Does the brain 'remember' antidepressants?

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Individuals with major depressive disorder (MDD) often undergo multiple courses of antidepressant treatment during their lives. This is because the disorder can recur despite treatment and because finding the right medication for a specific individual can take time.

While the relationship between prior treatment and the brain's response to subsequent treatment is unknown, a new study by UCLA researchers suggests that how the brain responds to antidepressant medication may be influenced by its remembering of past antidepressant exposure.

Interestingly, the researchers used a harmless placebo as the key to tracking the footprints of prior antidepressant use.

Aimee Hunter, the study's lead author and an assistant professor of psychiatry at UCLA's Semel Institute for Neuroscience and Human Behavior, and colleagues showed that a simple placebo pill, made to look like actual medication for depression, can "trick" the brain into responding in the same manner as the actual medication.

The report was published online March 23 in the journal *European Neuropsychopharmacology*.

The investigators examined changes in brain function in 89 depressed persons during eight weeks of treatment, using either an antidepressant medication or a similar-looking placebo pill. They set out to compare the two treatments — medication versus placebo — but they also added a twist: They separately examined the data for subjects who had never

previously taken an antidepressant and those who had.

The researchers focused on the prefrontal cortex, an area of the brain thought to be involved in planning complex cognitive behavior, personality expression, decision-making and moderating social behavior, all things depressed people wrestle with.

Brain changes were assessed using electroencephalograph (EEG) measures developed at UCLA by study co-authors Dr. Ian Cook, UCLA's Miller Family Professor of Psychiatry, and Dr. Andrew Leuchter, a professor of psychiatry and director of the Laboratory of Brain, Behavior and Pharmacology at UCLA's Semel Institute. The EEG measure, recorded from scalp electrodes, is linked to blood flow in the cerebral cortex, which suggests the level of brain activity.

The antidepressant medication given during the study appeared to produce slight decreases in prefrontal brain activity, regardless of whether subjects had received prior antidepressant treatment during their lifetime or not. (A decrease in brain activity is not necessarily a bad thing, the researchers note; with depression, too much activity in the brain can be as bad as too little.)

However, the researchers observed striking differences in the power of placebo, depending on subjects' prior antidepressant use. Subjects who had never been treated with an antidepressant exhibited large increases in prefrontal brain activity during placebo treatment. But those who had used antidepressant medication in the past showed slight decreases in prefrontal activity — brain changes that were indistinguishable from those produced by the actual drug.

"The brain's response to the placebo pill seems to depend on what happened previously — on whether or not the brain has ever 'seen' antidepressant medication before," said Hunter, who is a member of the

placebo research team at the Laboratory of Brain, Behavior and Pharmacology. "If it has seen it before, then the brain's signature 'antidepressant-exposure' response shows up."

According to Hunter, the effect looks conspicuously like a classical conditioning phenomenon, wherein prior exposure to the actual drug may have produced the specific prefrontal brain response and subsequent exposure to the cues surrounding drug administration — the relationship with the doctor or nurse, the medical treatment setting, the act of taking a prescribed pill and so forth — came to elicit a similar brain response through 'conditioning' or 'associative learning.'

While medication can have a powerful effect on our physiology, said Hunter, "the behaviors and cues in the environment that are associated with taking medication can come to elicit their own effects. One's personal treatment history is one of the many factors that influence the overall effects of treatment."

Still, she noted, there are other possible explanations, and further research is needed to tease out changes in brain function that are related to antidepressant exposure, compared with brain changes that are related to clinical improvement during treatment.

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