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TRANSLATIONAL PERSPECTIVE

Does dopamine mediate the effects of exercise on cognition?

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Dopamine is a neurotransmitter that plays an important role in a broad range of psychological and cognitive processes such as mood and emotional regulation, motivation, executive function, learning, memory, and motor control (Ko & Strafella, 2012). Alterations in the dopaminergic activity of the brain have been shown to contribute to age-related cognitive decline and to the pathogenesis of several psychiatric and neurodegenerative disorders. Parkinson's disease, a disorder characterized by the progressive degeneration of dopaminergic neurons that is initiated in the substantia nigra pars compacta (Lotharius & Brundin, 2002), is perhaps the most paradigmatic example of the devastating effects that the reductions of dopamine activity in the brain can have on human health and behaviour.

Scientists have explored the effectiveness of different interventions to maintain or improve the dopaminergic capacity of the brain. Given its accessibility, low implementation costs, and safety, physical exercise is the non-pharmaceutical intervention that has received most attention. Animal studies have consistently demonstrated that both acute and chronic treadmill based cardiovascular exercise interventions can increase the levels of dopamine in regions of the brain such as the striatum, hypothalamus, and brainstem (Petzinger et al., 2010). Similarly, some animal studies have revealed that this type of exercise can also increase the expression of D2 dopaminergic receptors in the striatum and thus improve neurotransmission (Petzinger et al., 2010).

Despite the evidence in support of the use of cardiovascular exercise to alleviate some of the symptoms of clinical conditions characterized by the loss of dopamine such as Parkinson's disease, the degree to which this or other types of exercise can improve the dopaminergic capacity of the human brain is still a matter of study (Fisher et al., 2013). Even less is known about the exact role of this neurotransmitter in mediating the benefits that exercise has been shown to have in multiple aspects of cognition. If exercise can improve the dopaminergic activity of the human brain, is this one of the main mechanisms mediating the cognitive benefits of exercise?

A recent study in this new issue of *The Journal of Physiology* shed new light on this question (Ando, 2024). The study used an elegant multimodal approach to investigate the modulatory role of dopamine on reaction time in response to a single bout of cardiovascular exercise in healthy young individuals. In a first experiment, participants performed 40 min of supine cycling at mild-to-moderate intensity while being scanned with positron emission tomography (PET). The dopamine D2 receptor antagonist [^{11}C]raclopride was injected 10 min after the start of exercise to assess changes in endogenous dopamine release. The Go/No-Go task was completed before and after 25 min of exercise or a control condition to investigate the potential effects of exercise on reaction time.

Besides reducing reaction time, exercise also increased the release of endogenous dopamine in the dorsal striatum. This finding is novel because a previous PET study had failed to show a significant increase in dopamine after a single bout of exercise (Wang et al., 2000). Since exercise-induced increases in dopamine release in the brain are temporary, the fact that the PET assessment was performed while participants were still exercising possibly allowed investigators to capture transient increases in dopamine. The study also showed that the increase in dopamine in the putamen and caudate nucleus was correlated with a reduction of reaction time during the Go/No Go task. While the correlational design of the study does not allow causality to be inferred, these findings indicate that exercise increases dopamine and that this neurotransmitter could be an important mediator of the effects of exercise on cognition.

In a second and third experiment, the investigators used lower limb electrical stimulation applied alone or in combination with upper limb (cranking) exercise to determine if peripherally elicited muscle contractions were sufficient to improve cognition or improvements occurred only when a bout of voluntary exercise of sufficient intensity was performed. The results showed that only when electrical stimulation was accompanied by upper limb voluntary exercise performed with resistance, the reaction time of the Go/No Go task was significantly improved. Taken together, the results of these two last experiments of the study indicate that to improve cognition, exercise must involve the voluntary activation of muscles through central commands generated from higher brain centres.

Due to the lack of reliable and easy-to-use biomarkers, studying the effects of exercise on dopamine in the human brain has been challenging. An acute bout of cardiovascular exercise can transiently increase the peripheral concentration of dopamine through the sympathetic activation of noradrenergic nerves (Skriver et al., 2014). However, since dopamine does not cross the blood brain barrier, exercise-induced peripheral increases in dopamine cannot be used as a reliable surrogate of the central release of this neurotransmitter and, more importantly, to study the action of this neurotransmitter during cognitive processing. This study confirms the feasibility of using PET to investigate the effects of exercise on dopamine in the human brain and its potential implication in mediating the effects on cognition.

The results of this study lead to other new important questions that warrant future investigation. First, is dopamine the main neurotransmitter mediating the effects of exercise on cognition or other neurotransmitters also triggered by exercise (e.g. norepinephrine) are also involved? Second, would increases in endogenous dopamine release also be associated with exercise-induced improvements in other aspects of cognition such as memory and

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learning? And third, if the exercise-induced increases in dopamine release are mostly transient, how can this acute exercise experimental paradigm be adapted to investigate the chronic effects of exercise on the dopaminergic brain and their association with cognition?

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Additional information

Competing interests

None.

Author contributions

M.R.: Conception or design of the work; Drafting the work or revising it critically for important intellectual content; Final approval of the version to be published; Agreement to be accountable for all aspects of the work J.C.: Conception or design of the work; Drafting the work or revising it critically for important intellectual content; Final approval of the version to be published; Agreement to be accountable for all aspects of the work.

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Supporting information

Additional supporting information can be found online in the Supporting Information section at the end of the HTML view of the article. Supporting information files available:

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