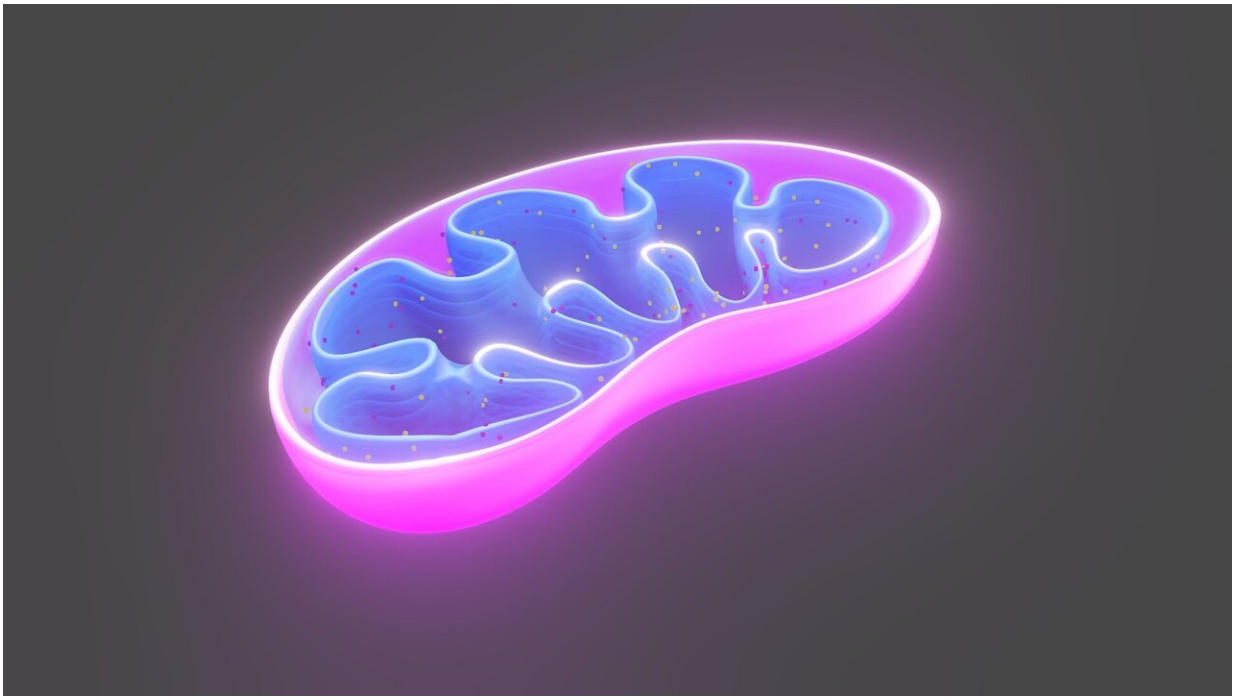
Exploring the mind-mitochondria connection

September 20 2023



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As befits the child of a scientist, Martin Picard's young son, 3, is already learning about biology with an age-appropriate textbook, "Cell Biology for Babies." Picard winces a little whenever the book calls mitochondria the "powerhouses of the cell" but figures he has plenty of time as his son grows older to explain why the tiny organelles are much more than simple energy sources.

Picard is a leading proponent of mitochondrial psychobiology (a phrase he coined), an emerging field that examines how psychological states like stress influence mitochondrial functions, which in turn influence mental and physical health.

"The powerhouse analogy is outdated and one-dimensional and can impede science by limiting researchers' perceptions of what mitochondria can do," says Picard, associate professor of behavioral medicine in psychiatry and neurology.

Among other roles, mitochondria are now known to trigger cell death when needed, synthesize all circulating steroid hormones related to reproduction, and command the nucleus to turn on or turn off genes.

"It makes more sense to think of mitochondria as the information processors of the cell," he says. "They are equipped with a surprisingly wide variety of receptors to sense what's going on in the cell, they integrate all this information, and they then tell the nucleus and other organelles what to do to maintain the health of the organism."

It's hard not to admire these crafty organelles, hundreds or thousands of which are packed into some cells.

And for Picard, it's not a stretch to think that mitochondria may have a bigger impact than the genome on our mental and physical health: "Genes are inert. Mitochondria are dynamic and give us the ability to sense and perceive, integrate information, adapt, and thrive."

Mitochondria, stress, and health

Though he's not a clinician, Picard spends half a day in a Columbia neurology clinic with Michio Hirano, MD, who specializes in treating people who are born with mutations or deletions in their mitochondrial

genome.

Mitochondrial diseases are rare, but they show that cognitive and psychiatric issues can arise if there's something wrong with mitochondria.

That stress could cause subtle changes in mitochondria that affect mental health is a hypothesis that Picard has been testing since he joined the Columbia faculty in 2015, quickly building a lab with an array of interdisciplinary research projects.

The latest results from the lab are starting to back up the idea.

In a study published in August and highlighted in *Nature*, Picard's team found that stress can alter the activity of the brain's mitochondria and predict subsequent anxiety-like and social behaviors in mice. But not all brain mitochondria had the same impact. Only changes in a specific network of mitochondria, mostly in the cortex and striatum, correlated with anxiety while other networks of mitochondria showed no to little connection with behaviors.

Picard is now working to understand the diversity of mitochondria in the human brain to see how networks of the organelles may be affecting mental health in people.

Other research in people conducted by Picard and collaborators at UCSF suggests that positive feelings may have effects on mitochondria that improve health. In one study, emotions people felt on Tuesday nights influenced the energy transformation capacity of mitochondria in blood immune cells measured on Wednesdays. The study provided the first directional evidence that mood may affect mitochondria. Picard says if the finding can be verified—the findings still need to be replicated in a bigger study—the next question is to ask if the same effect happens in

the brain. Caroline Trumpff, Ph.D., assistant professor in psychiatry who works in Picard's group, is now testing that question in post-mortem human brains.

A focus on health, not disease

In hindsight, it seems that Picard, a native of Montreal, was destined to take a fresh look at all things biological. "My mom's a nurse who started a company to do home care," he says. "She was well-tuned to the effect of psychological factors, such as social support, on healing."

Toward the end of high school, Picard, a hockey and cycling enthusiast, became interested in exercise physiology and sports psychology. But his initial undergraduate studies of physiology left him wanting. "There was nothing about what connects the mind and the body," he says.

During a short break after college, one of his mentors—a mitochondrial biologist—persuaded him to join her lab by giving him the freedom to pursue outside interests, be it cycling or integrative medicine. Picard's doctoral thesis focused on the role of mitochondria in aging, yet he also carved out time to study systems biology and psychosocial oncology.

These experiences and the emerging science of mitochondrial psychobiology have Picard questioning the dominance of genes in biomedical research, a concept he unpacks in a TEDx talk.

"For the most part, genetics do not explain why or when one person becomes ill and another stays healthy," he says. "For most disorders, disease risk is mostly attributable to behavioral, psychosocial, and environmental factors."

What keeps people healthy may come down to what keeps their mitochondria healthy, Picard speculates. "The reason we have a heart

and lungs is oxygen delivery," he says. "And what needs oxygen? Mitochondria, of course. You could argue that over the eons, mitochondria built an infrastructure—the human body—to feed themselves."

More information: Ayelet M. Rosenberg et al, Brain mitochondrial diversity and network organization predict anxiety-like behavior in male mice, *Nature Communications* (2023). DOI: 10.1038/s41467-023-39941-0

Brain mitochondria predict a mouse's stress level, *Nature* (2023). DOI: 10.1038/d41586-023-02575-9

Provided by Columbia University Irving Medical Center