Medical Xpress

Obsessive-compulsive disorder: Should I stay or should I go?

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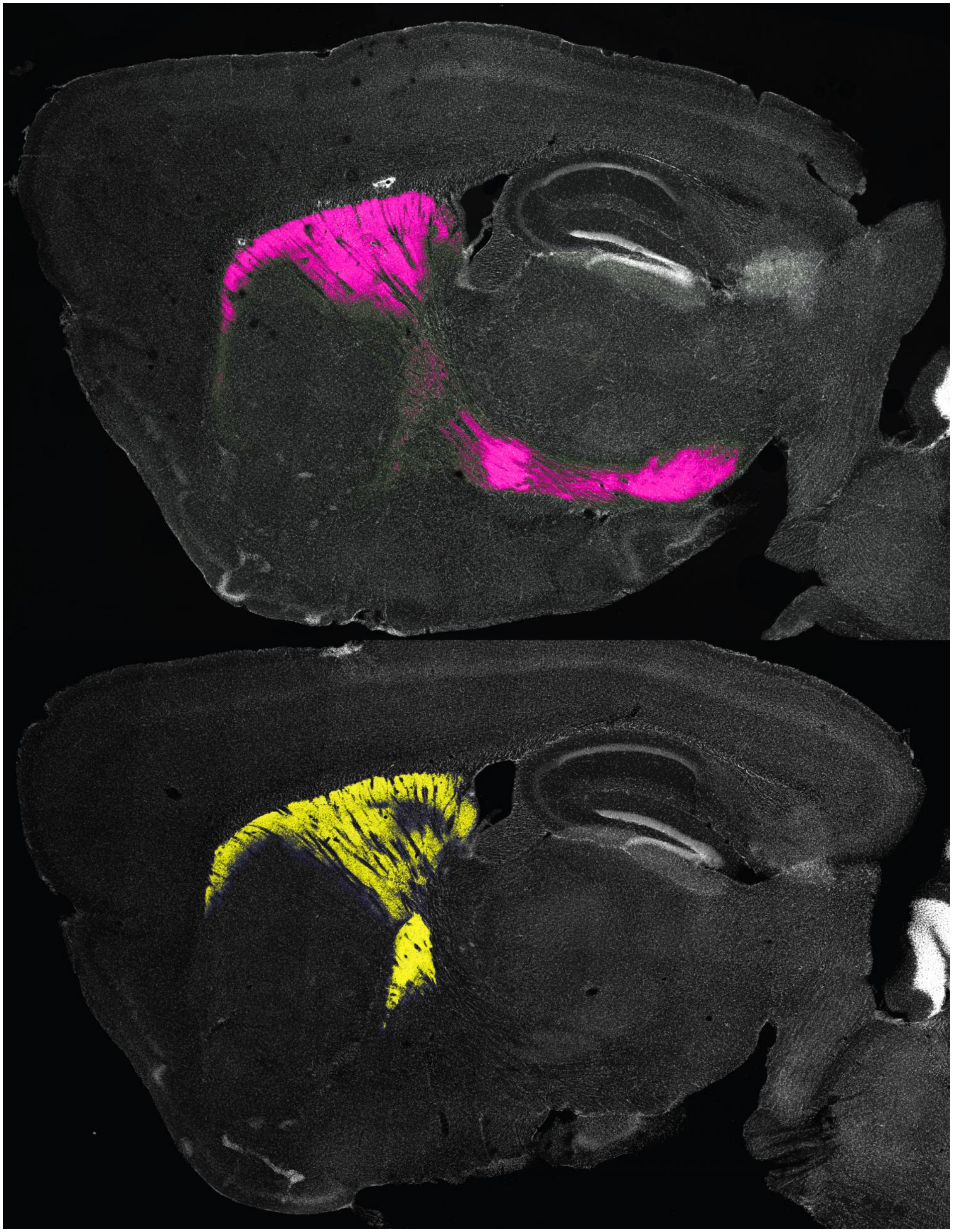


A longitudinal cut of the mouse brain with a fluorescent protein marking the direct pathway (top) and the indirect pathway (bottom) of the basal ganglia. Credit: Tecuapetla, F. et al.

People who suffer from OCD (obsessive-compulsive disorder) are unable to stop performing certain motor tasks, such as washing their hands. They can literally spend hours stuck to the sink.

At the other end of the spectrum, people with ADHD (attention deficit-hyperactive disorder), are unable to pursue the same motor action for long: they sit, they get up, they walk around, always restless, constantly doing this or that for no apparent reason.

What makes these people incapable of controlling their most everyday voluntary motions - and in some cases, their thoughts - thus enslaving them in endless repetition of the same action, or in endless change from one action to another?

A study published today (July 21) in *Cell* by a group of neuroscientists led by Rui Costa at the Champalimaud Centre for the Unknown, in Lisbon, Portugal, may contribute to our understanding of what triggers these brain disorders - and to conceive more efficient ways to treat these and other neuropsychiatric diseases.

Experts have long thought that the process of selecting a given action is mediated, in the brain, by two neural circuits, known as the direct and indirect pathways and located in an area of the brain called the basal ganglia.

"All the diseases that affect the basal ganglia - Parkinson's, Huntington's, Tourette's [tic disease] - have something in common", says Costa: "Patients cannot control their movements".

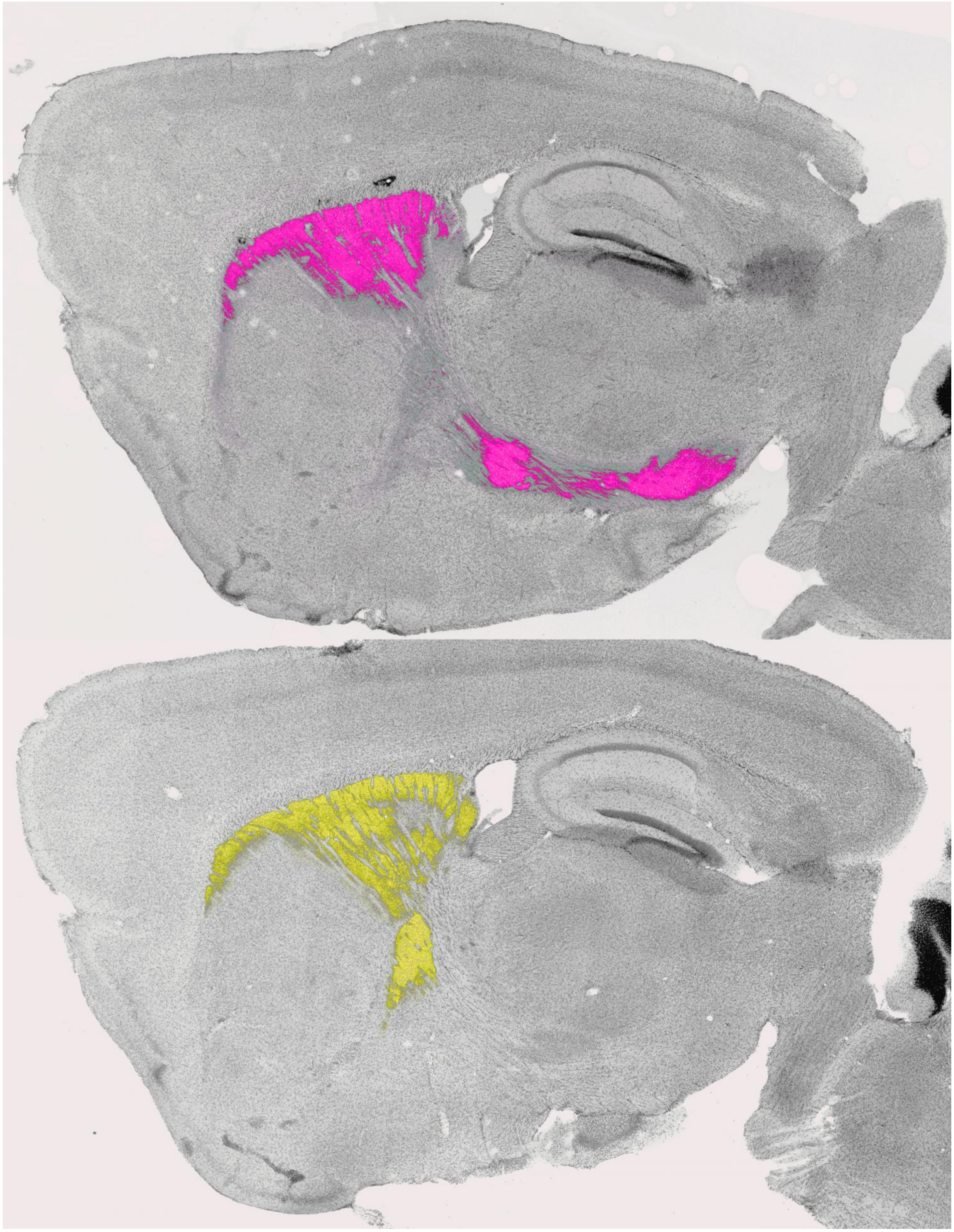
According to him, it is also very likely that the repetitive gestures seen in autism and the pervasive repetitive thoughts that plague patients with OCD and psychosis are linked to anomalous activity in these circuits.

So the fundamental question boils down to determining how, in normal conditions, those circuits interact to allow movements to flow smoothly and to ensure that the choice of actions, especially motor actions, to be timely and not random.

Outdated dichotomy

According to the theoretical model that up to now described the respective functions of the two pathways, activating the first one triggered action, while activating the second inhibited it. This view was first challenged by a study published by Costa in 2013 in Nature. Since then, it has also been questioned by other labs in several countries, losing terrain in light of experimental results obtained in the past few years.

In particular, in April this year, Costa's team published, in *Current Biology*, a paper showing that these pathways are not always competing with each other, but sometimes function simultaneously to promote different outcomes.



A longitudinal cut of the mouse brain with a fluorescent protein marking the direct pathway (top) and the indirect pathway (bottom) of the basal ganglia. Credit: Tecuapetla, F. et al.

"It's not a question of good cop, bad cop", says Costa. "It's not simply one pathway saying 'do this' and the other saying 'don't do this'. Reality is more complex than that and both pathways are required to promote or to interrupt an action."

The work published in Cell - whose first author is Fatuel Tecuapleta, now working at Universidade Nacional Autónoma de México, in Mexico City - now proposes an alternative model of the joint functioning of the two pathways that explains the experimental data, including that based on the classical model.

For six years, the team has been doing experiments using optogenetics, a technique that makes it possible to selectively activate each pathway in the mouse brain.

In a series of experiments, the animals were put inside an experimental arena where they had to press a lever around eight times to obtain food. During several weeks of training, they learned to execute a sufficient number of lever-presses to elicit reward.

After completing the training, the team started submitting the mice, during the performance of the task, to bursts of high-frequency light pulses so as to strongly activate either the direct or the indirect pathway.

Veto power

What they found was that, when the direct pathway is disrupted, the mice stop pressing the lever and "freeze".

On the contrary, when the indirect pathway is activated, the animals don't stay put: interrupting their action, they move away from the lever and start exploring other parts of the arena. It's as if, although perfectly trained to perform the task, they suddenly decided to do something else, namely go for a walk.

According to Costa, these results suggest that the role of the direct pathway is to sustain action, while the role of the indirect pathway is to allow - or prevent - switching from one action to another. "What we see is that, for different reasons, the direct pathway 'tells' the animal what action he must continue to perform, while the indirect pathway allows the performance of that action to continue, approves it - but also has the power to stop allowing it, that is, the power of veto."

This corresponds to what specialists currently understand about the underlying mechanisms of diseases that affect the basal ganglia. Says Costa: "It is thought that in OCD, which is characterized by repetitiousness, it is the direct pathway that is overly active, thus promoting the repetition of actions. On the other hand, ADHD, characterized by erratic and unpredictable gestures, has to do with dysfunctions of the indirect pathway".

The new model could have therapeutic implications. Today, Parkinson's disease, for instance, is treated with a drug, L-Dopa, that activates the direct pathway and inhibits the indirect one. One of the consequences of the treatment is that patients develop uncontrollable repetitive movements. And haloperidol, a well-known antipsychotic drug, which acts by strongly activating the indirect pathway, leads to undesirable motor and cognitive side effects, with patients feeling "slowed down" in their movements and thoughts.

"Instead of massively activating one of the two pathways, it might be possible to treat the disorders of the basal ganglia with weaker modulators of both circuits. This could be a more efficient alternative", says Costa. "It isn't a question of inhibiting or activating one of them, but of restoring the balance between them.

Provided by JLM&A, SA