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Study uncovers how Ritalin works in brain to boost cognition, focus attention

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Stimulant medications such as Ritalin have been prescribed for decades to treat attention deficit hyperactivity disorder (ADHD), and their popularity as "cognition enhancers" has recently surged among the healthy, as well

What's now starting to catch up is knowledge of what these drugs actually do in the brain. In a paper publishing online this week in *Biological Psychiatry*, University of Wisconsin-Madison psychology researchers David Devilbiss and Craig Berridge report that Ritalin fine-tunes the functioning of neurons in the prefrontal cortex (PFC) - a brain region involved in attention, decision-making and impulse control - while having few effects outside it.

Because of the potential for addiction and abuse, controversy has swirled for years around the use of stimulants to treat ADHD, especially in children. By helping pinpoint Ritalin's action in the brain, the study should give drug developers a better road map to follow as they search for safer alternatives.

At the same time, the results support the idea that today's ADHD drugs may be safer than people think, says Berridge. Mounting behavioral and neurochemical evidence suggests that clinically relevant doses of Ritalin primarily target the PFC, without affecting brain centers linked to over-arousal and addiction. In other words, Ritalin at low doses doesn't appear to act like a stimulant at all.

"It's the higher doses of these drugs that are normally associated with their effects as stimulants, those that increase locomotor activity, impair cognition and target neurotransmitters all over the brain," says Berridge. "These lower doses are diametrically opposed to that. Instead, they help the PFC better do what it's supposed to do."

A behavioral disorder marked by hyperactivity, impulsivity and the inability to concentrate, ADHD has been treated for more than a half-century with Ritalin, Adderall and other stimulant drugs. New reports also indicate these meds have lately been embraced by healthy Americans of all ages as a means to boost mental performance.

Yet, despite their prevalence, we know remarkably little about how these drugs work, especially at lower doses that have been proven clinically to calm behavior and focus attention in ADHD patients, says Berridge. In 2006, his team reported that therapeutic doses of Ritalin boosted neurotransmitter levels primarily in the PFC, suggesting a selective targeting of this region of the brain. Since then, he and Devilbiss have focused on how Ritalin acts on PFC neurons to enhance cognition.

To answer this, the pair studied PFC neurons in rats under a variety of Ritalin doses, including one that improved the animals' performance in a working memory task of the type that ADHD patients have trouble completing. Using a sophisticated new system for monitoring many neurons at once through a set of microelectrodes, the scientists observed both the random, spontaneous firings of PFC neurons and their response to stimulation of an important pathway into the PFC, the hippocampus.

Much like tiny microphones, the electrodes record a pop every time a neuron fires, Devilbiss explains. Analyzing the complex patterns of "voices" that emerge is challenging but also powerful, because it allows study of neurons on many levels.

"Similar to listening to a choir, you can understand the music by listening to individual voices," says Devilbiss, "or you can listen to the interplay between the voices of the ensemble and how the different voices combine."

When they listened to individual PFC neurons, the scientists found that while cognition-enhancing doses of Ritalin had little effect on spontaneous activity, the neurons' sensitivity to signals coming from the hippocampus increased dramatically. Under higher, stimulatory doses, on the other hand, PFC neurons stopped responding to incoming information.

"This suggests that the therapeutic effects of Ritalin likely stem from this fine-tuning of PFC sensitivity," says Berridge. "You're improving the ability of these neurons to respond to behaviorally relevant signals, and that translates into better cognition, attention and working memory." Higher doses associated with drug abuse and cognitive impairment, in contrast, impair functioning of the PFC.

More intriguing still were the results that came from tuning into the entire chorus of neurons at once. When groups of neurons were already "singing" together strongly, Ritalin reinforced this coordinated activity. At the same time, the drug weakened activity that wasn't well coordinated to begin with. All of this suggests that Ritalin strengthens dominant and important signals within the PFC, while lessening weaker signals that may act as distractors, says Berridge.

"These results show a new level of action for cognition-enhancing doses of Ritalin that couldn't have been predicted from single neuron analyses," he says. "So, if you're searching for drugs that might replace Ritalin, this is one effect you could potentially look for."

He and Devilbiss also hope the research will help unravel an even deeper mystery: exactly how neurons encode complex behavior and cognition.

"Most studies look at how something that impairs cognition affects PFC neurons. But to really understand how neurons encode cognitive function, you want to see what neurons do when cognition is improved," says Berridge. "So this work sets the stage for examining the interplay among PFC neurons, higher cognition, and the action of therapeutic drugs."

Source: University of Wisconsin-Madison