



A research lead for prevention: Omega-3 Supplementation.



Leader

PICRIs (Partnerships between Institutions and Citizens for Research and Innovation) were launched in 2005 by the Ile-de-France region to promote research programs based on a close collaboration between public research laboratories and non-profit organizations stemming from civil society. The objective is to produce common knowledge base and to share it with citizens. PICRIs are part of a wider scientific and technical democratization movement.

Through this structure, the region brings financial support as a priority to young researchers, by contributing towards doctoral and postdoctoral grants. In this way, La Fondation Motrice, along with Pierre Gressens, Sophie Layé and Agnès Nadjar's laboratories, was able to get funding for Quentin Leyrolle's research project, regarding the interest of nutrition strategies to prevent neurodevelopmental disorders. The foundation will also communicate on the project's progress and results. This letter aims to summarise these.

Dr Nathalie Genès, Scientific Project Manager at La Fondation Motrice

A research project that opens new avenues to prevent Cerebral Palsy: an obvious choice for Quentin Leyrolle, in his first year PhD within the laboratories NutriNeuro and UMR 1141.



Why did you chose this subject for your PhD ?

During my first internship in MD, where I was able to observe the laboratory's approach, I wanted to study the

possible effects of nutrition on brain. When I was offered the opportunity to continue this work in the context of a PhD, I accepted without hesitation: I was looking for a subject with a practical approach, which is the case here, thanks to my supervisors, neurologist Pr Pierre Gressens, and professionals of integrated research Dr Sophie Layé and Agnès Nadjar

How does your collaboration in this project take form?

I benefit from my supervisors' availability and from the technical staff's expertise in two laboratories (UMR 1141Neuroprotection of the developing brain in Paris, and UMR NutriNeuro in Bordeaux). On a daily basis, I share my time between bibliographical research and scientific and technical observation on the one hand, and experiments defined within the framework of the project on the other hand. I find this job very varied and very rich.

I did not have to look for funding as my supervisors have been handling that aspect so far. But it is crucial ! Without funding, you find yourself cut off!

And after your PhD, what are your plans ?

I would like to keep studying the role of microglia in brain development (see following pages). At any rate, I would like to stay in translational research (the alliance between basic and applied research). To this aim, I must find a post-doctoral fellowship abroad before I can come back and look for a job in France. It's a long way to go !

Acting on cognition: what could bring nutritional supplementation ?

Improving brain function with nutriments is a promising research path. Dr Sophie Layé, research director in the laboratory Nutrition and Integrated Neurobiology (University Bordeaux 2) tells us why.

The relationship between nutrition and health is now well known, translating into official recommendations across the board, for instance with the famous '5 A DAY' campaign. But if the beneficial effects of certain nutriments to prevent diseases are well established, there is still much to find out about the biological mechanisms at play.

In our laboratory, we will study in particular the role of molecules called 'polyunsaturated fatty acids', essential to brain function, brought to man through nutrition.

Polyunsaturated fatty acids consist of two nutriments groups, omega-3 and omega-6 (see the chart opposite) which, once metabolised in the body, are represented notably by arachidonic acid, EPA and DHA. Their proportion in the body are identical to the proportion of omega-3 and omega-6 absorbed in one's diet.

Preclinical studies showed a strong correlation between the metabolism of these fatty acids on the one hand and cognition and mood on the other hand, namely:

- a decrease in consumption of fatty fish, sources of DHA, leads to an increase in the prevalence of depression and age-related cognitive decline ;
- **and conversely, patients with depression or elderly subjects suffering from cognitive troubles show a decrease in the rate of omega-3 in blood and brain.**

Studying this mechanism led us to ask questions on the influence of diets on cerebral functions.

Polyunsaturated acids are found in large quantities in the brain, where they play an important role. Indeed they are incorporated at the level of the neurone membrane and the glial cells that surround them, and they impact on neurotransmitter receptors functionality located in this membrane. Besides, omega-3 derivatives like DHA have pro-inflammatory activities. So it could be asked whether variations in proportions of omega-3, compared to the omega-6 absorbed, can impact on brain activity.

A first study showed that a decrease in proportion of omega-3 compared to omega-6 in one's diet led to the same unsteadiness at the level of the neurons membranes, with consequences on brain function:

- an alteration of spatial memory and cerebral plasticity
- an increase in stress.

Thus it should be asked whether these polyunsaturated fatty acids can have a protective role. A second study indicated that an omega-3 enriched diet led to an increased rate of DHA in the central nervous system, which helps protect against chronic stress and behavioral alterations.

So it can be said that polyunsaturated play a major role in brain function. Very few omega-3 can lead to alterations in cerebral plasticity as well as cognitive troubles and mood swings. Raising their proportion, on the contrary, can help protect these functions.

WHERE TO FIND OMEGA-3 AND OMEGA-6:

Omega-3: walnuts ; fatty fish (salmon, sardines, ...) ; green leafy vegetables (spinach, green beans...) ; linseed and linseed oil ; colza oil

omega-6: sunflower oil and most vegetable oils ; meat ; eggs

The World Health Organization (WHO) recommendations for the whole population is to absorb a proportion of 1 omega-3 for 5 omega-6. While our occidental diet is unsteady, with a proportion of 1 omega-3 for 10 omega-6 (until 30 in some countries).

Could maternal omega-3 supplementation during pregnancy protect the child's brain ?

A study coordinated by Dr Agnès Nadjar, researcher and lecturer in the laboratory Nutrition and Integrated Neurobiology (University Bordeaux 2).



Infection during pregnancy is an important risk factor for Cerebral Palsy.

The mechanism is the following: maternal infection generates an inflammatory reaction in the foetal compartment, which leads to the development of immature neural networks in the fetus, and later to behavioural deficits. So far we don't know enough about the intervening factors in this mechanism, but we recently discovered the role played by microglia, the cells surrounding neurons who represent the first immunity reserve of the central nervous system.

Microglia intervenes in the functional brain development by participating to the maturation work of the neuronal circuits. Hit by inflammation, microglia doesn't do its job of selecting neuronal circuits correctly, which has functional consequences on the adult brain.

We are interested in the role that might play omega-3 and their anti-inflammatory power in preserving this work done by microglia.

Indeed our laboratory already demonstrated that omega-3 are preferentially targeting microglia by keeping it in homeostatic state.

First tests have enabled us to observe that an omega-3 enriched diet in mice during the gestation period lowered the inflammatory response in the mother and in the foetus. Thus we were able to demonstrate that protective effects of omega-3 brought in the perinatal period continued at adult age.

By studying precisely the microglia's activity, we were able to see that the supply of omega-3 during the phase of brain development was protecting the microglia's activity regarding the maturation of neuronal circuits, and thus even in a situation of prenatal inflammation.

We must now confirm these results, but an omega-3 enriched diet for the mother during pregnancy is a serious lead to preserve optimal cognitive performance, by protecting the microglia's activity, and thus the development of functional neural networks, from the harmful effect of an inflammation.

GLOSSARY

Arachidonic Acid: omega-3 polyunsaturated fatty acid

DHA: docosahexaenoic acid

EPA: Eicosapentaenoic acid

DHA and EPA are omega-3 polyunsaturated fatty acid found in oily fish and fish oil.

Omeostatic state: state of stability in normal values

Microglia: microglia is a set of microglial cells ; it is part of the nervous central system and its role is to provide immunity.

From experimental to therapeutics: what nutrition strategies for individuals ?



Can the first results from the study apply to people ? Interview with Pr Pierre Gressens, director of the laboratory of neurosciences UMR 1141 (Inserm-Hospital Robert Debré, Paris) and professor of Fetal and Neonatal Neurology in King's College (London, United Kingdom).

The work done by the laboratory NutriNeuro seems to propose a great lead to prevent Cerebral Palsy: raise the omega-3 supply. Is that so simple ?

To answer your question, one must first remind some **fundamental mechanisms** when cerebral palsy occurs. If you focus on premature children, who are a population at risk, we observed that their brain structure presented:

- a defect in myelin (a substance composed essentially of lipids surrounding nervous cells),
- altered connectivity between the different brain regions,
- a problem with synapsis or neurons arborization.

One of the main hypotheses regarding the causes of cerebral palsy is intrauterine infection provoking an inflammation in the fetus, leading to preterm birth and brain defects. Knowing that microglia is present very early in the brain, we made the hypothesis that it plays a role

in the genesis of brain lesions, by generating myelination defects and synaptic defects when, hit by inflammation, it doesn't do correctly its job of synaptic pruning (see previous pages).

To try to modulate microglial activity and favor its restorative activity rather, we got interested in a nutrition strategy in individuals. Studies showed that:

- an alteration of lipids' metabolism increased the risk of brain defects
- premature fed with breast milk or a substitute rather than cow's milk, the first ones containing more DHA and omega-3, have less white matter lesions
- children fed with breast milk or a substitute rather than cow's milk, at two years old, show an improvement of their cerebral imaging and a better psychomotor development.

In this line, the first results of an ongoing study seem to show that premature supplemented with oily fish also present an improved psychomotor prognosis.

So there is a body of evidence indicating that an **omega-3 supplementation could probably be beneficial to premature**.

Should this supplementation limit itself to the period around birth ?

It's a question, since we discovered that contrary to what we thought, cerebral palsy was not « fixed » after the acute phase, but had a posterior phase that can last a few months or a few years during which the situation can degrade, but also when we might be able to intervene.

We observed a persistence of brain inflammation a few years after birth, that might be caused by a « memory » of the inflammation in microglia.

So it can be asked whether an omega-3 supplementation to erase this memory from microglia is an interesting lead.

But before we start clinical trials, we must better define what we call the metabolic targets (only omega-3 ?) as well as the window of opportunity : neonatal, perinatal, or later ?

More information on www.lafondationmotrice.org

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