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Trends in
Cognitive Sciences

Spotlight

Ritalin as a causal perturbation

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Causal perturbations provide the strongest tests of the relationships between brain mechanism and brain function. In cognitive neuroscience, persuasive causal perturbations are difficult to achieve. In a recent paper, Ni *et al.* cleverly use the neuropsychiatric drug methylphenidate (Ritalin) to causally test the brain mechanisms that support goal-directed attention.

Methylphenidate is a first-line treatment for adults and children with Attention Deficit Hyperactivity Disorder (ADHD) and is commonly used recreationally by college students to improve attention while studying [1]. Although over 2 million people in the USA take methylphenidate annually, we understand little about its mechanism of action in the brain [2]. A new study by Ni *et al.* [3] provides important insights into how methylphenidate works as well as a causal test of a hypothesis about the brain mechanisms that support goal-directed attention.

Correlative studies are the foundation of cognitive neuroscience. They involve the manipulation of task conditions in an experiment, coupled with observations of changes in brain activity and behavior, to infer the brain mechanisms that support cognitive function. However, correlative approaches alone cannot rule out that the observed brain activity patterns are epiphenomena with no causal contribution to behavior. Consequently, once inferences are made, causal tests provide the strongest evidence to support or refute existing hypotheses. In practice, persuasive causal manipulations are rare in cognitive neuroscience because they are extremely difficult to achieve.

Establishing causality requires the randomization of experimental variables [4]. While experimental conditions can be randomized in a straightforward way to determine their effects on behavior, randomizing patterns of brain activity independent of experimental conditions is more challenging. Cruder types of perturbation modulate brain activity in unnatural ways as a subject performs a task. More refined types of perturbation mimic natural brain activity patterns. The latter type of perturbation is important for testing hypotheses about how brain activity reflects latent variables, such as attentional state [4]. However, achieving these more refined types of perturbation is an enormous challenge for cognitive neuroscience.

In their study, Ni *et al.* [3] cleverly used the neuropsychiatric drug methylphenidate as a refined causal test of their hypothesis about the relationship between brain activity and goal-directed attention. Their previous work [5] demonstrated a correlation between one signature of brain activity in visual area V4 (trial-by-trial response variability, shared between neurons) and the performance of rhesus macaques on a visual task. This relationship was correlative but consistent, remaining unchanged when different cognitive processes, including attention and learning, were deployed to modulate behavior and brain activity. If causal, a randomized external manipulation should change task performance exactly when it changes this neural signature in V4.

Ni *et al.* [3] tested causality using methylphenidate as a nonspecific manipulation that they applied in a subset of experimental sessions. They found that methylphenidate improved the performance of rhesus macaques only when attention was directed to a cued spatial location (but not at an unattended location). Consistent with their hypothesis, methylphenidate changed the V4 neural signature only at the attended location, and the relationship between the neural signature and behavior was the same as in their previous, correlative study. These results suggest that this V4 neural signature is not an epiphenomenon, but rather is causally related to behavior.

In their study, methylphenidate was administered orally and its action was not isolated to V4. The authors do not interpret their results as methylphenidate acting only within V4, but more broadly. Methylphenidate may influence neurons in frontal cortex, which have been hypothesized to direct attention [6] and have a large concentration of dopamine receptors [2]. In this scenario, methylphenidate would act via naturally selective cognitive mechanisms that involve interactions between top-down control areas and V4. The use of a drug to perturb this mechanism, which is reflected in V4 by a specific neural signature, provides a causal test of the hypothesis that the mechanism that changes V4 activity is responsible for attention-related improvements in behavior.

Brain research is often envisioned as happening via a 'bench to bedside' trajectory in which basic discoveries about the brain provide the foundation for new treatments for brain dysfunction. In the study by Ni *et al.* [3], this trajectory was reversed insofar as a clinical treatment was used as a causal test of a basic research hypothesis (Figure 1). Methylphenidate is an old drug that was first synthesized in 1944 by the chemist Leandro Panizzon. Panizzon's wife Rita found that it improved her tennis game and he decided to name it after her, 'Rita-lin'. Later, researchers determined that it acts by blocking the reuptake of dopamine and norepinephrine [7], thereby increasing their levels in the synapse. By focusing on a complementary system and a computational-level description of how patterns of brain activity give rise to behavior, Ni *et al.* [3] fill an important gap in the

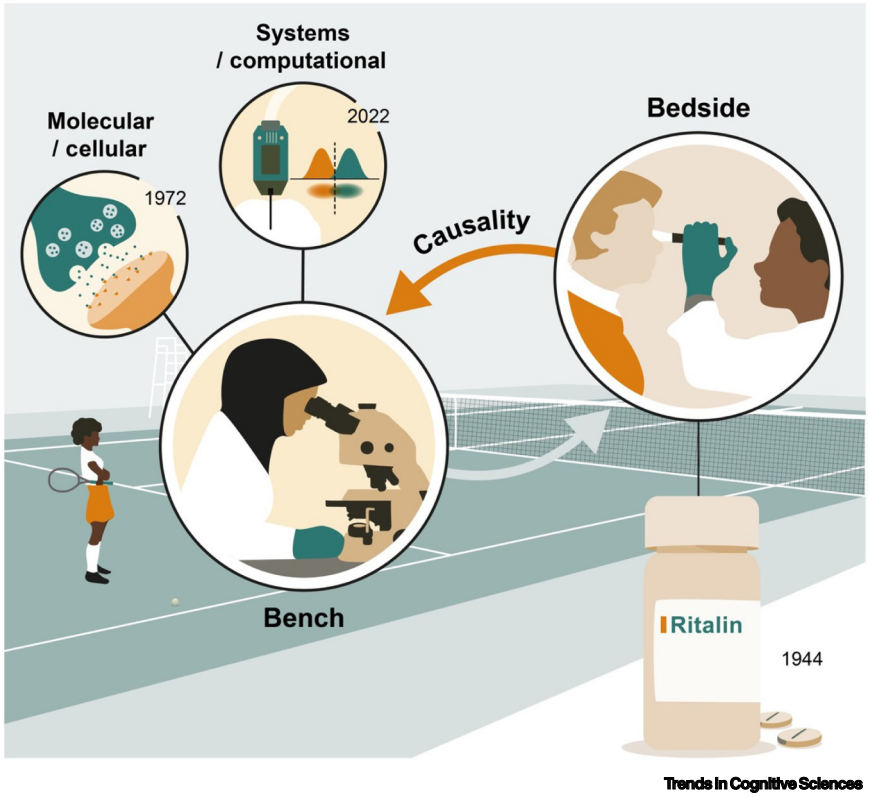

Figure 1. Ritalin as a bedside-to-bench test of causality. Methylphenidate (trade name Ritalin) was first synthesized in 1944 by a chemist who named it after his wife, Rita, after she found that it improved her tennis game. Only later, in 1972, was its mechanism of action discovered at the molecular level: it blocks the reuptake of dopamine and norepinephrine, thereby increasing their levels in the synaptic cleft. Today, Ritalin continues to be used clinically to treat Attention Deficit Hyperactivity Disorder. In their 2022 study [3], Ni *et al.* used Ritalin as a causal test of a hypothesis about attention formulated at the systems and computational level. Thus, while brain research is often envisioned as a 'bench-to-bedside' trajectory, the use of Ritalin by Ni *et al.* reverses it. Illustration by Gil Costa.

mechanistic understanding of the relationship between methylphenidate and behavior (Figure 1).

The use of chemical compounds to probe brain function is not new: pharmacology is one of the oldest subfields of brain research. Pharmacology has traditionally targeted hypotheses about what is happening in the brain at the level of molecules, such as neurotransmitters and receptors, and their relationships with behavior. However, there are intervening levels of explanation between molecules and behavior: molecules organize themselves into neurons, and then into circuits, and it is the activation patterns of brain circuits that give rise to cognitive function and behavior. What is new in the study by Ni *et al.* [3] is the application of a neuropsychiatric drug to causally test a hypothesis formulated at the level of brain activation, where convincing persuasive causal perturbations have been most difficult to achieve.

Going forward, the approach of using neuropsychiatric drugs to causally test hypotheses about the relationship between brain activity and cognitive function should also be useful for other processes, including mood, anxiety, reward valuation, and memory. Moreover, it may be useful for brain drug discovery. Brain drug development has almost exclusively targeted molecular-level descriptions, and it has stalled: following large numbers of failures, many major pharmaceutical companies abandoned or massively reduced their brain drug development efforts about a decade ago [8]. The illustration that the mechanisms of neuropsychiatric drugs can be described at the level of brain activation patterns, which lie intermediate to molecules and behavior, leads one to naturally wonder: will targeting drugs at this level be the key to revitalizing brain drug development?

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Declaration of interests

None declared by authors.

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