Researchers gain a better understanding of how the most commonly used ADHD medication works

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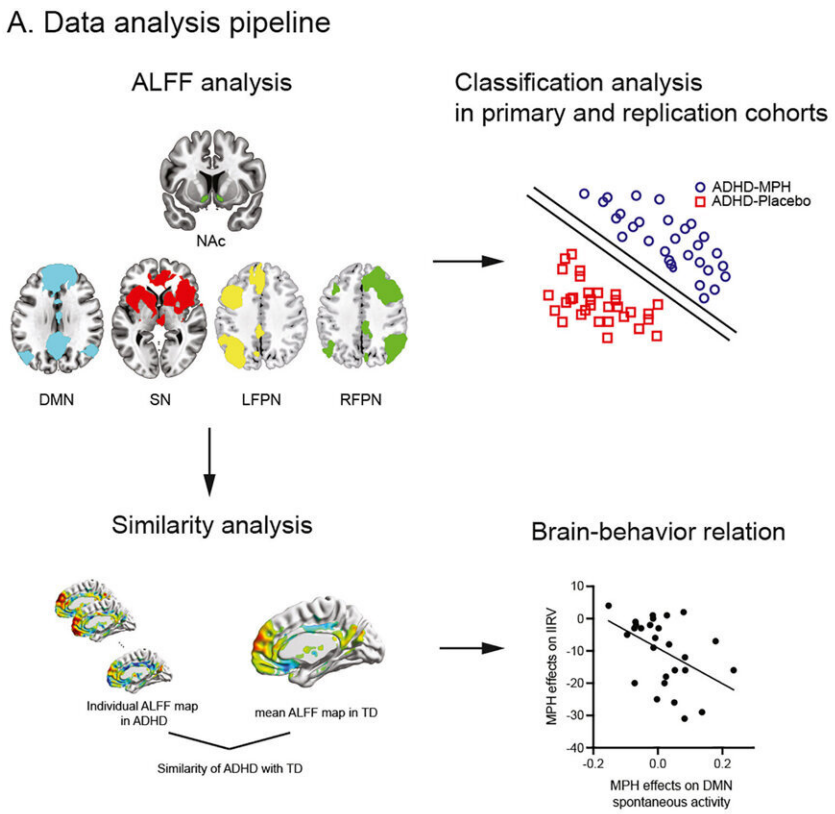

(A) Data analysis pipeline. We first computed ALFF within the bilateral NAc and three brain networks implicated in ADHD: SN, DMN, and left and right FPN. Paired t-tests were used to examine the medication effects (ADHD in methylphenidate versus placebo conditions) and two-sample t-tests were used to examine the difference between ADHD and TD controls. Second, we conducted ALFF pattern similarity analysis (illustrated in detail in Panel B) to quantify the

extent to which ALFF values are similar between children with ADHD and TD children, and examined whether children with ADHD whose post-medication spontaneous activity patterns are more similar to TD children would exhibit greater improvement in IIRV with medication. Third, we used classification analysis to test whether the multivariate pattern of ALFF in the NAc and the three brain networks could distinguish children with ADHD in medication or placebo conditions (primary cohort) and crucially whether this can be replicated in another independent dataset (replication cohort). (B) Overview of ALFF pattern similarity analysis between children with ADHD and TD controls. We first computed the correlation between ALFF values within SN or DMN from each child with ADHD and those from the mean ALFF map in the TD group. The correlation coefficient was standardized using Fisher's r-to-z transformation. Next, we calculated methylphenidate-induced changes in the similarity measures of ALFF in the SN or DMN between ADHD-Placebo and ADHD-MPH conditions. Higher values indicate that medication leads to more TD-like spontaneous neural activity patterns. ADHD-MPH: children with attention-deficit/hyperactivity disorder under methylphenidate administration; ADHD-Placebo: children with attention-deficit/hyperactivity disorder under placebo; ALFF: amplitude of low-frequency fluctuations; DMN: default mode network; IIRV: intra-individual response variability; LFPN: left frontoparietal network; NAc: nucleus accumbens; RFPN: right frontoparietal network; ROI: region of interest; SN: salience network; TD: typically developing. Credit: *Biological Psychiatry: Cognitive Neuroscience and Neuroimaging* (2022). DOI: 10.1016/j.bpsc.2022.10.001

For decades, doctors have treated kids with attention-deficit/hyperactivity disorder (ADHD) with methylphenidate, a stimulant drug sold as Ritalin and Concerta, making it one of the most widely prescribed medications aimed at the central nervous system. One might expect that researchers would know how methylphenidate works in the brain by now, but little is known about the drug's mechanism of action. Now, a new study seeks to close this gap and understand how methylphenidate interacts with cognitive control networks and

attentional behavior.

The new study appears in *Biological Psychiatry: Cognitive Neuroscience and Neuroimaging*.

What researchers do know is that individuals with ADHD have lower dopamine signaling activity than neurotypical individuals in the interconnected brain networks that control attention and goal-directed behaviors. Specifically, methylphenidate is hypothesized to ameliorate ADHD symptoms by increasing dopamine levels in the nucleus accumbens (NAc), a hub for dopamine signaling.

In the new study, researchers led by Yoshifumi Mizuno, MD, Ph.D., Weidong Cai, Ph.D., and Vinod Menon, Ph.D., used brain imaging to explore the effects of methylphenidate on the NAc and a so-called triple network system that plays a key role in behaviors that require adaptive control of attention.

The three networks include the salience, frontoparietal, and default mode networks. Aberrant activity was detected in the NAc and in multiple brain networks in children with ADHD, suggesting that dysregulation in the system may underlie ADHD symptoms, and that correcting the dysfunction might alleviate those symptoms.

"Our findings demonstrate in two independent cohorts that methylphenidate changes spontaneous neural activity in reward and cognitive control systems in children with ADHD. Medication-induced changes in cognitive control networks result in more stable sustained attention. Our findings reveal a novel brain mechanism underlying methylphenidate treatment in ADHD and inform biomarker development for evaluating treatment outcomes," noted Dr. Menon, Department of Psychiatry & Behavioral Sciences, Stanford University School of Medicine.

The researchers used functional magnetic resonance imaging (fMRI) to measure the effects of methylphenidate on spontaneous brain activity in 27 children with ADHD and 49 typically developing controls. Children with ADHD were scanned during two different visits one to six weeks apart—once while receiving methylphenidate and once while receiving a placebo. (Typically developing children did not receive medication or placebo.)

Outside the scanner, children with ADHD also performed a standardized task to assess sustained attention. Additionally, the researchers tested the replicability of methylphenidate's effects on spontaneous brain activity in a second independent cohort.

Not surprisingly, children performed better on the attention tasks when they were medicated. And as the researchers hypothesized, they also saw greater spontaneous neural activity in the NAc and the salience and default mode networks when methylphenidate was administered. Children with ADHD who displayed enhanced changes in brain activity patterns in the default mode network with medication performed better on the attention tasks with medication.

Findings were replicated across two independent cohorts, providing further evidence that methylphenidate may alleviate ADHD symptoms by its actions on the NAc and the triple network cognitive system.

Cameron Carter, MD, editor of *Biological Psychiatry: Cognitive Neuroscience and Neuroimaging*, said of the study, "The findings, which used the widely available technique of resting-state functional MRI, confirm the positive effects of methylphenidate on attention in children with ADHD and reveal the likely mechanism of action, through improved coordinated brain network activity and a likely key role for enhanced dopamine effects in the NAc region of the brain."

The work advances researchers' understanding of how ADHD affects cognitive control networks in the brain and how methylphenidate interacts with these networks to shift behavior. The findings could guide future work using brain imaging as a clinically useful biomarker of response to treatments.

More information: Yoshifumi Mizuno et al, Methylphenidate enhances spontaneous fluctuations in reward and cognitive control networks in children with attention-deficit/hyperactivity disorder, *Biological Psychiatry: Cognitive Neuroscience and Neuroimaging* (2022). DOI: 10.1016/j.bpsc.2022.10.001

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