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Researchers discover new mechanism for attentional control in the human brain

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A study by UC Davis researchers appearing in the journal *Science* reports the discovery of a new mechanism of attention in the human brain. Previous studies in animals implicated changes in the state of a portion of the brainstem, called the locus ceruleus (LC), in shifts from distractible to attentive states.

By administering a drug that modifies the state of the LC, which was visualized using functional magnetic resonance (fMRI) brain imaging techniques, the researchers were able to shift volunteers into a more attentive state in which they showed enhanced coordinated brain activity and performance on a test of attention control.

The UC Davis study also provides new insights into the workings of a stimulant-like drug that could have broad applications for enhancing the cognition of people with conditions ranging from autism to schizophrenia.

The drug modafinil is approved by the Food and Drug Administration (FDA) for treating narcolepsy, shift-work related sleep disorders and obstructive sleep apnea, and indicated for conditions including ADHD, Parkinson's disease and depression. But how it works has not been well understood until now.

"We have shown that the way modafinil works is by quieting activity in the LC and increasing its connections with the frontal cortex," said Cameron Carter, a UC Davis professor of psychiatry and behavioral

sciences and senior author of the study.

"Now that we know how it works, we can develop better cognitive enhancers that can treat more people suffering from a wider variety of neurodevelopmental disorders, like ADHD, autism and schizophrenia," he said.

Clues to the drug's mechanism came from work done in animals, said Michael Minzenberg, lead author of the paper and a UC Davis assistant professor of clinical psychiatry. The animal studies indicated that it was the shift in brain activity of the pre-frontal cortex caused by norepinephrine that was responsible for improvements in cognition. Studies in primates also showed that norepinephrine increased attentiveness.

"Now we know that, although these parts of the brain are far from each other, their activity is correlated," said Minzenberg.

Previous studies in primates showed that, when not performing a complex task, neurons in the prefrontal cortex fire often and seemingly at random. During the performance of a focused task, however, that area of the brain is quiet and the cells fire only in concert with actions associated with the task. These modes are called exploration and exploitative, respectively.

"We found that modafinil shifts the human brain into exploitation mode and study subjects perform better on tasks," Minzenberg said.

In the current study the research team used fMRI to look at brain activity in real time in 21 healthy adults who were asked to perform a standardized test called a POP Task (Preparing to Overcome Prepotency) that requires the subject to pay close attention.

The subjects performed this task on different days after taking either a sugar pill or a dose of modafinil. Researchers then looked at the differences in brain-activity patterns.

"Subjects performed much better on these tasks after taking modafinil, but, more importantly, using fMRI we were able to see the shift to quieter, more focused brain activity ," Minzenberg said.

According to Minzenberg, this study is one of the few to look at the pharmacological activity of a drug in real time using a non-invasive method.

"This is a proof-of-concept study supporting the use of fMRI to study drug effects on the brain as a way of gaining insight into how the drugs work," he said.

While fMRI may help speed up the drug development process in general, the results of the study promise to accelerate development of drugs to treat neurodevelopmental disorders in particular, Carter said.

"Future development will be more targeted because this study builds a bridge between basic science and human cognition," he said.

Source: University of California - Davis