and a resulting rapid increase in protein synthesis of BDNF as well as other synaptic proteins (10). This study showed that loss of BDNF or TrkB in broad forebrain regions blocked ketamine's antidepressant action, demonstrating a requirement for BDNF-TrkB signaling in the rapid antidepressant-like effects in animal models. Anisomycin, a protein synthesis inhibitor, was also shown to block ketamine's rapid antidepressant action, thus demonstrating a key role for protein translation that was due to eEF2K in the fast-acting behavioral effects. Ketamine, in an eEF2K-dependent manner, was also shown to trigger the insertion of AMPA receptors that resulted in an expected effect on synaptic plasticity, namely, synaptic potentiation at hippocampal Schaffer collateral inputs to CA1 synapses (10,11). The notion that an NMDA receptor antagonist produces an augmentation of synaptic responses at CA3-CA1 synapses is at first perplexing, as data over the past 2 decades have shown that brief applications of NMDA receptor antagonists on hippocampal slices results in no detectable synaptic effects. However, when ketamine is perfused for 30 minutes on a hippocampal slice, similar to the time of the ketamine infusion, and then washed out, a robust augmentation of field excitatory postsynaptic potentials is observed at CA3-CA1 synapses. This augmentation is observed by blocking NMDA receptors, suggesting that it is due to a form of homeostatic, non-Hebbian type of plasticity (13). This form of homeostatic synaptic plasticity is closely associated with ketamine's antidepressant effects in that deletion of eEF2K inhibits ketamine's antidepressant-like action and the augmented synaptic potentiation. Deletion of BDNF also blocks ketamine's antidepressant-like effects as well as the synaptic potentiation. This body of work has built a crucial link between synaptic transmission and antidepressant action. The identification of the engagement of homeostatic plasticity by ketamine provides an avenue to an understanding of how ketamine may compensate circuit dysfunction or activate dormant mechanisms of patients with depression that are not evoked under normal physiological circumstances.

A third hypothesis for how ketamine exerts antidepressant effects suggests direct binding to the TrkB receptor. As described above, typical antidepressants were found to directly bind to a site formed by two transmembrane domains of TrkB within the plasma membrane, which promotes the synaptic localization TrkB, thereby increasing the probability of BDNF binding to TrkB and activating it (Figure 1) (100). Unexpectedly, ketamine and esketamine displace fluoxetine from this binding site with an affinity that is in the same range as the affinity of ketamine to NMDA receptors, suggesting that they, too, bind to this same site on TrkB. This study also reported that the Y433F mutation of the TrkB receptor blocks the binding and antidepressant-like effects of typical antidepressants as well as those of ketamine (100). This TrkB receptor

mutation also blocked ketamine's effects on surface localization of AMPA receptors, indicating that increased AMPA signaling is a downstream effect of TrkB activation (100). Moreover, (2*R*,6*R*)-hydroxynorketamine, the ketamine metabolite reported to be NMDA receptor–independent (131) [but see (132)], directly binds to TrkB with an affinity comparable to that of ketamine, but clearly higher than its affinity to NMDA receptor, and this binding is lost in the Y433F TrkB mutants. Collectively, these data suggest that direct binding to TrkB may be a common mechanism of action for typical as well as rapid-acting antidepressants (100).

It is intriguing that these three main hypotheses on the rapid antidepressant effects of ketamine all involve a critical role for BDNF and/or TrkB signaling. In support of this premise, deletion of BDNF or TrkB in broad forebrain regions of mice blocks ketamine's antidepressant-like behavioral effects as well as the hippocampal synaptic potentiation that has been suggested as a key correlate of rapid antidepressant action (11,133). Other studies have also reported a key role for BDNF in the antidepressant action of ketamine (134,135). In addition, BDNF signaling has been implicated in the effects of other anesthetic agents with putative antidepressant effects (136,137). Moreover, knock-in mice expressing the BDNF Val66Met polymorphism, which have impaired BDNF mRNA trafficking to dendrites, do not show antidepressant-like responses to ketamine (51). However, studies examining ketamine action in patients with a Met allele compared with individuals with the Val/Val allele have yielded conflicting data. An initial study examined ketamine response in depressed patients and reported an increase in the likelihood of response in individuals with the BDNF Val/Val allele compared with patients with a Met allele (138). However, a larger study did not find any difference in ketamine response between depressed patients with the Val/Val allele and patients the Met allele (139). While more research is necessary to elucidate the role of BDNF signaling in the antidepressant response of patients, it will also be important to identify the full scope of genetic determinants that influence antidepressant responsiveness.

We have focused on the three main hypotheses of ketamine action; however, others have been proposed that were not discussed owing to space limitations. While there is still much work to be done to understand ketamine's mechanism of action, the current models provide testable hypotheses that will hopefully contribute to the development of faster-acting antidepressants without the associated side effects. One key consideration when comparing studies is the dose of ketamine administered, which can often vary widely and provide conflicting data. Preclinical work has shown that a low dose of ketamine produces an antidepressant-like response, while increasing doses curtail antidepressant responses, intracellular signaling, and the synaptic potentiation in the hippocampus (140). Another key issue to consider is that ketamine's antidepressant effects are not mimicked by the closely related NMDA receptor antagonist memantine (141–143). The second model described above can explain why ketamine exerts antidepressant effects while memantine cannot (12). Therefore, alternative proposals should also include memantine as a negative control. Work over the next several years will hopefully provide critical insight into rapid antidepressant action as well as whether these effects can be extended.

CONCLUSIONS

Twenty-five years have passed since Duman's group (1,5,6) proposed the connection between neurotrophic factors, mood disorders, and the antidepressant effect. Since then, converging data from a variety of preclinical and clinical studies implicate impaired BDNF signaling through TrkB in the pathophysiology of mood disorders, although especially genetic evidence has recently not supported this notion, and deficiencies in BDNF signaling are not specific to mood disorders. However, there is solid evidence to indicate that increased expression and signaling of BDNF is critical in the mechanisms of both typical and rapid-acting antidepressant drugs. As BDNF is a critical mediator of various types of synaptic plasticity, these data suggest that restricted plasticity may underlie depression and that promotion of plasticity enhances mood recovery. As plastic networks need experience-dependent activity to guide their selection (13,144,145), these data suggest a new paradigm for the treatment of mood disorders, where pharmacological and psychological approaches are closely intertwined, emphasizing the need for the active participation of the patient in successful antidepressant drug treatment.

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REFERENCES

1. Duman RS, Monteggia LM (2006): A neurotrophic model for stress-related mood disorders. Biol Psychiatry 59:1116–1127.
2. Bjorkholm C, Monteggia LM (2016): BDNF—a key transducer of antidepressant effects. Neuropharmacology 102:72–79.
3. Castrén E, Kojima M (2017): Brain-derived neurotrophic factor in mood disorders and antidepressant treatments. Neurobiol Dis 97(Pt B):119–126.
4. Hing B, Sathyaputri L, Potash JB (2018): A comprehensive review of genetic and epigenetic mechanisms that regulate BDNF expression and function with relevance to major depressive disorder. Am J Med Genet B Neuropsychiatr Genet 177:143–167.
5. Nibuya M, Morinobu S, Duman RS (1995): Regulation of BDNF and trkB mRNA in rat brain by chronic electroconvulsive seizure and antidepressant drug treatments. J Neurosci 15:7539–7547.
6. Duman RS, Heninger GR, Nestler EJ (1997): A molecular and cellular theory of depression. Arch Gen Psychiatry 54:597–606.
7. Duman RS, Deyama S, Fogaca MV (2021): Role of BDNF in the pathophysiology and treatment of depression: Activity dependent

effects distinguish rapid acting antidepressants. Eur J Neurosci 53:126–139.
8. Park H, Poo MM (2013): Neurotrophin regulation of neural circuit development and function. Nat Rev Neurosci 14:7–23.
9. Zagrebelsky M, Korte M (2014): Form follows function: BDNF and its involvement in sculpting the function and structure of synapses. Neuropharmacology 76(Pt C):628–638.
10. Autry AE, Adachi M, Nosyreva E, Na ES, Los MF, Cheng PF, *et al.* (2011): NMDA receptor blockade at rest triggers rapid behavioural antidepressant responses. Nature 475:91–95.
11. Nosyreva E, Szabla K, Autry AE, Ryazanov AG, Monteggia LM, Kavalali ET (2013): Acute suppression of spontaneous neurotransmission drives synaptic potentiation. J Neurosci 33:6990–7002.
12. Gideons ES, Kavalali ET, Monteggia LM (2014): Mechanisms underlying differential effectiveness of memantine and ketamine in rapid antidepressant responses. Proc Natl Acad Sci U S A 111:8649–8654.
13. Kavalali ET, Monteggia LM (2020): Targeting homeostatic synaptic plasticity for treatment of mood disorders. Neuron 106:715–726.
14. Dwivedi Y (2013): Involvement of brain-derived neurotrophic factor in late-life depression. Am J Geriatr Psychiatry 21:433–449.
15. Dunham JS, Deakin JF, Miyajima F, Payton A, Toro CT (2009): Expression of hippocampal brain-derived neurotrophic factor and its receptors in Stanley consortium brains. J Psychiatr Res 43:1175–1184.
16. Ray MT, Weickert CS, Wyatt E, Webster MJ (2011): Decreased BDNF, trkB-TK+ and GAD67 mRNA expression in the hippocampus of individuals with schizophrenia and mood disorders. J Psychiatry Neurosci 36:195–203.
17. Ray MT, Shannon Weickert C, Webster MJ (2014): Decreased BDNF and TrkB mRNA expression in multiple cortical areas of patients with schizophrenia and mood disorders. Transl Psychiatry 4:e389.
18. Guilloux JP, Douillard-Guilloux G, Kota R, Wang X, Gardier AM, Martinowich K, *et al.* (2012): Molecular evidence for BDNF- and GABA-related dysfunctions in the amygdala of female subjects with major depression. Mol Psychiatry 17:1130–1142.
19. Dwivedi Y, Rizavi HS, Conley RR, Roberts RC, Tamminga CA, Pandey GN (2003): Altered gene expression of brain-derived neurotrophic factor and receptor tyrosine kinase B in postmortem brain of suicide subjects. Arch Gen Psychiatry 60:804–815.
20. Dwivedi Y, Rizavi HS, Zhang H, Mondal AC, Roberts RC, Conley RR, *et al.* (2009): Neurotrophin receptor activation and expression in human postmortem brain: Effect of suicide. Biol Psychiatry 65:319–328.
21. Chen B, Dowlatshahi D, MacQueen GM, Wang JF, Young LT (2001): Increased hippocampal BDNF immunoreactivity in subjects treated with antidepressant medication. Biol Psychiatry 50:260–265.
22. Youssef MM, Underwood MD, Huang YY, Hsiung SC, Liu Y, Simpson NR, *et al.* (2018): Association of BDNF Val66Met polymorphism and brain BDNF levels with major depression and suicide. Int J Neuropsychopharmacol 21:528–538.
23. Pandey GN, Ren X, Rizavi HS, Conley RR, Roberts RC, Dwivedi Y (2008): Brain-derived neurotrophic factor and tyrosine kinase B receptor signalling in post-mortem brain of teenage suicide victims. Int J Neuropsychopharmacol 11:1047–1061.
24. Dwivedi Y (2009): Brain-derived neurotrophic factor: Role in depression and suicide. Neuropsychiatr Dis Treat 5:433–449.
25. Carlino D, De Vanna M, Tongiorgi E (2013): Is altered BDNF biosynthesis a general feature in patients with cognitive dysfunctions. Neuroscientist 19:345–353.
26. Michalski B, Corrada MM, Kawas CH, Fahnestock M (2015): Brain-derived neurotrophic factor and TrkB expression in the "oldest-old," the 90+ Study: Correlation with cognitive status and levels of soluble amyloid-beta. Neurobiol Aging 36:3130–3139.
27. Roy B, Shelton RC, Dwivedi Y (2017): DNA methylation and expression of stress related genes in PBMC of MDD patients with and without serious suicidal ideation. J Psychiatr Res 89:115–124.
28. Kim JM, Kang HJ, Bae KY, Kim SW, Shin IS, Kim HR, *et al.* (2014): Association of BDNF promoter methylation and genotype with suicidal ideation in elderly Koreans. Am J Geriatr Psychiatry 22:989–996.
29. Schroter K, Brum M, Brunkhorst-Kanaan N, Tole F, Ziegler C, Domschke K, *et al.* (2020): Longitudinal multi-level biomarker analysis of BDNF in major depression and bipolar disorder. Eur Arch Psychiatry Clin Neurosci 270:169–181.
30. Keller S, Sarchiapone M, Zarrilli F, Videtic A, Ferraro A, Carli V, *et al.* (2010): Increased BDNF promoter methylation in the Wernicke area of suicide subjects. Arch Gen Psychiatry 67:258–267.
31. Tripp A, Oh H, Guilloux JP, Martinowich K, Lewis DA, Sibille E (2012): Brain-derived neurotrophic factor signaling and subgenual anterior cingulate cortex dysfunction in major depressive disorder. Am J Psychiatry 169:1194–1202.
32. Kohli MA, Salyakina D, Pfennig A, Lucae S, Horstmann S, Menke A, *et al.* (2010): Association of genetic variants in the neurotrophic receptor-encoding gene NTRK2 and a lifetime history of suicide attempts in depressed patients. Arch Gen Psychiatry 67:348–359.
33. Egan MF, Kojima M, Callicott JH, Goldberg TE, Kolachana BS, Bertolino A, *et al.* (2003): The BDNF val66met polymorphism affects activity-dependent secretion of BDNF and human memory and hippocampal function. Cell 112:257–269.
34. Shimizu E, Hashimoto K, Iyo M (2004): Ethnic difference of the BDNF 196G/A (val66met) polymorphism frequencies: The possibility to explain ethnic mental traits. Am J Med Genet B Neuropsychiatr Genet 126B:122–123.
35. Chen ZY, Jing D, Bath KG, Ieraci A, Khan T, Siao CJ, *et al.* (2006): Genetic variant BDNF (Val66Met) polymorphism alters anxiety-related behavior. Science 314:140–143.
36. Baj G, Carlino D, Gardossi L, Tongiorgi E (2013): Toward a unified biological hypothesis for the BDNF Val66Met-associated memory deficits in humans: A model of impaired dendritic mRNA trafficking. Front Neurosci 7:188.
37. Bath KG, Lee FS (2006): Variant BDNF (Val66Met) impact on brain structure and function. Cogn Affect Behav Neurosci 6:79–85.
38. Gyekis JP, Yu W, Dong S, Wang H, Qian J, Kota P, *et al.* (2013): No association of genetic variants in BDNF with major depression: A meta- and gene-based analysis. Am J Med Genet B Neuropsychiatr Genet 162B:61–70.
39. Li M, Chang H, Xiao X (2016): BDNF Val66Met polymorphism and bipolar disorder in European populations: A risk association in case-control, family-based and GWAS studies. Neurosci Biobehav Rev 68:218–233.
40. Verhagen M, van der Meij A, van Deurzen PA, Janzing JG, Arias-Vasquez A, Buitelaar JK, *et al.* (2010): Meta-analysis of the BDNF Val66Met polymorphism in major depressive disorder: Effects of gender and ethnicity. Mol Psychiatry 15:260–271.
41. Licinio J, Dong C, Wong ML (2009): Novel sequence variations in the brain-derived neurotrophic factor gene and association with major depression and antidepressant treatment response. Arch Gen Psychiatry 66:488–497.
42. Hing B, Davidson S, Lear M, Breen G, Quinn J, McGuffin P, *et al.* (2012): A polymorphism associated with depressive disorders differentially regulates brain derived neurotrophic factor promoter IV activity. Biol Psychiatry 71:618–626.
43. Juhasz G, Dunham JS, McKie S, Thomas E, Downey D, Chase D, *et al.* (2011): The CREB1-BDNF-NTRK2 pathway in depression: Multiple gene-cognition-environment interactions. Biol Psychiatry 69:762–771.
44. Kaufman J, Yang BZ, Douglas-Palumberi H, Grasso D, Lipschitz D, Houshyar S, *et al.* (2006): Brain-derived neurotrophic factor-5-HTTLPR gene interactions and environmental modifiers of depression in children. Biol Psychiatry 59:673–680.
45. Aguilera M, Arias B, Wichers M, Barrantes-Vidal N, Moya J, Villa H, *et al.* (2009): Early adversity and 5-HTT/BDNF genes: New evidence of gene-environment interactions on depressive symptoms in a general population. Psychol Med 39:1425–1432.
46. Frodl T, Skokauskas N, Frey EM, Morris D, M. Gill M, Carballedo A (2014): BDNF Val66Met genotype interacts with childhood adversity and influences the formation of hippocampal subfields. Hum Brain Mapp 35:5776–5783.

47. Carballedo A, Morris D, Zill P, Fahey C, Reinhold E, Meisenzahl E, *et al.* (2013): Brain-derived neurotrophic factor Val66Met polymorphism and early life adversity affect hippocampal volume. Am J Med Genet B Neuropsychiatr Genet 162B:183–190.
48. Hosang GM, Shiles C, Tansey KE, McGuffin P, Uher R (2014): Interaction between stress and the BDNF Val66Met polymorphism in depression: A systematic review and meta-analysis. BMC Med 12:7.
49. Zhao M, Chen L, Yang J, Han D, Fang D, Qiu X, *et al.* (2018): BDNF Val66Met polymorphism, life stress and depression: A meta-analysis of gene-environment interaction. J Affect Disord 227:226–235.
50. Bath KG, Jing DQ, Dincheva I, Neeb CC, Pattwell SS, Chao MV, *et al.* (2012): BDNF Val66Met impairs fluoxetine-induced enhancement of adult hippocampus plasticity. Neuropsychopharmacology 37:1297–1304.
51. Liu RJ, Lee FS, Li XY, Bambico F, Duman RS, Aghajanian GK (2012): Brain-derived neurotrophic factor Val66Met allele impairs basal and ketamine-stimulated synaptogenesis in prefrontal cortex. Biol Psychiatry 71:996–1005.
52. Fukumoto K, Fogaca MV, Liu RJ, Duman C, Kato T, Li XY, *et al.* (2019): Activity-dependent brain-derived neurotrophic factor signaling is required for the antidepressant actions of (2R,6R)-hydroxynorketamine. Proc Natl Acad Sci U S A 116:297–302.
53. Yan T, Wang L, Kuang W, Xu J, Li S, Chen J, *et al.* (2014): Brain-derived neurotrophic factor Val66Met polymorphism association with antidepressant efficacy: A systematic review and meta-analysis. Asia Pac Psychiatry 6:241–251.
54. Choi MJ, Kang RH, Lim SW, Oh KS, Lee MS (2006): Brain-derived neurotrophic factor gene polymorphism (Val66Met) and citalopram response in major depressive disorder. Brain Res 1118:176–182.
55. Colle R, Deflesselle E, Martin S, David DJ, Hardy P, Taranu A, *et al.* (2015): BDNF/TRKB/P75NTR polymorphisms and their consequences on antidepressant efficacy in depressed patients. Pharmacogenomics 16:997–1013.
56. Domschke K, Lawford B, Laje G, Berger K, Young R, Morris P, *et al.* (2010): Brain-derived neurotrophic factor (BDNF) gene: No major impact on antidepressant treatment response. Int J Neuropsychopharmacol 13:93–101.
57. Niitsu T, Fabbri C, Bentini F, Serretti A (2013): Pharmacogenetics in major depression: A comprehensive meta-analysis. Prog Neuropsychopharmacol Biol Psychiatry 45:183–194.
58. Yamamoto H, Gurney ME (1990): Human platelets contain brain-derived neurotrophic factor. J Neurosci 10:3469–3478.
59. Radka SF, Holst PA, Fritsche M, Altar CA (1996): Presence of brain-derived neurotrophic factor in brain and human and rat but not mouse serum detected by a sensitive and specific immunoassay. Brain Res 709:122–301.
60. Serra-Millas M (2016): Are the changes in the peripheral brain-derived neurotrophic factor levels due to platelet activation. World J Psychiatry 6:84–101.
61. Korhonen L, Riikonen R, Nawa H, Lindholm D (1998): Brain derived neurotrophic factor is increased in cerebrospinal fluid of children suffering from asphyxia. Neurosci Lett 240:151–154.
62. Naegelin Y, Dingsdale H, Sauberli K, Schadelin S, Kappos L, Barde YA (2018): Measuring and validating the levels of brain-derived neurotrophic factor in human serum. eNeuro 5.. ENEURO.0419-17.2018.
63. Lommatzsch M, Zingler D, Schuhbaeck K, Schloetcke K, Zingler C, Schuff-Werner P, *et al.* (2005): The impact of age, weight and gender on BDNF levels in human platelets and plasma. Neurobiol Aging 26:115–123.
64. Fujimura H, Altar CA, Chen R, Nakamura T, Nakahashi T, Kambayashi J, *et al.* (2002): Brain-derived neurotrophic factor is stored in human platelets and released by agonist stimulation. Thromb Haemost 87:728–734.
65. Seifert T, Brassard P, Wissenberg M, Rasmussen P, Nordby P, Stallknecht B, *et al.* (2010): Endurance training enhances BDNF release from the human brain. Am J Physiol Regul Integr Comp Physiol 298:R372–R377.
66. Tamura S, Suzuki H, Hirowatari Y, Hatase M, Nagasawa A, Matsuno K, *et al.* (2011): Release reaction of brain-derived neurotrophic factor (BDNF) through PAR1 activation and its two distinct pools in human platelets. Thromb Res 128:e55–e61.
67. Tamura S, Nagasawa A, Masuda Y, Tsunematsu T, Hayasaka K, Matsuno K, *et al.* (2012): BDNF, produced by a TPO-stimulated megakaryocytic cell line, regulates autocrine proliferation. Biochem Biophys Res Commun 427:542–546.
68. Chacón-Fernández P, Säuberli K, Colzani M, Moreau T, Ghevaert C, Barde YA (2016): Brain-derived neurotrophic factor in megakaryocytes. J Biol Chem 291:9872–9881.
69. Karege F, Perret G, Bondolfi G, Schwald M, Bertschy G, Aubry JM (2002): Decreased serum brain-derived neurotrophic factor levels in major depressed patients. Psychiatry Res 109:143–148.
70. Shimizu E, Hashimoto K, Okamura N, Koike K, Komatsu N, Kumakiri C, *et al.* (2003): Alterations of serum levels of brain-derived neurotrophic factor (BDNF) in depressed patients with or without antidepressants. Biol Psychiatry 54:70–75.
71. Sen S, Duman R, Sanacora G (2008): Serum brain-derived neurotrophic factor, depression, and antidepressant medications: Meta-analyses and implications. Biol Psychiatry 64:527–532.
72. Karege F, Bondolfi G, Gervasoni N, Schwald M, Aubry JM, Bertschy G (2005): Low brain-derived neurotrophic factor (BDNF) levels in serum of depressed patients probably results from lowered platelet BDNF release unrelated to platelet reactivity. Biol Psychiatry 57:1068–1072.
73. Bocchio-Chiavetto L, Bagnardi V, Zanardini R, Molteni R, Nielsen MG, Placentino A, *et al.* (2010): Serum and plasma BDNF levels in major depression: A replication study and meta-analyses. World J Biol Psychiatry 11:763–773.
74. Gonul AS, Akdeniz F, Taneli F, Donat O, Eker C, Vahip S (2005): Effect of treatment on serum brain-derived neurotrophic factor levels in depressed patients. Eur Arch Psychiatry Clin Neurosci 255:381–386.
75. Piccinni A, Marazziti D, Catena M, Domenici L, Del Debbio A, Bianchi C, *et al.* (2008): Plasma and serum brain-derived neurotrophic factor (BDNF) in depressed patients during 1 year of antidepressant treatments. J Affect Disord 105:279–283.
76. Matrisciano F, Bonaccorso S, Ricciardi A, Scaccianoce S, Panaccione I, Wang L, *et al.* (2009): Changes in BDNF serum levels in patients with major depression disorder (MDD) after 6 months treatment with sertraline, escitalopram, or venlafaxine. J Psychiatr Res 43:247–254.
77. Yoshimura R, Mitoma M, Sugita A, Hori H, Okamoto T, Umene W, *et al.* (2007): Effects of paroxetine or milnacipran on serum brain-derived neurotrophic factor in depressed patients. Prog Neuropsychopharmacol Biol Psychiatry 31:1034–1037.
78. Hellweg R, Ziegenhorn A, Heuser I, Deuschle M (2008): Serum concentrations of nerve growth factor and brain-derived neurotrophic factor in depressed patients before and after antidepressant treatment. Pharmacopsychiatry 41:66–71.
79. Molendijk ML, Bus BA, Spinhoven P, Penninx BW, Kenis G, Prickaerts J, *et al.* (2011): Serum levels of brain-derived neurotrophic factor in major depressive disorder: State-trait issues, clinical features and pharmacological treatment. Mol Psychiatry 16:1088–1095.
80. Bocchio-Chiavetto L, Zanardini R, Bortolomasi M, Abate M, Segala M, Giacopuzzi M, *et al.* (2006): Electroconvulsive therapy (ECT) increases serum brain derived neurotrophic factor (BDNF) in drug resistant depressed patients. Eur Neuropsychopharmacol 16:620–624.
81. Rocha RB, Dondossola ER, Grande AJ, Colonetti T, Ceretta LB, Passos IC, *et al.* (2016): Increased BDNF levels after electroconvulsive therapy in patients with major depressive disorder: A meta-analysis study. J Psychiatr Res 83:47–53.
82. Lang UE, Bajbouj M, Gallinat J, Hellweg R (2006): Brain-derived neurotrophic factor serum concentrations in depressive patients during vagus nerve stimulation and repetitive transcranial magnetic stimulation. Psychopharmacology (Berl) 187:56–59.
83. Molendijk ML, Spinhoven P, Polak M, Bus BA, Penninx BW, Elzinga BM (2014): Serum BDNF concentrations as peripheral

manifestations of depression: Evidence from a systematic review and meta-analyses on 179 associations (N=9484). Mol Psychiatry 19:791–800.
84. Polacchini A, Metelli G, Francavilla R, Baj G, Florean M, Mascaretti LG, *et al.* (2015): A method for reproducible measurements of serum BDNF: Comparison of the performance of six commercial assays. Sci Rep 5:17989.
85. Yoshida T, Ishikawa M, Niitsu T, Nakazato M, Watanabe H, Shiraishi T, *et al.* (2012): Decreased serum levels of mature brain-derived neurotrophic factor (BDNF), but not its precursor proBDNF, in patients with major depressive disorder. PLoS One 7:e42676.
86. Sodersten K, Palsson E, Ishima T, Funa K, Landen M, Hashimoto K, *et al.* (2014): Abnormality in serum levels of mature brain-derived neurotrophic factor (BDNF) and its precursor proBDNF in mood-stabilized patients with bipolar disorder: A study of two independent cohorts. J Affect Disord 160:1–9.
87. Zhao G, Zhang C, Chen J, Su Y, Zhou R, Wang F, *et al.* (2017): Ratio of mBDNF to proBDNF for differential diagnosis of major depressive disorder and bipolar depression. Mol Neurobiol 54:5573–5582.
88. Toyooka K, Asama K, Watanabe Y, Muratake T, Takahashi M, Someya T, *et al.* (2002): Decreased levels of brain-derived neurotrophic factor in serum of chronic schizophrenic patients. Psychiatry Res 110:249–257.
89. Fernandes BS, Steiner J, Berk M, Molendijk ML, Gonzalez-Pinto A, Turck CW, *et al.* (2015): Peripheral brain-derived neurotrophic factor in schizophrenia and the role of antipsychotics: Meta-analysis and implications. Mol Psychiatry 20:1108–1119.
90. Kimhy D, Vakhrusheva J, Bartels MN, Armstrong HF, Ballon JS, Khan S, *et al.* (2015): The impact of aerobic exercise on brain-derived neurotrophic factor and neurocognition in individuals with schizophrenia: A single-blind, randomized clinical trial. Schizophr Bull 41:859–868.
91. Hashimoto K, Iwata Y, Nakamura K, Tsujii M, Tsuchiya KJ, Sekine Y, *et al.* (2006): Reduced serum levels of brain-derived neurotrophic factor in adult male patients with autism. Prog Neuropsychopharmacol Biol Psychiatry 30:1529–1531.
92. Katoh-Semba R, Wakako R, Komori T, Shigemi H, Miyazaki N, Ito H, *et al.* (2007): Age-related changes in BDNF protein levels in human serum: Differences between autism cases and normal controls. Int J Dev Neurosci 25:367–372.
93. Tuomisto J, Tukiainen E (1976): Decreased uptake of 5-hydroxytryptamine in blood platelets from depressed patients. Nature 262:596–598.
94. Blair P, Flaumenhaft R (2009): Platelet alpha-granules: Basic biology and clinical correlates. Blood Rev 23:177–189.
95. Girgenti MJ, Pothula S, Newton SS (2021): Stress and its impact on the transcriptome. Biol Psychiatry 90:102–108.
96. Ploski JE, Vaidya VA (2021): The neurocircuitry of posttraumatic stress disorder and major depression: Insights into overlapping and distinct circuit dysfunction—A tribute to Ron Duman. Biol Psychiatry 90:109–117.
97. Autry AE, Monteggia LM (2012): Brain-derived neurotrophic factor and neuropsychiatric disorders. Pharmacol Rev 64:238–258.
98. Saarelainen T, Hendolin P, Lucas G, Koponen E, Sairanen M, MacDonald E, *et al.* (2003): Activation of the TrkB neurotrophin receptor is induced by antidepressant drugs and is required for antidepressant-induced behavioral effects. J Neurosci 23:349–357.
99. Rantamäki T, Hendolin P, Kankaanpaa A, Mijatovic J, Piepponen P, Domenici E, *et al.* (2007): Pharmacologically diverse antidepressants rapidly activate brain-derived neurotrophic factor receptor TrkB and induce phospholipase-C gamma signaling pathways in mouse brain. Neuropsychopharmacology 32:2152–2162.
100. Casarotto PC, Girych M, Fred SM, Kovaleva V, Moliner R, Enkavi G, *et al.* (2021): Antidepressant drugs act by directly binding to TRKB neurotrophin receptors. Cell 184:1299–1313.e19.
101. Karson CN, Newton JE, Livingston R, Jolly JB, Cooper TB, Sprigg J, *et al.* (1993): Human brain fluoxetine concentrations. J Neuropsychiatry Clin Neurosci 5:322–329.
102. Monteggia LM, Barrot M, Powell CM, Berton O, Galanis V, Gemelli T, *et al.* (2004): Essential role of brain-derived neurotrophic factor in adult hippocampal function. Proc Natl Acad Sci U S A 101:10827–10832.
103. Adachi M, Barrot M, Autry AE, Theobald D, Monteggia LM (2008): Selective loss of brain-derived neurotrophic factor in the dentate gyrus attenuates antidepressant efficacy. Biol Psychiatry 63:642–649.
104. Li Y, Luikart BW, Birnbaum S, Chen J, Kwon CH, Kernie SG, *et al.* (2008): TrkB regulates hippocampal neurogenesis and governs sensitivity to antidepressive treatment. Neuron 59:399–412.
105. Guirado R, Perez-Rando M, Sanchez-Matarredona D, Castrén E, Nacher J (2014): Chronic fluoxetine treatment alters the structure, connectivity and plasticity of cortical interneurons. Int J Neuropsychopharmacol 17:1635–1646.
106. Gerhard DM, Pothula S, Liu RJ, Wu M, Li XY, Girgenti MJ, *et al.* (2020): GABA interneurons are the cellular trigger for ketamine's rapid antidepressant actions. J Clin Invest 130:1336–1349.
107. Wohleb ES, Wu M, Gerhard DM, Taylor SR, Picciotto MR, Alreja M, *et al.* (2016): GABA interneurons mediate the rapid antidepressant-like effects of scopolamine. J Clin Invest 126:2482–2494.
108. Yang C, Shirayama Y, Zhang JC, Ren Q, Yao W, Ma M, *et al.* (2015): R-ketamine: A rapid-onset and sustained antidepressant without psychotomimetic side effects. Transl Psychiatry 5:e632.
109. Ohira K, Takeuchi R, Iwanaga T, Miyakawa T (2013): Chronic fluoxetine treatment reduces parvalbumin expression and perineuronal nets in gamma-aminobutyric acidergic interneurons of the frontal cortex in adult mice. Mol Brain 6:43.
110. Sagi Y, Medrihan L, George K, Barney M, McCabe KA, Greengard P (2020): Emergence of 5-HT5A signaling in parvalbumin neurons mediates delayed antidepressant action. Mol Psychiatry 25:1191–1201.
111. Donegan JJ, Lodge DJ (2017): Hippocampal perineuronal nets are required for the sustained antidepressant effect of ketamine. Int J Neuropsychopharmacol 20:354–358.
112. Umemori J, Winkel F, Castren E, Karpova NN (2015): Distinct effects of perinatal exposure to fluoxetine or methylmercury on parvalbumin and perineuronal nets, the markers of critical periods in brain development. Int J Dev Neurosci 44:55–64.
113. Pozzi L, Pollak Dorocic I, Wang X, Carlen M, Meletis K (2014): Mice lacking NMDA receptors in parvalbumin neurons display normal depression-related behavior and response to antidepressant action of NMDAR antagonists. PLoS One 9:e83879.
114. Winkel F, Ryazantseva M, Voigt MB, Didio G, Lilja A, Pou ML, *et al*. (In press): Pharmacological and optical activation of TrkB in Parvalbumin interneurons regulates intrinsic states to orchestrate cortical plasticity. Mol Psychiatry.
115. Lesnikova A, Casarotto PC, Fred SM, Voipio M, Winkel F, Steinzeig A, *et al.* (2021): Chondroitinase and antidepressants promote plasticity by releasing TRKB from dephosphorylating control of PTPσ in parvalbumin neurons. J Neurosci 41:972–980.
116. Carceller H, Perez-Rando M, Castren E, Nacher J, Guirado R (2018): Effects of the antidepressant fluoxetine on the somatostatin interneurons in the basolateral amygdala. Neuroscience 386:205–213.
117. Siuciak JA, Lewis DR, Wiegand SJ, Lindsay RM (1997): Antidepressant-like effect of brain-derived neurotrophic factor (BDNF). Pharmacol Biochem Behav 56:131–137.
118. Adachi M, Autry AE, Mahgoub M, Suzuki K, Monteggia LM (2017): TrkB signaling in dorsal raphe nucleus is essential for antidepressant efficacy and normal aggression behavior. Neuropsychopharmacology 42:886–894.
119. Sahu MP, Pazos-Boubeta Y, Steinzeig A, Kaurinkoski K, Palmisano M, Borowecki O, *et al.* (2021): Depletion of TrkB receptors from adult serotonergic neurons increases brain serotonin levels, enhances energy metabolism and impairs learning and memory. Front Mol Neurosci 14:616178.
120. Cao L, Jiao X, Zuzga DS, Liu Y, Fong DM, Young D, *et al.* (2004): VEGF links hippocampal activity with neurogenesis, learning and memory. Nat Genet 36:827–835.

121. Greene J, Banasr M, Lee B, Warner-Schmidt J, Duman RS (2009): Vascular endothelial growth factor signaling is required for the behavioral actions of antidepressant treatment: Pharmacological and cellular characterization. Neuropsychopharmacology 34:2459–2468.
122. Warner-Schmidt JL, Duman RS (2007): VEGF is an essential mediator of the neurogenic and behavioral actions of antidepressants. Proc Natl Acad Sci U S A 104:4647–4652.
123. Kiuchi T, Lee H, Mikami T (2012): Regular exercise cures depression-like behavior via VEGF-Flk-1 signaling in chronically stressed mice. Neuroscience 207:208–217.
124. Deyama S, Bang E, Kato T, Li XY, Duman RS (2019): Neurotrophic and antidepressant actions of brain-derived neurotrophic factor require vascular endothelial growth factor. Biol Psychiatry 86:143–152.
125. Widman AJ, McMahon LL (2018): Disinhibition of CA1 pyramidal cells by low-dose ketamine and other antagonists with rapid antidepressant efficacy. Proc Natl Acad Sci U S A 115:E3007–E3016.
126. Fuchs T, Jefferson SJ, Hooper A, Yee PH, Maguire J, Luscher B (2017): Disinhibition of somatostatin-positive GABAergic interneurons results in an anxiolytic and antidepressant-like brain state. Mol Psychiatry 22:920–930.
127. Pothula S, Kato T, Liu R-J, Wu M, Gerhard D, Shinohara R, *et al.* (2020): Cell-type specific modulation of NMDA receptors triggers antidepressant actions [published online ahead of print Jun 2]. Mol Psychiatry.
128. Picard N, Takesian AE, Fagiolini M, Hensch TK (2019): NMDA 2A receptors in parvalbumin cells mediate sex-specific rapid ketamine response on cortical activity. Mol Psychiatry 24:828–838.
129. Li N, Lee B, Liu RJ, Banasr M, Dwyer JM, Iwata M, *et al.* (2010): mTOR-Dependent synapse formation underlies the rapid antidepressant effects of NMDA antagonists. Science 329:959–964.
130. Abdallah CG, Averill LA, Gueorguieva R, Goktas S, Purohit P, Ranganathan M, *et al.* (2020): Modulation of the antidepressant effects of ketamine by the mTORC1 inhibitor rapamycin. Neuropsychopharmacology 45:990–997.
131. Zanos P, Moaddel R, Morris PJ, Georgiou P, Fischell J, Elmer GI, *et al.* (2016): NMDAR inhibition-independent antidepressant actions of ketamine metabolites. Nature 533:481–486.
132. Suzuki K, Nosyreva E, Hunt KW, Kavalali ET, Monteggia LM (2017): Effects of a ketamine metabolite on synaptic NMDAR function. Nature 546:E1–E3.
133. Nosyreva E, Autry AE, Kavalali ET, Monteggia LM (2014): Age dependence of the rapid antidepressant and synaptic effects of acute NMDA receptor blockade. Front Mol Neurosci 7:94.
134. Zhou W, Wang N, Yang C, Li XM, Zhou ZQ, Yang JJ (2014): Ketamine-induced antidepressant effects are associated with AMPA receptors-mediated upregulation of mTOR and BDNF in rat hippocampus and prefrontal cortex. Eur Psychiatry 29:419–423.
135. Yang C, Hu YM, Zhou ZQ, Zhang GF, Yang JJ (2013): Acute administration of ketamine in rats increases hippocampal BDNF and mTOR levels during forced swimming test. Ups J Med Sci 118:3–8.
136. Antila H, Ryazantseva M, Popova D, Sipila P, Guirado R, Kohtala S, *et al.* (2017): Isoflurane produces antidepressant effects and induces TrkB signaling in rodents. Sci Rep 7:7811.
137. Rantamaki T, Kohtala S (2020): Encoding, consolidation, and renormalization in depression: Synaptic homeostasis, plasticity, and sleep integrate rapid antidepressant effects. Pharmacol Rev 72:439–465.
138. Laje G, Lally N, Mathews D, Brutsche N, Chemerinski A, Akula N, *et al.* (2012): Brain-derived neurotrophic factor Val66Met polymorphism and antidepressant efficacy of ketamine in depressed patients. Biol Psychiatry 72:e27–e28.
139. Su TP, Chen MH, Li CT, Lin WC, Hong CJ, Gueorguieva R, *et al.* (2017): Dose-related effects of adjunctive ketamine in Taiwanese patients with treatment-resistant depression. Neuropsychopharmacology 42:2482–2492.
140. Kim JW, Monteggia LM (2020): Increasing doses of ketamine curtail antidepressant responses and suppress associated synaptic signaling pathways. Behav Brain Res 380:112378.
141. Lenze EJ, Skidmore ER, Begley AE, Newcomer JW, Butters MA, Whyte EM (2012): Memantine for late-life depression and apathy after a disabling medical event: A 12-week, double-blind placebo-controlled pilot study. Int J Geriatr Psychiatry 27:974–980.
142. Ferguson JM, Shingleton RN (2007): An open-label, flexible-dose study of memantine in major depressive disorder. Clin Neuropharmacol 30:136–144.
143. Zarate CAJ, Singh JB, Quiroz JA, De Jesus G, Denicoff KK, Luckenbaugh DA, *et al.* (2006): A double-blind, placebo-controlled study of memantine in the treatment of major depression. Am J Psychiatry 163:153–155.
144. Maya Vetencourt JF, Sale A, Viegi A, Baroncelli L, De Pasquale R, O'Leary OF, *et al.* (2008): The antidepressant fluoxetine restores plasticity in the adult visual cortex. Science 320:385–388.
145. Castrén E (2013): Neuronal network plasticity and recovery from depression. JAMA Psychiatry 70:983–989.