Are the effects of rapid-acting antidepressants consolidated in sleep?

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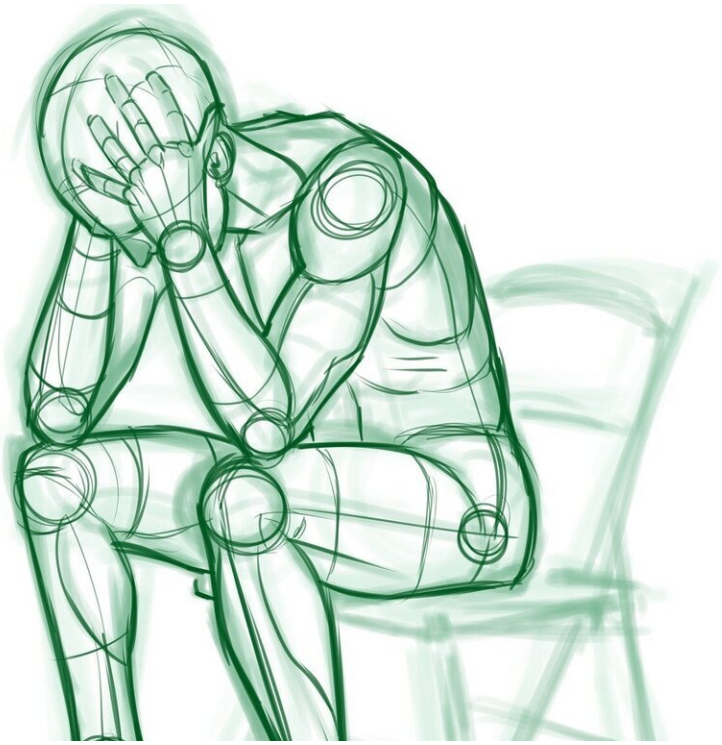

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Depression and long-term stress have been demonstrated to cause changes in the brain which offer a partial explanation for depressive moods, apathy, memory difficulties and other symptoms commonly associated with depression. Unbroken circles of negative thoughts are also often a distinct aspect of the mental status of depressed patients.

This is down to very active and selective brain function.

"In turn, this strengthens the neural connections associated with precisely this type of thinking. Less active connections and neural networks supporting normal brain function weaken due to a lack of use, which completes the circle of negativity. The result is an imbalance of activity among neural networks, and clinical depression," says Associate Professor Tomi Rantamäki from the Faculty of Pharmacy, University of Helsinki.

The vicious circle could be broken by guiding the brain back towards a more comprehensive mode of action. Such guidance can be boosted by means of psychotherapy, but the effects manifest slowly. In recent years, rapid-acting modes of treatment for depression have been investigated, potentially offering entirely novel approaches. The latest new product is a nasal spray that contains esketamine, which was just granted a marketing authorisation in Europe.

"What ketamine, psychiatric electroconvulsive therapy, nitrous oxide and certain other therapies already in use or currently being trialled have in common is the fact that they increase the activity of broad cortical areas and strengthen synaptic connections. At their best, they force the broad neural networks of the cerebral cortex into an entirely new kind of interaction, which makes it possible to weaken the previous imbalance," notes Samuel Kohtala, a postdoctoral researcher at the University of Helsinki.

However, such rapid relief is only temporary, unless the plasticity mechanisms endogenous to the nervous system are utilised.

"According to the synaptic homeostasis hypothesis, synapses strengthened during the day undergo a process of renormalisation in deep sleep, which is dominated by slow-wave activity. The most

potentiated synapses may retain their relative strength better than weaker synapses, which presents an opportunity for learning new information while purging the network of excessive noise. We think that rapid antidepressant treatments share the ability to regulate both synaptic potentiation and the reciprocal homeostatic mechanisms, which weaken synaptic strength during sleep. Either of these mechanisms can contribute to how the brain can reorganise its activity to defeat depression," Kohtala says.

Based on the studies, molecular mechanisms implicated in neuronal plasticity are particularly activated during periods of slow-wave activity. Thus, slow-wave responses could be a useful measure for determining treatment efficacy and developing novel treatments.

The researchers point out that, boosted by similar mechanisms, brain function may again be derailed during subsequent sleep periods, unless the neural networks driving the depression are sufficiently controlled, for example, by means of psychotherapy.

"The main symptoms of depression can be artificially affected by destabilising the functioning of neural networks. A more permanent effect requires tackling the root causes of the problem as well," Rantamäki emphasises.

More information: Tomi Rantamäki et al, Encoding, Consolidation, and Renormalization in Depression: Synaptic Homeostasis, Plasticity, and Sleep Integrate Rapid Antidepressant Effects, *Pharmacological Reviews* (2020). DOI: 10.1124/pr.119.018697

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