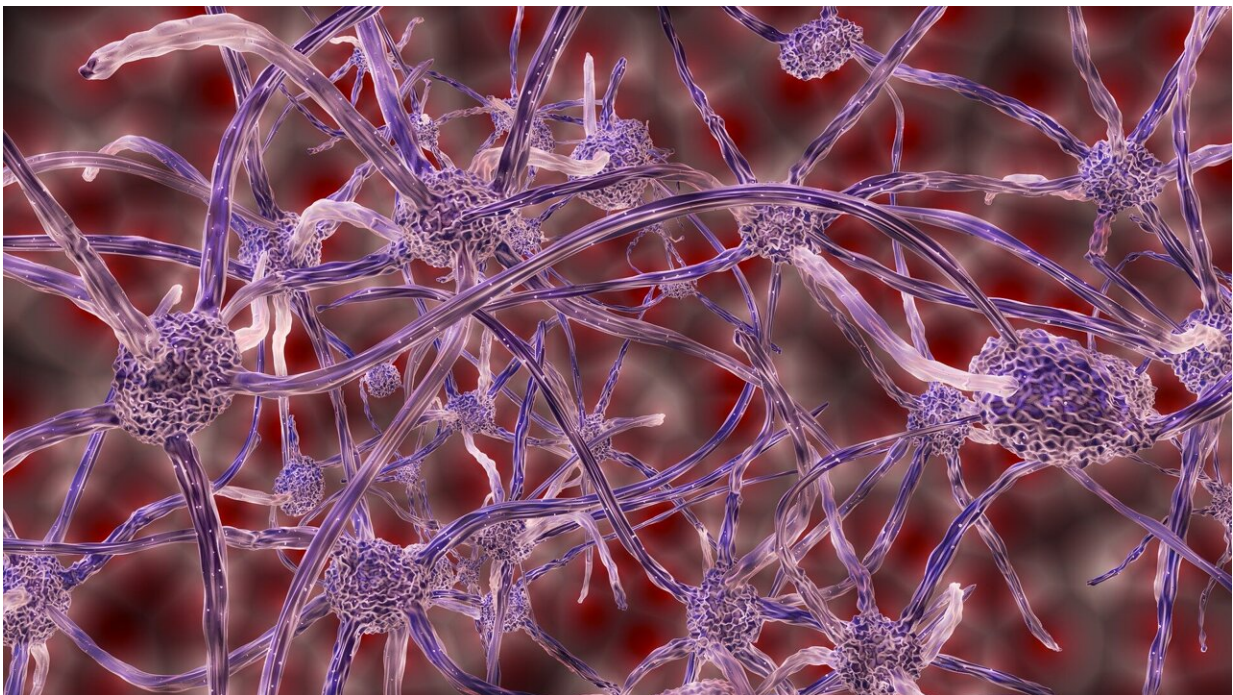


One step forward, no steps back: New study advances understanding of dopamine's role in movement

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Dopamine, a chemical messenger in the brain, is mostly known for its role in how we experience pleasure and reward. However, new research from the Champalimaud Foundation (CF) shifts the spotlight toward dopamine's critical involvement in movement, with implications for our

understanding and treatment of symptoms in Parkinson's Disease (PD).

Imagine the act of walking. It's something most able-bodied people do without a second thought. Yet it is actually a complex process involving various neurological and physiological systems. PD is a condition where the brain slowly loses specific cells, called [dopamine neurons](#), resulting in reduced strength and speed of movements.

However, there's another important aspect that gets affected: the length of actions. Someone with PD might not only move more slowly but also take fewer steps in a walking sequence or bout before stopping. This study shows that dopamine signals directly affect the length of movement sequences, taking us a step closer to unlocking new therapeutic targets for enhancing motor function in PD.

"Dopamine is most closely associated with reward and pleasure, and is often referred to as the 'feel-good' neurotransmitter," points out Marcelo Mendonça, first author of the study [published](#) in *Current Biology*. "But, for dopamine-deficient individuals with PD, it's typically the movement impairments that most impact their quality of life."

"One aspect that has always interested us is the concept of lateralization. In PD, symptoms manifest asymmetrically, often beginning on one side of the body before the other. With this study, we wanted to explore the theory that dopamine cells do more than just motivate us to move, they specifically enhance movements on the opposite side of our body."

To this end, the researchers developed a novel behavioral task, which required freely moving mice to use one paw at a time to press a lever in order to obtain a reward (a drop of sugar water). To understand what was happening in the brain during this task, the researchers used one-photon imaging, similar to giving the mice a tiny, wearable microscope. This microscope was aimed at the Substantia nigra pars compacta (SNc), a

dopamine-rich region deep within the brain that is significantly impacted in PD, allowing the scientists to see the activity of brain cells in real-time.

They genetically engineered these mice so that their dopamine neurons would light up when active, using a special protein that glows under the microscope. This meant that every time a mouse was about to move its paw or succeeded in getting a reward, the scientists could see which neurons were lighting up and getting excited about the action or the reward.

Observing these glowing neurons, the discoveries were, quite literally, illuminating. "There were two types of dopamine neurons mixed together in the same area of the brain," notes Mendonça. "Some neurons became active when the mouse was about to move, while others lit up when the mouse got its reward. But what really caught our attention was how these neurons reacted depending on which paw the mouse used."

How dopamine chooses sides

The team noticed that the neurons excited by movement lit up more when the mouse used the paw opposite to the brain side being observed. For example, if they were looking at the right side of the brain, the neurons were more active when the mouse used its left paw, and vice versa. Digging deeper, the scientists found that the activity of these movement-related neurons not only signaled the start of a movement but also seemed to encode, or represent, the length of the movement sequences (the number of lever presses).

Mendonça elaborates, "The more the mouse was about to press the lever with the paw opposite the brain side we were observing, the more active neurons became. For example, neurons on the right side of the brain became more excited when the mouse used its left paw to press the lever

more often. But when the mouse pressed the lever more with its right paw, these neurons didn't show the same increase in excitement. In other words, these neurons care not just about whether the mouse moves, but also about how much they move, and on which side of the body."

To study how losing dopamine affects movement, the researchers used a neurotoxin to selectively reduce dopamine-producing cells on one side of a mouse's brain. This method mimics conditions like PD, where dopamine levels drop and movement becomes difficult.

By doing this, they could see how less dopamine changes the way mice press a lever with either paw. They discovered that reducing dopamine on one side led to fewer lever presses with the paw on the opposite side, while the paw on the same side remained unaffected. This provided further evidence for the side-specific influence of dopamine on movement.

Implications and future directions

Rui Costa, the study's senior author, states, "Our findings suggest that movement-related dopamine neurons do more than just provide general motivation to move—they can modulate the length of a sequence of movements in a contralateral limb, for example. In contrast, the activity of reward-related dopamine neurons is more universal, and doesn't favor one side over the other. This reveals a more complex role of dopamine neurons in movement than previously thought."

Costa says, "The different symptoms observed in PD patients could be perhaps related to which dopamine neurons are lost—for instance, those more linked to movement or to reward. This could potentially enhance management strategies in the disease that are more tailored to the type of dopamine neurons that are lost, especially now that we know there are different types of genetically defined dopamine neurons in the brain."

More information: Dopamine neuron activity encodes the length of upcoming contralateral movement sequences, *Current Biology* (2024). DOI: [10.1016/j.cub.2024.01.067](https://doi.org/10.1016/j.cub.2024.01.067). [www.cell.com/current-biology/f ... 0960-9822\(24\)00104-0](https://www.cell.com/current-biology/fulltext/S0960-9822(24)00104-0)

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