The origin of brain fatigue

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A study reports that the great fatigue caused by intense brain work is due to an accumulation of toxic metabolites in the prefrontal cortex of the brain.

The human brain is truly an evolutionary marvel, a unique assembly of several billion neurons that manage to generate brain activities as complex as abstract thought and language, unique to our species.

These functions, however, come at an energy cost: although it represents only about 2% of body weight, the brain alone consumes about 20% of all the energy used for the functioning of the entire human body.

At equal weight, the brain is therefore 8 to 10 times greedier than other organs (on average) and is therefore particularly vulnerable to metabolic fluctuations.

GREEDIER, EVEN AT REST

Although a significant portion of the energy consumed by the brain is due to the electrical activity of neurons, several observations suggest that its basic metabolism contributes significantly to its constant need for energy.

For example, in patients who are comatose or in a vegetative state, whose electrical activity of the brain is at a strict minimum, the energy consumption is only reduced by half and remains much higher than for other organs.

According to a recent study, this constant demand for energy is due to a leak at the level of the vesicles where the neurotransmitters of the synapses (the region where the neurons communicate with each other) are stored (1).

It seems that even in the absence of electrical stimulation, these synaptic vesicles continuously lose hydrogen ions (protons) and must therefore constantly use ATP to pump these ions back inside the vesicles, even at rest.

Since the brain contains millions of billions of these synapses, this energy expenditure is very significant and represents a good part of the energy required for brain function.

MENTAL FATIGUE

Fortunately, energy consumption by the brain is extremely well controlled, so that it remains constant and is not significantly affected by cognitive processes.

How, then, to explain the well-documented mental fatigue that occurs after intense intellectual effort? Unlike a computer that can analyze data continuously, humans become fatigued after performing complex mental processes for a while, so even the brightest among us make silly mistakes when this mental fatigue sets in.

To better understand this phenomenon, researchers used magnetic resonance to compare the biochemistry of the brain between people who performed difficult cognitive work for several hours and another group, subjected to an easier task (2).

They observed that in addition to the physical signs of fatigue (reduced dilation of the pupil), the people who had made the mental efforts had higher levels of glutamate at the level of the synapses of the prefrontal cortex (the site of different higher cognitive functions such as language, working memory, reasoning). This accumulation of glutamate plays a role in cognitive fatigue, as it is well established that its presence can interfere with the transmission of information by neurons.

In other words, feeling exhausted after a demanding mental effort is a completely normal phenomenon, caused by the accumulation of toxic metabolites produced by the metabolism of neurons involved in cognition.

As with the physical fatigue associated with sport, which serves to signal to the body that it must slow down to avoid injury and allow the muscles to recover, the fatigue caused by a "brain sport" can therefore be considered as a protective reaction to preserve brain integrity.

Fortunately, these toxic metabolites are eliminated from the brain during sleep, so it is possible to recover quickly from this fatigue and regain our mental acuity (3).

(1) Pulido C and TA Ryan. Synaptic vesicle pools are a major hidden resting metabolic burden of nerve terminals. Sci. Adv. 2021 ; 7 : eabi9027.

(2) Wiehler A et al. A neuro-metabolic account of why daylong cognitive work alters the control of economic decisions. Curr. Biol. 2022 ; 32: 3564-3575.e5.

(3) Xie L et al. Sleep drives metabolite clearance from the adult brain. Science 2013; 342: 373-377.

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