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2013

Castren , E 2013 , ' Neuronal Network Plasticity and Recovery From Depression ' , JAMA Psychiatry , vol. 70 , no. 9 , pp. 983-989 . <https://doi.org/10.1001/jamapsychiatry.2013.1>

<http://hdl.handle.net/10138/42896>

<https://doi.org/10.1001/jamapsychiatry.2013.1>

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Neuronal Network Plasticity and Recovery from Depression

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Originally published in: JAMA Psychiatry (formerly Arch.Gen.Psychiatry), 70: 983-989, 2013.

The brain processes sensory information in neuronal networks that are shaped by experience, particularly during early life, to optimally represent the internal and external milieu. Recent surprising findings have revealed that antidepressant drugs reactivate a window of juvenile-like plasticity in the adult cortex. When antidepressant-induced plasticity was combined with appropriate rehabilitation, it brought about a functional recovery of abnormally wired neuronal networks. These observations suggest that antidepressants act permissively to facilitate environmental influence on neuronal network reorganization and so provide a plausible neurobiological explanation for the enhanced effect of combining antidepressant treatment with psychotherapy. The results emphasize that pharmacological and psychological treatments of mood disorders are closely entwined: The effect of antidepressant-induced plasticity is facilitated by rehabilitation, such as psychotherapy, that guides the plastic networks, and psychotherapy benefits from the enhanced plasticity provided by the drug treatment. Optimized combinations of pharmacological and psychological treatments might help make best use of existing antidepressant drugs and reduce the number of treatment-resistant patients. The network hypothesis of antidepressant action presented here proposes that recovery from depression and related mood disorders is a gradual process that develops slowly and is facilitated by structured guidance and rehabilitation.

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Monoamine oxidase inhibitors and tricyclic antidepressants, the first effective antidepressant drugs, were discovered over fifty years ago, but, remarkably, it is still unclear exactly how they contribute to recovery from depression. Recognition that both drug classes increased brain levels of monoamines formed the basis for the monoamine hypothesis of depression, which proposed that this condition was caused by a deficiency in monoaminergic neuromodulators and that antidepressant drugs act by replenishing them¹. This hypothesis has dominated thinking about mood disorders ever since, albeit becoming more focused on serotonin levels since the clinical success of selective serotonin reuptake inhibitors. Even theories not focused on monoamines have conceptualized depression (and other psychiatric conditions) as being caused by too little or too much of a single molecule that is normalized by successful treatment.

It has long been recognized, however, that despite rapid drug-induced elevations of monoamine levels, symptom improvement requires weeks of antidepressant treatment. Although a tremendous amount of information is available about the pharmacology of antidepressant drugs and their early direct biochemical effects²⁻⁴, less is known about the neurobiological and structural changes that temporally correlate with their clinical time course. Critically, a better comprehension of the delayed neural changes that mediate the beneficial

effects of antidepressants will instruct us in how best to maximize the usefulness of these drugs in the clinic.

During the last decade, neuroscientists have worked hard to redress this balance and, as a result, focus has shifted to neuronal plasticity, neurogenesis in the adult brain, and to the ability of antidepressants to regulate the expression of genes related to plasticity and resilience⁵⁻¹⁰. However, it remains unclear how exactly increased neural plasticity influences mood.

This review will present the growing evidence that antidepressants impact plasticity and will focus on recent findings suggesting that antidepressants reactivate juvenile-like plastic state in the adult brain. The possibility that this network level reactivation of plasticity might be an essential part of the therapeutic action of antidepressants will be proposed and the implications of this will be discussed.

Antidepressants reactivate a juvenile-like plasticity in adult brain

All brain functions, including cognition and emotions, are based on information processing and storage in neural networks. Although neurotransmitters mediate information transfer between neurons, it is the wiring and activity of these networks, not the levels of neurotransmitters, that underlies information processing. Neuronal plasticity mediates structural and functional changes in these networks, and experience-dependent

Box: Visual cortex as a model of neuronal network plasticity.

Network plasticity refers to the ability of the nervous system to change the structure and function of neuronal networks in response to environmental experiences. While the basic anatomical plan of neuronal projections is largely directed by genetic influences, the fine-tuning of the network takes place under environmental guidance^{11, 12, 92}. Neuronal networks form and are constantly shaped through an activity-dependent process whereby individual experiences and neuronal activity selects and strengthens those synapses which optimally mediate the presented environmental information while the connections that mediate random noise are weakened and pruned away^{11, 93}. Network plasticity is active during critical periods of postnatal life and become much more restricted after their closure in adulthood¹⁴⁻¹⁶.

Mammalian visual cortex has over the last few decades become one of the best-characterized models of neuronal network plasticity. During postnatal development in primates and cats, visual inputs from each eye segregate into alternating eye-specific regions in the primary visual cortex, called ocular dominance (OD) columns, such that each column receives predominant innervation from one eye only¹⁴⁻¹⁶. This segregation process takes place during a critical period of early postnatal development and requires the balanced use of both eyes¹⁴. If vision of one eye is blocked by eye patching during the critical period, the more active inputs from the open eye take over the majority of the visual cortex and the closed eye loses its connectivity, thereby becoming poor in vision, or amblyopic. If the patch is removed during the critical period and the use of the weaker eye is encouraged by patching the better eye, the vision of the amblyopic eye can be recovered. However, if the patching extends beyond the end of the critical period, amblyopia becomes permanent and cannot be revised by patching of the better eye. Thus, in this process a perfectly healthy eye, which has grown its projections to the visual cortex completely normally, loses its connectivity and becomes permanently deficient only because it is deprived of activation during the critical period. In humans, patching of the better eye is being successfully used for the prevention of amblyopia diagnosed in young children, but it is ineffective in adults. Although rodent visual cortex does not show OD columns, response to visual stimulation and visual acuity are impaired by monocular deprivation during early life. This model system has been extensively utilized to reveal the underlying mechanisms of the plastic process whereby the visual experience, through the activity of retinal projections, gradually shapes neuronal networks within the visual cortex to optimally represent the visual environment. It is widely considered that similar processes govern the development and tuning of neuronal connectivity in other cortical areas as well^{92, 94}.

plasticity tunes the networks to represent environmental input during development and underlies our ability to learn in adulthood^{11, 12} (Box 1). It is increasingly recognized that mood disorders are often associated with structural abnormalities within the networks implicated in depression¹³, raising the possibility that changes in information processing are a key component of these conditions.

The seminal work of Hubel and Wiesel in the early 1960s established that sensory experience shapes how the brain develops, demonstrating that visual input molds the structure and functionality of the networks that process that information¹⁴. Additionally, they clearly showed that the degree to which the brain can be changed by experience was variable and age-dependent, with plasticity highest during "critical periods" that occurred at stereotyped developmental stages¹⁴⁻¹⁶. Subsequently, similar critical periods have been observed in numerous neural systems, including emotional processing centers^{16, 17}, suggesting that visual cortical plasticity might be used as a model to investigate the mechanisms that mediate plasticity in brain regions that are more difficult to examine in the living animals or, even more so, in humans. Use-dependent plasticity continues to take place in adulthood and this adult plasticity underlies our ability to form memories and learn. However, after the closure of critical periods, plasticity is more restricted than during the early life and is mostly confined to changes in strength of existing synapses, either strengthening (long-term potentiation, LTP) or weakening (long-term depression, LTD)¹⁸. LTP, LTD and learning are differentially modified by internal or external experiences such as stress, depression and antidepressant drugs¹⁹⁻²¹.

New evidence published during the last few years suggests that recovery from depression, rather than resulting from an increase or a decrease in the concentration of a single molecule or the expression of a particular gene, reflects structural and functional changes in critical neuronal networks that allow them to better adapt to environmental conditions²²⁻²⁴. According to this network hypothesis, mood disorders might, at least partially, reflect an inability of the neuronal networks that guide mood-related behavior to optimally, or appropriately, adjust to inputs from the external world. In this framework, the early chemical effects of antidepressants initiate a process whereby neuronal networks, guided by activity, readjust their structure to better represent the external and internal milieu²². Consistent with the delayed emergence of the clinical effects of antidepressant drugs; this process would take weeks either to occur or to be of sufficient magnitude to alter mood and behavior.

To directly address the effects of antidepressant treatment of plasticity, Lamberto Maffei and his collaborators used rat primary visual cortex as an experimental system, because of the wealth of data relating to experience-dependent plasticity in this system (see Box 1). Rats were chronically treated with fluoxetine and its effects on these networks were assessed using well-established assays²⁵. When adult rats were treated with fluoxetine, closing one eye produced a dramatic shift in the responsiveness of visual cortical neurons in favor of the open eye, a response normally only seen during the early postnatal critical

period²⁵ (Box 1). Furthermore, fluoxetine-induced reactivation of such critical period-like plasticity also allowed functional recovery of a network that was miswired during postnatal development: When one eye was kept closed during early life but opened in adulthood, it only generated weak visual response (amblyopic) in the visual cortex even when its use was enforced by patching the previously open healthy eye. However, when patching of the better eye was combined with fluoxetine treatment in adult rats, visual acuity of the reopened eye was fully recovered²⁵. Again, recovery of visual acuity of an amblyopic eye, both in rats and humans, is normally only possible if the eye is opened and the other eye patched during the juvenile critical period.

These remarkable findings demonstrate that fluoxetine treatment in adult animals reactivates a critical period-like plasticity, which can facilitate the reorganization and functional recovery of a network that was miswired during development. Importantly, recovery only occurred when the drug treatment was combined with appropriate rehabilitation, such as the patching of the better eye. Interestingly, living in a stimulating environment may also boost neuronal plasticity in ways that parallel the effects of fluoxetine treatment. In a study where adult rats were transferred from their home cage to an enriched environment, there was also an induction of plasticity in the adult visual cortex and a recovery in the visual acuity of an amblyopic eye²⁶. In this context it is interesting to note that treatment of depressed patients with placebo brings about a noticeable response that in mild depression is often comparable to that produced antidepressants^{27, 28}. The magnitude of placebo response correlates positively with the number of visits to a study assistant during a 6-week trial and effect of these follow-up visits represent about 40% of the total placebo effect²⁹, suggesting that social interaction has a large impact on the placebo effect. It is possible that such interaction might be experienced as enrichment by some patients, which might, at least partially, underlie the response to placebo in antidepressant trials. Furthermore, placebo response is not immediate, as would be expected, but shows a delayed time course similar to that of antidepressant drugs^{30, 31}, suggesting a possibility that similar mechanisms might underlie the response to the active drug and the experienced enrichment produced by the inactive placebo, even though maximal responses would be different.

To investigate if antidepressant treatment reactivates juvenile-like plasticity not only in the visual cortex but also in mood-relevant networks, a recent series of experiments used fear conditioning and an extinction-training paradigm³². Pairing a neutral tone with a mild foot-shock quickly conditions mice to be fearful of that tone, which is manifest in the extent to which they stop moving and freeze when the tone is played³³. Analogous to exposure therapy for phobias in humans, repeated exposure to the tone alone, without a paired foot-shock, gradually extinguishes the freezing response in rodents. However, the learned extinction is not permanent and, again comparable to human exposure therapy where spontaneous recovery of phobia after extinction is problematic³⁴, playing a tone after a period of one week again produces a freezing response indicating a spontaneous recovery of fearfulness³⁵.

Extinction training after fear conditioning in mice produced only short-lasting effects, but in combination with chronic fluoxetine treatment, extinction training brought about a long-lasting decrease of the fear response³². Fluoxetine treatment alone did not affect post-conditioning freezing responses. A recent study showed that extinction training produces long-lasting effects when fear conditioning is induced and extinguished in early postnatal life³⁶, indicating that there is a developmentally regulated critical period for efficient extinction. These data suggest that chronic fluoxetine treatment reactivates a juvenile-like plasticity in mood-related neuronal networks, which in combination with extinction training leads to long-lasting beneficial effects. Indeed, evidence was provided that fluoxetine induces a plastic state in the basolateral amygdala, reminiscent of that present during early life³². These findings are consistent with observations that combined antidepressant treatment and exposure therapy worked better in the treatment of patients with posttraumatic stress disorder than either treatment alone³⁷, although a significant beneficial effect of a combination has not been seen in all studies^{38, 39}.

The key point of the network hypothesis is that the neurobiological alteration that underlies improved affect is the operational state of the neural networks that underlie mood and related information processing. Although it argues against equating mood with the level of any particular signaling molecule or protein, it will be instructive to determine the mechanisms by which antidepressants enhance network plasticity. In both the visual cortex and the amygdala of adult animals, long-term potentiation of synaptic transmission by high frequency stimuli is difficult to induce but was clearly observed after fluoxetine treatment^{25, 32}. Brain-derived neurotrophic factor (BDNF) was elevated and at least partially contributed to the changes observed in both systems. Serotonin, acting through 5HT1A receptors, was shown to play a critical role in the plastic effects of fluoxetine in the visual cortex⁴⁰. Levels of the inhibitory neurotransmitter GABA were reduced by fluoxetine in visual cortex, and the drug's effects were attenuated by augmenting GABAergic function²⁵. An independent group showed that fluoxetine-induced plasticity in visual cortex was associated with increases in both the elongation and retraction of interneuron dendritic branches⁴¹, suggesting that synaptic turnover on GABAergic neurons is elevated. It is, therefore, evident that the interplay between multiple neurotransmitter and modulator systems is mediating effects on plasticity. Determining the routes and interactions by which enhanced plasticity is achieved should provide clues for developing novel therapeutic agents that can better achieve clinical goals.

In addition to fluoxetine, histone deacetylase (HDAC) inhibitors have also been shown to reactivate a critical period-like plasticity in the rodent visual cortex^{40, 42, 43}. HDAC inhibition increases acetylation of histone tails, an epigenetic response that promotes gene transcription. Notably, Nestler's lab has shown that chromatin remodeling and histone acetylation control behavioral adaptations to chronic emotional stimuli⁴⁴⁻⁴⁶ and that HDAC inhibitors show antidepressant-like activity in animal models of depression⁴⁷. Additional studies are needed to assess whether other effective antidepressant treatments,

including the fast-acting ketamine²⁴, may share the ability to reactivate juvenile-like plasticity in the adult brain. Finally, critical period-like plasticity has been induced in adult visual cortex through several other pharmacological or non-pharmacological methods, including exposure to enriched environment²⁶, dark exposure⁴⁸, caloric restriction⁴⁹, treatment with cholinesterase inhibitors⁵⁰, and local injection of nerve growth factor^{51, 52}, insulin-like growth factor⁵³ or enzymes degrading perineural nets⁵⁴ (for review, see⁵⁵). It remains unclear whether any of these treatments might have an influence on mood in humans.

Do antidepressants induce juvenile-like plastic state in human brain?

If antidepressants, drugs used by millions of people over several decades, reactivate juvenile-like plasticity in human brains, how is it possible that such effects could have gone unnoticed? One possibility is that the induced plasticity is detectable only after combined rehabilitation or training. Another is that these changes are subtle and have not been extensively investigated. However, there are reports indicating that antidepressants, indeed, induce plasticity in adult human cortex. For example, Normann and coworkers used EEG to record visually evoked potentials from the visual cortex of depressed patients, control subjects, and healthy volunteers given the antidepressant sertraline⁵⁶. They found they could alter the visual cortical response to a visual stimulus by presenting it repeatedly at high frequency. Using the magnitude of this change as an index of neuronal plasticity, they found that depressed patients had lower levels of plasticity than controls. Strikingly, the healthy volunteers given sertraline had significantly elevated signs of plasticity in their visual cortices⁵⁶, in a manner similar to that observed in the visual cortex of adult rats treated with fluoxetine²⁵.

These findings suggest that chronic treatment with antidepressants enhances neuronal plasticity in the visual cortex of both humans and rodents. Whether the effects seen in humans reflect a reactivation of early life-like plasticity remains to be tested. An ongoing clinical trial on whether antidepressants can be used in the treatment of human amblyopia in adulthood⁵⁷ may eventually provide a direct answer to this question.

Is there evidence for a network abnormality in depression?

If recovery from depression reflects network rewiring, are mood disorders, at least partially, produced by neuronal networks maladjusted to the realities of the external world? Such changes in network structure and function might be the result of adverse early life experiences, continuous stress in adulthood or genetic factors⁵⁸.

A number of studies have shown that there are morphological abnormalities in the brains of depressed patients within the circuitry connecting the medial prefrontal cortex, amygdala and hippocampus, a circuitry that has been implicated in depression^{13, 59}. Changes in gray matter volume, neuronal organization, electrophysiological activity and receptor pharmacology have been observed in these regions in depressed patients^{13, 59, 60}. Furthermore,

diffusion tensor imaging has revealed white matter abnormalities in these circuits in depressed patients⁶¹⁻⁶³, which suggests abnormalities in the connectivity within the mood-relevant networks. Activity of different regions in these circuits is selectively influenced in depressed patients: activity is reduced in the dorsal system, including the hippocampus and the dorsolateral prefrontal cortex, but increased in the ventral system, including the amygdala, the ventral striatum and the subgenual cingulate cortex^{20, 64}. Consistent with this, BDNF produces antidepressant-like effects when injected into hippocampus⁶⁵, but shows prodepressant effects when expressed in the dopaminergic projection neurons projecting to the nucleus accumbens in the ventral striatum^{66, 67}.

It should be noted that a structurally normal network might still represent abnormal function. Cortex that receives abnormal environmental input during its critical period proceeds through an otherwise normal developmental process to faithfully represent the abnormal information. When active inputs are strengthened and less active ones simultaneously weakened, structural changes may cancel each other out and no net volume changes may be observed⁶⁸, even though network structure is altered. Therefore, it becomes very difficult to anatomically or biochemically differentiate a functionally abnormal network from one that was guided by a normal environment^{69, 70}. While in experimental systems input to the visual cortex can be straightforwardly manipulated to assess changes to the network structure, there is no simple way of similarly altering inputs to higher brain areas such as the prefrontal cortex. It should be noted that the visual cortices of amblyopic patients with one eye essentially blind show only modest and non-specific differences in cortical thickness compared with binocular subjects^{70, 71}. This small reduction in grey matter volume in the amblyopic visual cortex resembles changes observed in the medial prefrontal cortex of depressed patients¹³. One possible solution to this problem is to use correlates of plasticity as indicators: LTP and LTD have successfully been used as correlates of plasticity in animal experiments¹⁹ and a recent innovative study used learning as a correlate of plasticity in depressed patients²⁰ pointing towards indirect measures to overcome this problem.

Implications of the network hypothesis of antidepressant action

The network hypothesis of antidepressant action suggests that antidepressant treatment, by enhancing plasticity within key networks, would create circumstances where these malfunctioning networks can be fixed, and that the chance of clinical improvement is maximized if a positive environmental model is present to guide the network towards optimal function²². This hypothesis has several important practical implications.

First, a combination of antidepressants with psychotherapy has been shown to work better than either of the treatments alone in most studies^{37, 72-74}, although not in all^{38, 75} and long-term effects of combined treatment has been reported to be inferior to that of psychotherapy alone³⁹. Furthermore, some patients remain resistant also to a combined treatment. Nevertheless, the network

hypothesis might provide a neurobiological basis for such a combined effect. In the experimental studies the visual acuity or fear response, fluoxetine treatment alone had no effects, drug treatment had to be combined with environmental rehabilitation to bring about beneficial effects^{25, 32}. Similarly, rehabilitation alone produced only transient effects, long-term effects were observed only when rehabilitation was combined with fluoxetine treatment³². Thus, drug therapy and rehabilitation were closely entwined and supported the action of each other. These data suggest that drug treatment alone is insufficient for mood recovery, and, hence, that pharmacotherapy needs to be combined with proper environmental guidance in order to achieve maximal benefit. Psychotherapy such as cognitive behavioral therapy (CBT) may provide such guidance, but other types of rehabilitation, including group therapy may also be beneficial.

It is conceivable that some depressed patients live in environments with features that beneficially guide the plastic network in the absence of therapy provided by health care professionals. At least a third of depressed patients do not respond to antidepressants and this has inspired the search for novel antidepressants with new mechanisms of action^{2-4, 76}. However, it is also possible that current treatment strategies are not taking the best advantage of the existing drugs. If the effectiveness of antidepressant treatment is enhanced by environmental guidance, it is possible that treatment-resistant patients may respond to the drug, but do not experience any guidance that would support recovery. Perhaps patients who have supportive family or other social contacts benefit from these interactions and therefore respond positively to drug treatment whereas patients lacking a positive support network are at increased risk of becoming treatment-resistant. In support of this notion, a study of the predictors of remission with antidepressant treatment found that patients with a family and a job benefited most from antidepressant treatment⁷⁶. Even though antidepressants have been given to depressed patients in hundreds of clinical trials, we know little about what the patients *did* while taking the drug and whether their living conditions might correlate with the treatment outcome. Further studies are needed where the living environment and social contacts of patients receiving antidepressants are evaluated and correlated with the treatment response. The network hypothesis provides strong support for attempts to organize health care services in such a manner that patients diagnosed with mood disorders would not only receive drug treatment, but would also from the beginning receive psychotherapy or another form of psychological assistance to optimally support the facilitating effects of antidepressant drugs on plasticity and mood recovery^{77, 78}.

It should also be noted that reactivation of critical periods should only work once they are closed. There is currently little information on whether antidepressants might influence plasticity in children while critical periods are still open. A recent study provided evidence that prenatal antidepressant treatment accelerated the opening of a critical period for language learning⁷⁹, which resembles the findings that physical enrichment in a form of massage accelerates the maturation of visual system in preterm human babies as well as in rats⁸⁰. Early exposure to

antidepressants have been found to produced long-lasting behavioral effects in rodents⁸¹⁻⁸⁴, but whether these findings are related to any effects on the regulation of critical periods remains to be investigated.

Finally, it will be important to investigate whether a window of plasticity remains open as long as drug treatment lasts or whether it spontaneously closes after a while even upon continuous treatment. Mood disorders typically show a chronic and relapsing course, where affective episodes tend to become increasingly independent of environmental stressors. Whether this relapsing course is somehow related to loss of drug effect on plasticity is an important topic for research in the future.

The second prediction of the network hypothesis is that antidepressants would be useful in any condition where neuronal network plasticity would expedite clinical recovery. Indeed, the clinical efficacy of antidepressant drugs is not limited to mood disorders; they are also used in a wide variety of neuropsychiatric disorders ranging from obsessive-compulsive and post-traumatic stress disorders to chronic pain and eating disorders^{2, 3}. Furthermore, there is evidence that patients recovering from stroke benefit from antidepressant treatment while undergoing rehabilitation⁸⁵⁻⁸⁷. These data suggest that a combination of antidepressant treatment and rehabilitation might be beneficial in a wider spectrum of clinical conditions than recognized today.

Third, antidepressant treatment appears to have only relatively mild effects on mood in healthy subjects⁸⁸⁻⁹⁰, although there is little information concerning long-term effects of antidepressants in healthy subjects. This observation is consistent with and explained by the network hypothesis. If the network is already optimally tuned to the environment, then plasticity provided by antidepressants is not expected to change that representation, if anything, it may strengthen it. On the other hand, the hypothesis predicts that taking antidepressants under adverse life conditions might promote maladaptive plasticity and train the network to model this unfavorable environment, which might lead to deterioration rather than improvement in the clinical state. Maladaptive plasticity may also underlie the induction of mania sometimes encountered in bipolar patients. It is conceivable that antidepressant treatment has multiple effects, the network plasticity being just one of them, and the net effect favors a positive treatment outcome. Consistent with this notion, antidepressant treatment shifts emotional processing biases towards positive direction in both depressed patients and healthy volunteers, indicating that antidepressants favor a shift towards normative direction^{90, 91}.

Overall, these new findings advance a conceptual shift that might reconcile the long-standing dispute of "talk vs. pill", a debate that continues between those who favor psychotherapy and those who consider drug treatment as key to the treatment of mood disorders. If talk benefits from pills that increase plasticity and pills are best guided by talk to instruct the plastic networks, then the two treatment strategies perfectly complement each other. Rather than arguing whether talk or pill is better, we should try to find an optimal combination of the two treatment strategies for as many patients as possible.

Conclusions

The network hypothesis proposes that antidepressants achieve their therapeutic effects via a gradual process in which enhanced plasticity facilitates the reorganization of cortical networks to better adjust to environmental experiences. The hypothesis suggests that antidepressants do not directly improve mood, but by reactivating a juvenile-like state of plasticity, they promote the effects of

rehabilitation and psychological therapy to bring about mood recovery. Thus, the antidepressants action might be likened to that of anabolic steroids: steroids facilitate a process where exercise increases muscle growth, but they are not expected to work alone without training, and nobody expects steroids to induce muscle growth within minutes and hours. Similarly, the antidepressant process develops gradually and requires training and guidance.

ARTICLE INFORMATION

Published Online: July 10, 2013. doi:10.1001/jamapsychiatry.2013.1.

Conflict of Interest Disclosures: Castrén has received research support from Orion Pharma, is a shareholder and advisor at Hermo Pharma, and holds a patent on the use of antidepressants to treat amblyopia.

Funding/Support: This review was partially written while Castrén was a visiting scholar at the Department of Psychiatry and Neuroscience, Columbia University, supported by the Schaefer Scholarship. Research in Castrén's laboratory has been supported by the Sigrid Jusélius Foundation and the Academy of Finland Centre of Excellence Programme.

Additional Contributions: Liam Drew, PhD, René Hen, PhD, Francis Lee, MD, Antonio Di Lieto, MD, and Olivia O'Leary, PhD, provided discussions and comments on the manuscript.

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