

Motivation is affected by oxidative stress, but nutrition can help

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In life, motivation can be the difference between success and failure, goal-setting and aimlessness, well-being and unhappiness. And yet, becoming and staying motivated is often the hardest step, a problem

which has prompted much research.

A very small part of that research has looked into the question of metabolism. "Do differences in metabolites in the [brain](#) affect our capacity for motivation?" asks Professor Carmen Sandi at EPFL's School of Life Sciences. "If that is the case, could nutritional interventions that can affect [metabolite levels](#) be an effective vehicle to improve motivated performance?"

Sandi's group, with their colleagues at the Nestlé Institute of Health Sciences, have now published a study that shines the first light into answering that question. The researchers focused on an area deep into the brain called the "[nucleus accumbens](#)", which is known to play a major role regulating functions like reward, reinforcement, aversion, and not least, motivation.

Metabolism and oxidative stress in the brain

The idea behind the study was that the brain itself—like all tissues in our body—is subjected to constant [oxidative stress](#), as a result of its metabolism.

What is oxidative stress? As cells "eat" various molecules for fuel, they produce a number of toxic waste products in the form of highly reactive molecules collectively known as "oxidative species". Of course, cells have a number of mechanisms in place to clear oxidative species out, restoring the cell's chemical balance. But that battle is ongoing, sometimes that balance is disturbed and that disturbance that's what we call "oxidative stress".

The glutathione connection

The brain then is often subjected to excessive oxidative stress from its neurometabolic processes—and the question for the researchers was whether [antioxidant levels](#) in the nucleus accumbens can affect motivation. To answer the question, the scientists looked at the brain's most important antioxidant, a protein called glutathione (GSH), and its relationship to motivation.

"We assessed relationships between metabolites in the nucleus accumbens—a key brain region—and motivated performance," says Sandi. "We then turned to animals to understand the mechanism and probe causality between the found metabolite and performance, proving as well that nutritional interventions modify behavior through this pathway."

Tracking GSH in the nucleus accumbens

First, they used a technique called "proton [magnetic resonance spectroscopy](#)," which can assess and quantify the biochemistry in a specific region of the brain in a non-invasive way. The researchers applied the technique to the nucleus accumbens of both humans and rats to measure the levels of GSH. They then compared those levels to how well or poorly their human and animal subjects performed in standardized, effort-related tasks that measure motivation.

What they found was that higher levels of GSH in the nucleus accumbens correlated with better and steady performance in the motivation tasks.

GSH levels and motivation

But correlation does not imply causation, so the team moved on to live experiments with rats that were given micro-injections of a GSH

blocker, downregulating the synthesis and levels of the antioxidant. The rats now showed less motivation, as seen in a poorer performance in effort-based, reward-incentivized tests.

On the contrary, when the researchers gave rats a nutritional intervention with the GSH precursor N-acetylcysteine—which increased GSH levels in the nucleus accumbens—the animals performed better. The effect was "potentially mediated by a cell-type specific shift in glutamatergic inputs to accumbal medium spiny neurons," as the authors write.

Can nutrition or supplements help motivation?

"Our study provides novel insights on how brain metabolism relates to behavior and puts forward nutritional interventions targeting key oxidative process as ideal interventions to facilitate effortful endurance," conclude the authors. The study's findings "suggest that improvement of accumbal antioxidant function may be a feasible approach to boost [motivation](#)."

"N-acetylcysteine, the nutritional supplement that we gave in our study can also be synthesized in the body from its precursor cysteine," says Sandi. "Cysteine is contained in 'high-protein foods', such as meat, chicken, fish or seafood. Other sources with lower content are eggs, whole-grain foods such as breads and cereals, and some vegetables such as broccoli, onions, and legumes."

"Of course, there are other ways beyond N-acetylcysteine to increase GSH levels in the body, but how they relate to levels in the brain—and particularly in the nucleus accumbens—is largely unknown. Our study represents a proof of principle that dietary N-acetylcysteine can increase brain GSH levels and facilitate effortful behavior."

The paper has been accepted for publication in *eLife*.

More information: Ioannis Zalachoras et al, Glutathione in the nucleus accumbens regulates motivation to exert reward-incentivized effort, (2022). [DOI: 10.1101/2022.02.14.480343](https://doi.org/10.1101/2022.02.14.480343)

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