Study pinpoints effects of different doses of an ADHD drug, finds higher doses may harm learning

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New research with monkeys sheds light on how the drug methylphenidate may affect learning and memory in children with attention deficit hyperactivity disorder.

The results parallel a 1977 finding that a low dose of the drug boosted cognitive performance of children with ADHD, but a higher dose that reduced their hyperactivity also impaired their performance on a memory test.

"Many people were intrigued by that result, but their attempts to repeat the study did not yield clear-cut results," says Luis Populin, an associate professor of neuroscience at the University of Wisconsin-Madison School of Medicine and Public Health.

Populin was senior author of the new study exploring the same topic, now available in the early access section of the Journal of Cognitive Neuroscience, published last week. In the study, three monkeys were taught to focus on a central dot on a screen, while a "target" dot flashed nearby. The monkeys were taught that they could earn a sip of water by waiting until the central dot switched off, and then looking at the location of the now-vanished target dot.

The system tests working (short-term) memory, impulsiveness and willingness to stick with the task, as the monkeys could quit "working" at

any time, says Populin. The study used different doses of methylphenidate -- the generic name for Ritalin -- that were comparable to the range of clinical prescriptions for ADHD.

According to the Centers for Disease Control, almost 5 percent of American children are taking medications for ADHD.

Strikingly, dosage had a major and unexpected impact. "At a low dose, the performance scores improved because the monkeys could control their impulses and wait long enough to focus their eyes on the target. All three were calmer and could complete a significantly larger number of trials," says Populin, who collaborated with Jeffrey Henriques and graduate student Abigail Rajala on the study.

At the higher dose, "performance on the task is impaired," Populin says, "but the subjects don't seem to care, all three monkeys continued making the same errors over and over." The monkeys stayed on task more than twice as long at the higher dose, even though they had much more trouble performing the task.

Although ADHD drugs are commonly thought to improve memory, "If we take the accuracy of their eye movements as a gauge of working memory, memory was not helped by either dose," says Populin. "It did not get better at the lower dose, and there actually was a small negative effect at the higher dose."

Memory is at the root of many intellectual abilities, but it can be affected by many factors, says Bradley Postle, a professor of psychology at UW-Madison.

Postle, an expert on working memory who was not involved in the study, says methylphenidate affects the brain's executive function, "which can create an internal environment that, depending on the dose, is either

more or less amenable to memory formation and/or retention. If you can concentrate, and are able to process information without being interrupted by distracting thoughts or distractions in your environment, you will perform much better on a memory test. Apparently, the lower dose of methylphenidate helped create the conditions for success without actually improving memory itself."

Monkeys are not people, but monkeys in the study still reminded him of school children, Populin says.

"They made premature movements, could not wait to look at the target before they could be rewarded for doing so. It's like a kid where the teacher says, 'When you complete the task, raise your hand.' But he can't wait, even if he knows that by responding prematurely he will not get rewarded," he says.

The study results had another parallel with daily life, Populin says. Drug dosages may be set high enough to reduce the characteristic hyperactivity of ADHD, "but some children say that makes them feel less creative and spontaneous; more like a robot. If learning drops off as it did in our study, that dose may not be best for them. Our monkeys actually did act like robots at the higher doses, keeping at it for up to seven hours even though their performance was so low."

The logical way forward would involve a similar study with people diagnosed with ADHD, Populin says. With millions of children, and an increasing number of adults, taking medicines for the condition, "We have to be very careful about finding the right spot on the dose curve, or we may get changes in behavior that we don't want. People think these drugs help improve memory, but our data say, 'No, your memory is not getting better.' At the higher dose, you get a behavioral improvement at a price, and that price is cognitive ability."