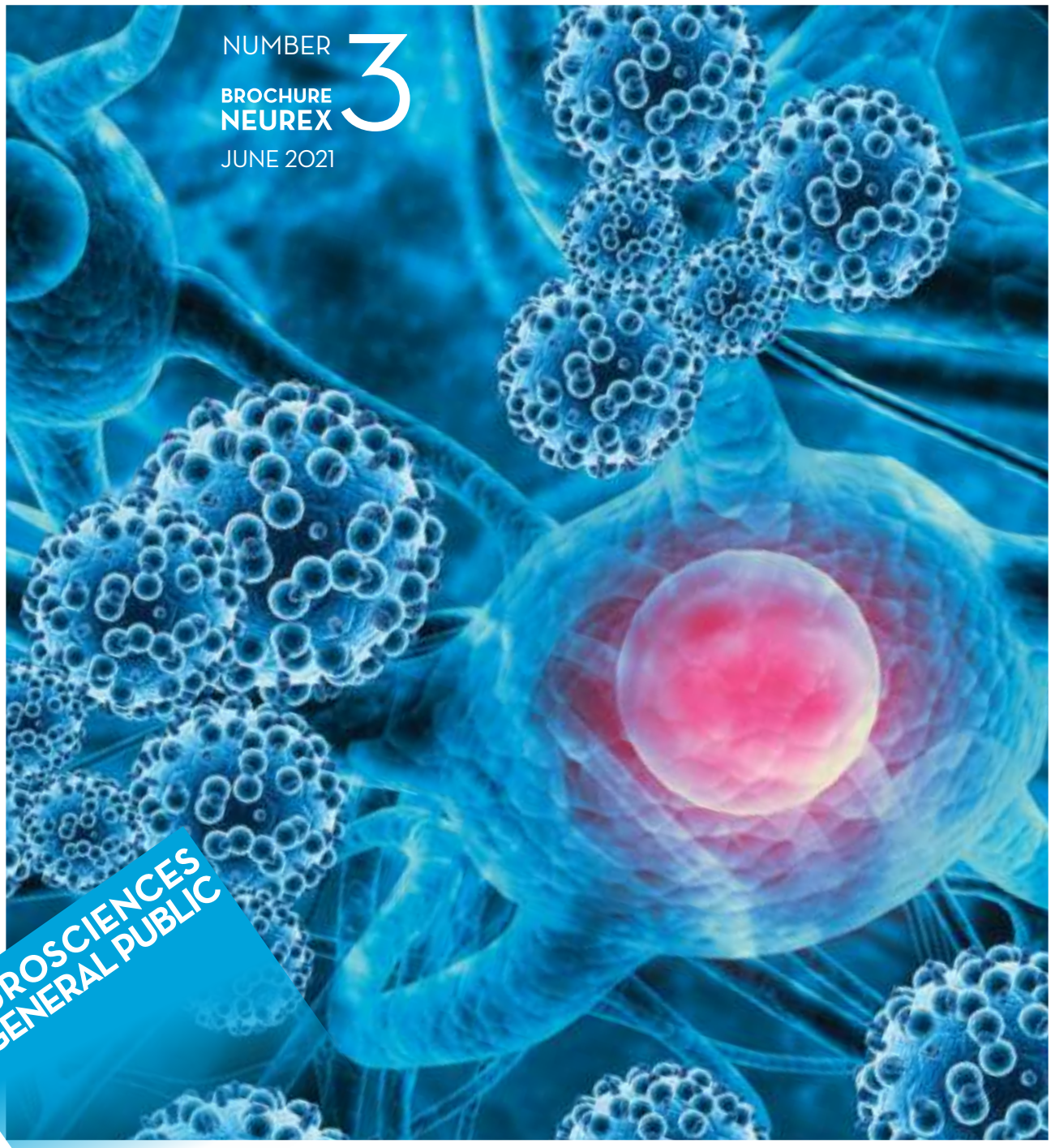

NUMBER 3

BROCHURE NEUREX

JUNE 2021

NEUROSCIENCES & GENERAL PUBLIC

COVID19, VIRUSES AND BRAIN DISEASES

PASCALE PIGUET

Interneuron

A Neurex initiative

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neuroscience·upper·rhine·network

NEUREX is the neuroscience network of the Upper Rhine Valley. It brings together the neuroscience research laboratories of the universities of Basel (Switzerland), Freiburg (Germany) and Strasburg (France).

As part of its new trinational research project InterNeuron, Neurex coordinates and supports both research efforts and training in the field of neuroscience. Through this project, expertise can be shared among neuroscientists and physicians in this trinational area. The neurosciences, including neurology and psychiatry, are facing one of the greatest challenges of the 21st century: the fight against neurological and psychiatric disorders.

The Neurex brochures are an initiative of Neurex, the Upper Rhine Valley Neuroscience Network, to familiarise the general public with topics from the neurosciences. In these brochures, a question related to the brain is discussed and the current hypotheses/knowledge on this topic is described for the general public.

For a full description of Neurex activities, including other neuroscience & public initiatives, please visit

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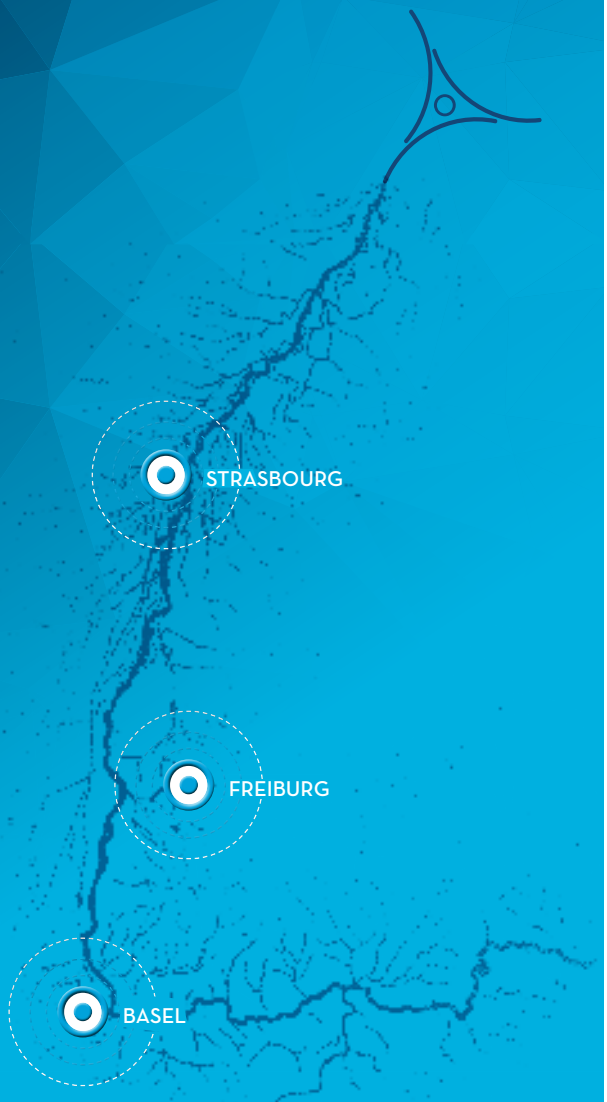


SUMMARY

The Covid19 pandemic that arose in December 2019 remains challenging for clinicians and researchers and has reserved its share of surprises. First considered as a respiratory virus, the coronavirus which spread worldwide was however soon observed to induce symptoms, suggesting that it may affect brain function in some patients. Moreover, a significant proportion of patients fails to fully recover after an infection, suffering from a bunch of sequelae called 'Long Covid'. While some viruses are known to specifically target the brain and nervous system (such as the infamous polio and rabies viruses), other viruses primarily affect other organs, inducing, for example, respiratory, gastrointestinal or other symptoms.

However, past pandemics have provided clues suggesting that some viruses –considered as not targeting the brain– may also cause neurological and/or psychiatric disorders in some patients. Moreover, it turns out that some common infections with –supposedly harmless– viruses can induce serious consequences for the brain, raising the following question: could it be that beyond the visible effects, viruses also exert hidden effects, sometimes after remaining silent for years? Such hypotheses exist for common neurodegenerative diseases which affect our memory, motricity and thoughts, like Alzheimer's disease, Parkinson's disease, multiple sclerosis and schizophrenia. If correct, these diseases could be regarded as the result of late payment of an unpaid bill during youth...

What about the coronavirus SARS-CoV2 that caused the Covid19 pandemic? What characterizes viruses in general, and SARS-CoV2 in particular? Why are some infected people more vulnerable than others? Why and how might SARS-CoV2 cause brain symptoms? Based on examples, this booklet illustrates how viruses may be compared to invading robots, endowed with the ability to evolve: even though elementary at a first look, they are able to defeat very advanced defense systems such as those that protect our brain, to hack into our cells, and potentially exert effects so late, that their cause might remain undetected.

It also considers the question of whether SARSCoV2 might also induce late brain diseases, how, and highlights the importance of assessing the potential impact of Covid19 on brain diseases on the long-term. One obvious consequence being the necessary change of view on the treatment of viral infections considered as benign or cured...

NUMBER 3

BROCHURE NEUREX

COVID19, VIRUSES AND BRAIN DISEASES

COVID19 & BRAIN DISEASES

The outbreak last December in China of a new, till then unknown coronavirus, has highlighted the limits and vulnerabilities of the health systems worldwide. First considered as a geographically restrained problem, the virus has demonstrated its powerful ability to spread between humans, triggering a pandemic (Covid19, Coronavirus Disease 2019) responsible for nearly 4,000,000 deaths worldwide, until June 2021.

At the origin of this pandemic, some particles of infinite smallness: a newly discovered virus, SARS-CoV2. Although initially thought to mainly induce respiratory effects, SARS-CoV2 has been shown to be capable of invading other systems. Among the potential targets of the virus, an unexpected one: the brain (§ 3 page 17)...

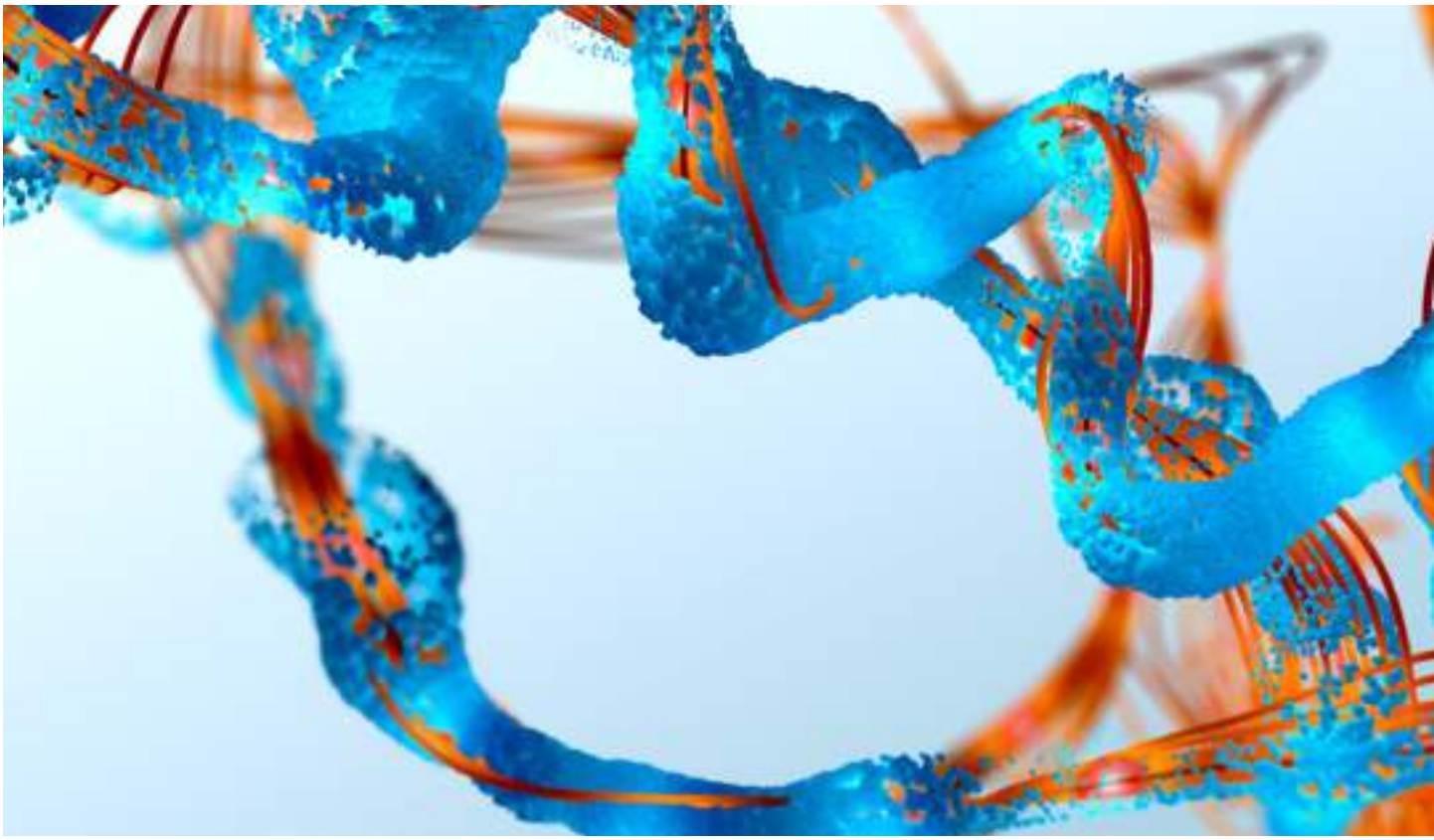
But were such effects on brain and nervous system really unexpected? The history of biomedicine illustrates that the suspected intricate relationship between viral infections and brain disorders is not a new topic ... Viruses may trigger acute[1] attacks of the brain and nervous system, inducing immediate effects. But viruses are also able to establish latent infections, opening the door to the occurrence of late effects. Because of the long delay that separates potential late effects from the initial infection, the resulting disorders may be difficult to diagnose, and their cause rarely traced back to an ancient infection. Could viral infections underlie the brain diseases that affect our memory, motor skills and thoughts, like Alzheimer's, Parkinson's, Multiple Sclerosis or schizophrenia? Some scientific hypotheses suggest that even viruses considered as harmless might indeed be a time bomb, at least in some susceptible people.

What is a virus and how might supposedly harmless viruses induce more harm than previously thought? What tricks do viruses use to enter the highly-protected brain? What is SARS-CoV2 in particular? Could it potentially affect our brain and nervous system, inducing late neurological and psychiatric diseases? Could even the asymptomatic[2] patients be at risk of such brain effects? Journey into a fascinating world where we will see that viruses have more than one trick up their sleeve...

(1)
Acute conditions occur suddenly, have rapidly developing symptoms, and are limited in their duration, while chronic conditions are longlasting. They develop and may worsen over time.

(2)
Patients who have been infected by the virus but did not demonstrate symptoms or signs of infection.

§1 LIVING CELLS AND VIRUSES

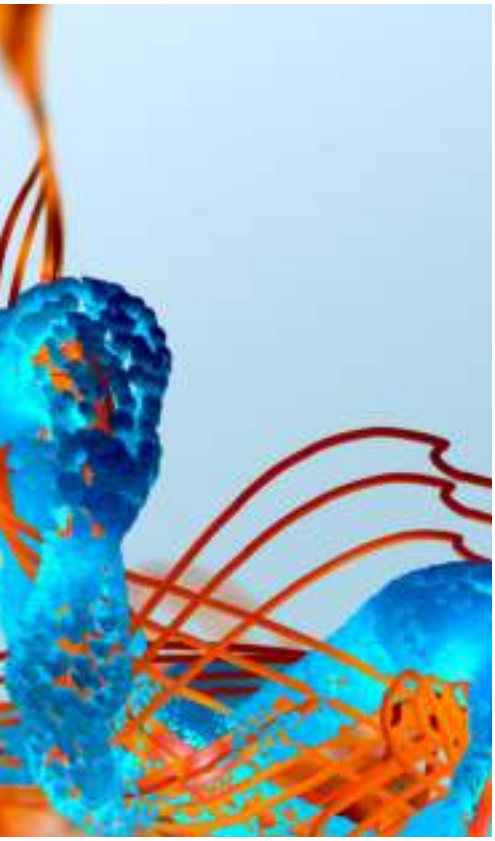


Every living cell, be it a single cell (like a bacterium) or part of a multicellular organism (like animals and humans) has a complex organization, in a way analogous to the one of cities. It is surrounded by a membrane (like a wall around the city) and it contains tiny structures comparable to small factories specializing in a specific job (like power plants, waste treatment plants, etc.). There is a system of transport inside each cell, in order to ensure communication between the different places: like railroads, they convey molecules from one place to the other, contributing to exchanges inside the city. Each city is part of its environment, be it a region (organ, like the heart) or even a country (organism, human, for example). Each city is active, transforming the resources of its environment (like glucose or lipids) to create energy and to perform multiple tasks.

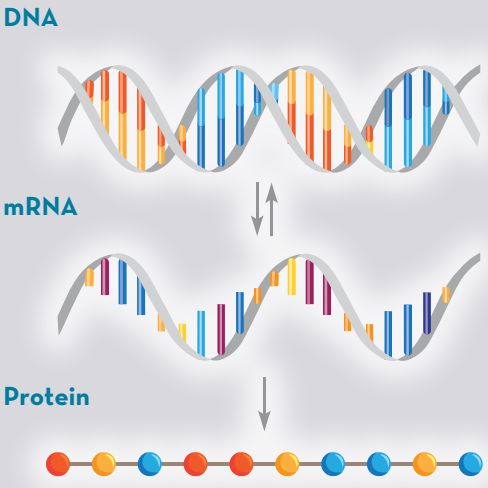
Apart from some vital functions common to all cells, the activity of cells within an organ is rather specialized: for example, the cells of the pancreas are specialized in the production of insulin whereas lung cells contribute to gas exchanges. This specialization is conferred by **proteins**. Like very sophisticated tools, the proteins perform thousands of reactions that characterize the life of the cell(s): they cut, glue, modify other molecules, play important roles in interactions (like keys and locks), etc.

(3)
DNA:
Desoxyribo Nucleic Acid.

(4)
Named C, G, A and T.



Proteins are made by decoding the information contained in our genome (**genetic material**, DNA[3]). The genetic material consists of a succession of genes (meaningful segments of DNA): one gene contains the information "coding" for one protein. Like in a handbook, all the information contained in DNA may be compared to a very long text written with an alphabet of 4 letters[4]. The ordered arrangement of the letters (the sequence) in a gene is of high importance, as it determines exactly the sequence of the protein (the order of the pearls) that will derive from the gene. Thus, mutations (changes in DNA sequence) may have a profound impact on the structure of the protein/tools and therefore on the cell tasks (see Box 1)...



** Like DNA, the RNA coding system is also comparable to an alphabet of 4 letters (C, G, A and U) where U is used instead of T*

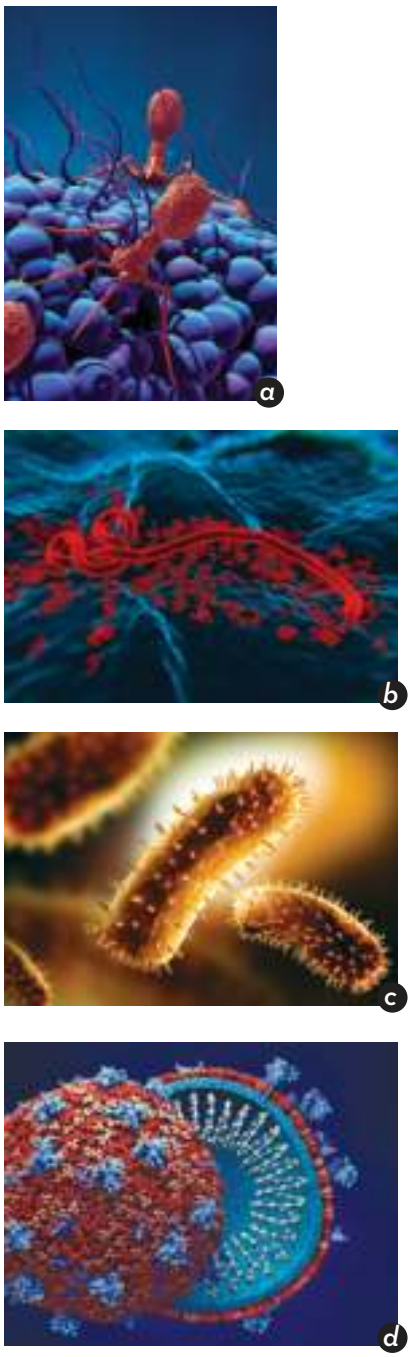
BOX 1 / FROM GENETIC MATERIAL TO PROTEINS... A CODE VULNERABLE TO MUTATIONS

Proteins are made by decoding DNA. The structure of a protein may be compared to a necklace: proteins are made of units, the "pearls". The arrangement of pearls – in a specific order along the necklace – is unique to each protein, defining its identity. There are 22 different "pearls" in humans that are used in proteins (which we might compare to 22 different colors of pearls). In order to make proteins, DNA is first "transcribed" into RNA (called "messenger" RNA, or mRNA). The mRNA sequence faithfully replicates the sequence – and thus meaning – of the DNA gene. The final product, the protein, is obtained, in a second step, by "decoding" the mRNA using a universal rule – the genetic code. This code carries a correspondence between a defined group of 3 RNA letters and a specific protein unit (the pearl). For example, the letters UCU on mRNA give rise to a blue pearl on the protein, while ACG codes for a pink pearl.*

The combination of letters in mRNA that gives rise to a specific pearl is not necessarily unique. In our example, the letters AGC or UCC will both give rise to a blue pearl. This flexibility in the genetic code explains why some mutations are not important: if one letter U in the triplet "UCU" is replaced by C, the resulting triplet "UCC" will anyway code for a blue pearl. This mutation has thus no effect on the protein (the necklace). Some mutations however result in changes in the pearls that make up the protein: for example, a green pearl may be replaced by an orange pearl. Yet, such changes may have no impact on the function of the protein, or they may inactivate, or on the contrary, potentiate the task performed by the protein. Proteins are bulky chains: they roll up like a ball of wool, acquiring a 3D shape. This 3D shape is important as it determines the interaction of proteins with other molecules (like the 3D shape of keys and locks).

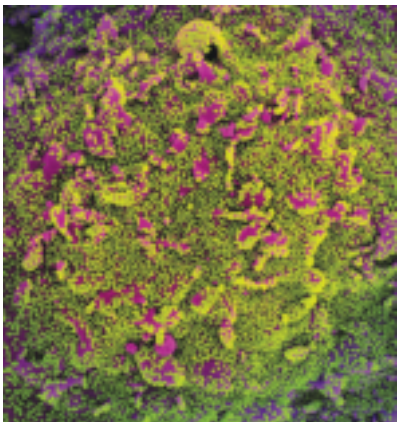
A – THE VIRUSES : MINIATURE ROBOTS...

Viruses are not cells: in contrast to them, viruses are not limited by a membrane and simply consist of two components: genetic material and proteins. In so-called "enveloped" viruses, this simple structure is enriched by a third component, lipids (fats). Thus, in contrast to cells which are analogous to complex cities (with plants, engines, railroads, etc), one could compare viruses to miniature robots simply made of a handbook (genetic material) surrounded by a shell equipped with a few tools (proteins). Despite this simple structure, viruses nevertheless display a fascinating variety of shapes: thus, the "bacteriophage" viruses look like a little space capsule, while the rabies virus has been compared to riffle bullets and the very dangerous Ebola virus is filamentous (Figure 1). SARS-Cov2, the coronavirus responsible for Covid19, looks like a spiny sphere. Viruses are of such very tiny size[5] in comparison to a cell (Figure 2) that their observation requires an electron microscope (Annex 1 page 32). The diameter of SARS-CoV2 is equal to 0.0000001 m.



<<< **Figure 1**

Pictures illustrating a bacteriophage (a), the Ebola virus (b), the rabies virus (c) and the coronavirus SARS-CoV2 responsible for Covid19 (d). Note that despite a very simple structure, viruses display a broad pattern of shapes. In terms of evolution, the main aim of viruses is simply to ... persist. Unfortunately, in some cases, they achieve this through high virulence (the degree of harm imposed on the host), like the Ebola virus. In some other cases, a high-virulence strategy does not prevail as, by killing their host, it would destroy their own habitat. In such cases, the virus and its host may adapt in order to co-habit.
But because of this evolutionary pressure to survive, viruses are capable of continuously changing their properties in order to adapt to their environment.



© : NIAID

Figure 2

Colorized scanning electron micrograph of a cell (purple) heavily infected with SARS-CoV2 virus particles (green), isolated from a patient sample. Image captured at the NIAID Integrated Research Facility (IRF) in Fort Detrick, Maryland. Credit: NIAID. Note the huge number of particles and the tiny size of the virus (green dots) as compared to a single human cell.

(5)
Except for some giant viruses.

B – ... WHICH HIJACK LIVING CELLS.

Some viruses contain DNA, while some others contain RNA instead. However, viruses cannot replicate independently from a host cell, which they must infect in order to reproduce. Like in a sci-fi-movie, viruses invading cells may be compared to tiny robots which invade some cities in order to reproduce and propagate. But any given virus is not able to attack any kind of living cell, it has specific targets. Successful targeting occurs when the robots possess the appropriate keys that fit the locks of the city's doors (Figure 3). When it fits, this recognition system triggers entry of –part or the whole– virus into the infected cell (Figure 4). Just before or after entering the city, they dissociate in order to begin their process of replication. Once in place, they hijack the city plants, diverting tools and assembly lines to their profit (Figure 5). The different parts (instruction manual [genetic material], tools & shell [proteins]) of the robot are reproduced.

Figure 3
The "key and lock" system that allows viruses to target specific cells. Viruses are endowed with surface proteins (the red spikes on this picture) that fit to specific receptors (the "keys", here in pink) inserted in the membrane (green) of target cells.

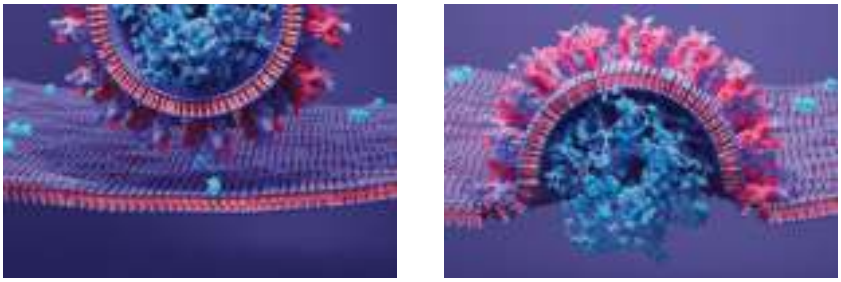


Figure 4 *This diagram illustrates (left) a coronavirus (upper particle) approaching the membrane (flat layer) of a cell equipped with receptors (blue). Upon recognition (right), the virus fuses with the membrane and enters the cell in order to reproduce.*

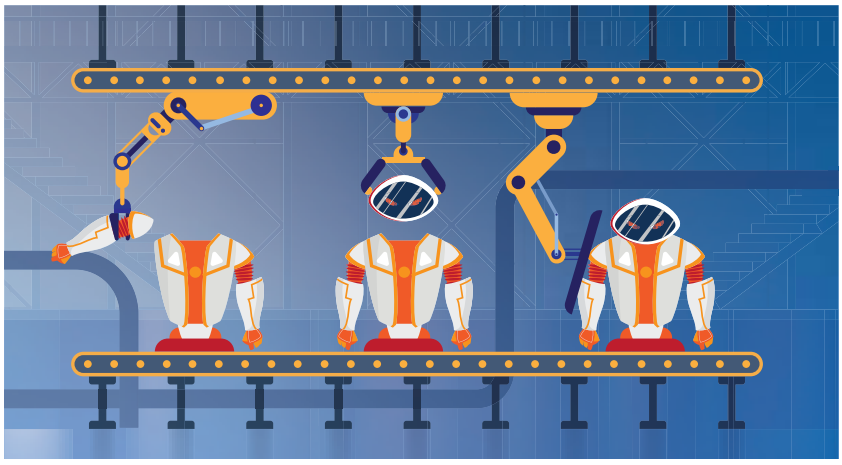


Figure 5
Like little robots invading a city, viruses have developed sophisticated strategy to multiply within living cells. Once inside a cell, viruses hijack the cell machinery to reproduce. They disassemble into elements, and use the assembly lines of the cell to replicate their different parts (genetic material, proteins). They then re-assemble into new particles that can leave the cell and propagate.

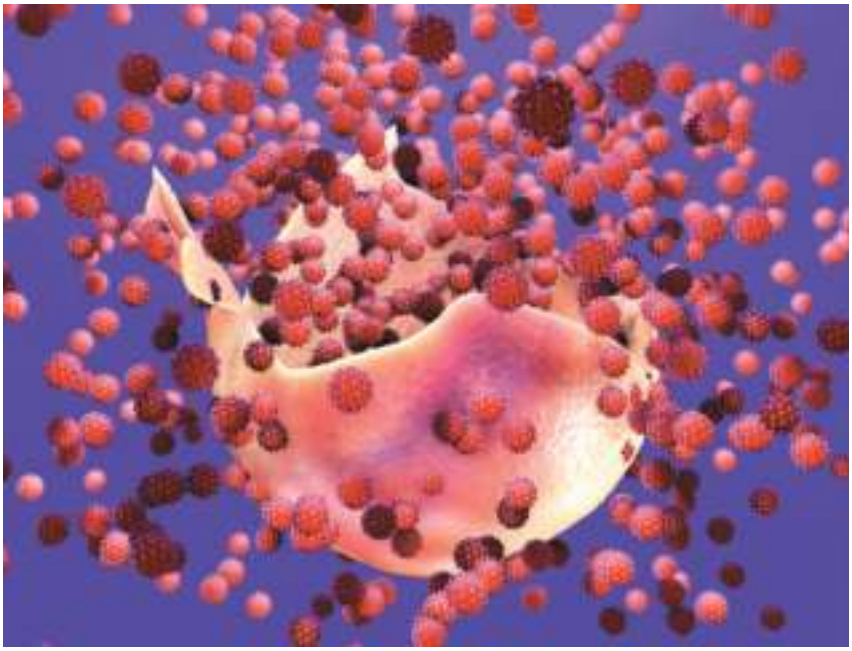


Figure 6 >>>
Following their multiplication, the newly generated coronaviruses leave the cell that they have used to replicate, inducing cell death and propagating to neighboring cells.

Once enough new viral proteins and genetic material has been produced, they assemble into new particles. The enveloped viruses complete the assembly by lipids, which they take from the membranes of the infected cells. This envelope hides most of the virus content from the immune system like a mask hides the face of a bank robber. On the other hand, it confers sensitivity to soap, making enveloped viruses more vulnerable to destruction by detergents than non-enveloped viruses. SARS-CoV2, the virus responsible for Covid19, is an enveloped virus. The new viruses then leave the infected cells, (killing them in some cases, Figure 6), and propagate the infection to the neighboring cells, initiating a new cycle of replication.

Besides this infectious process, viruses may also enter a dormant state. In that case, they stop replicating but hide within their host cells. However, they can get reactivated under certain conditions, initiating new cycles of replication. We shall see that this process may play a role in brain disease.

C – VIRUSES & IMMUNE SYSTEM: A BATTLE WITH UNCERTAIN OUTCOME

Like bacteria, viruses may be detected by the immune system, triggering an immune response. A first line of defense is rapid, and involves "killer" cells which detect, attack and kill the cells that are infected by a virus, so as to avoid its dissemination. During this process, several substances (distress signals) are released which inform the neighboring cells of an attack, which attract further immune cells and – for some of them – contain the replication of the virus. This strategy is based on the death of the host cell in order to prevent further propagation.
A second phase develops more slowly, in about 5 days, generating antibodies. Antibodies recognize a specific portion of the virus, for example a precise part of a surface protein and attach to it, blocking the viral propagation (i.e. blocking entry or egress from the cell, for example). The bound virus-antibody is then destroyed by specialized immune cells. If a second infection was to occur later, antibodies are already present, making the recognition of the virus more efficient prior to its propagation.

1 /////////// A WAR THAT PRODUCES COLLATERAL DAMAGE...

Activation of the immune system generates inflammation. This is a way for the infected organism to spread information about the attack and to trigger defensive mechanisms so as to kill the pathogen. However, inflammation is not harmless for the host: like in a war, fighting an enemy may induce collateral damage for the population. Thus, inflammation may induce very deleterious events, sometimes lethal for the infected organism. Such phenomenon has been largely observed in severely-affected Covid19 patients: this exaggerated inflammation, called a "cytokine storm" is due to cytokines, the distress signals that are released by the immune system to fight the virus.

2 /////////// WHEN VIRUSES JUMP FROM ANIMALS TO HUMANS...

Viruses are only able to infect cells that have suitable receptors. This is one reason why viruses display specificity for species (for example, birds, swines, bats, humans, etc). Mutations arising in the genes that code – for example – for the viral proteins (the keys) which recognize their target cells may confer new properties to a virus, allowing it to infect a new species that it was not able to infect previously. When a virus "jumps" from its usual animal host to the human, the disease is called **zoonotic**. Covid19 has been suggested to originate in bats and has been shown to use other animal reservoirs during the pandemic, as we shall see.

Importantly, there is specificity for *species* but there is also specificity for *cells* within one species. Since all the cells of an organism do not display the same receptors on their surface, again, viruses can only attach to cells which have receptors (locks) that fit their own surface proteins (the keys). For example, some viruses are rather specific for cells of respiratory organs (i.e. the influenza virus that gives the flu), some others for liver cells (the hepatitis virus), etc. What about the possibilities for viruses to infect the brain and nervous system?

D – THE BRAIN: A FORTRESS TOLERANT FOR THE ENEMY?

In general, the cells of an organism have the potential to replicate and multiply, ensuring natural replacement or, for example, replacement in case of injury. For this, they duplicate their genetic material before splitting into two "daughter" cells. However, a notable exception are the cells of the brain and nervous system, the neurons, whose population, with rare exceptions, multiply before birth and then stop this process. Because of their inability to regenerate, neurons must be particularly well protected from attacks so as to avoid death. This is probably why, contrarily to other organs, the brain benefits from a two-pronged protection: on the one hand, there is a barrier[6] that isolates brain cells from the bloodstream, in order to greatly reduce the possibilities of access to the brain for pathogens (Figure 7); on the other hand, when some pathogens succeed in bypassing this security system, strategies may engage that consist in minimizing the war (inflammatory response) against these pathogens in order not to induce collateral damage that would endanger the neurons. However, as we will see, these may prove to be high-risk strategy by letting the wolf persist in the sheepfold...

Figure 7

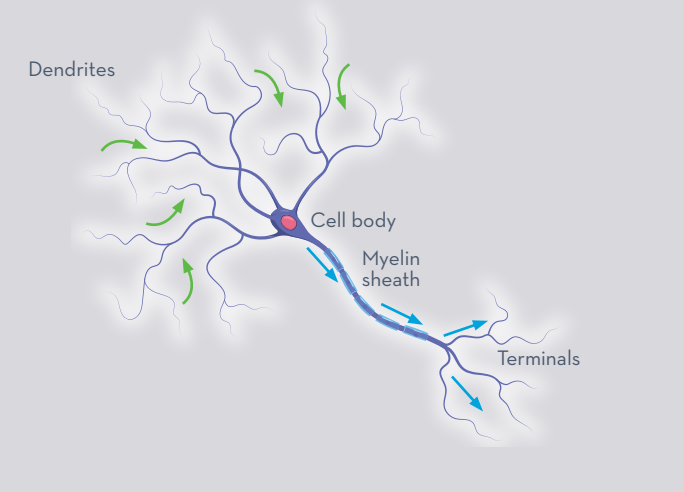
This picture illustrates a blood vessel traveling between neurons, inside the brain. A sophisticated Blood-Brain-Barrier consisting of tight junctions (to prevent leak) precludes the circulating blood cells (red) and potential pathogens (viruses, bacteria) to enter the brain. Unfortunately, this barrier is vulnerable and some viruses have developed the capacity to cross the walls of the blood vessel -with or without breaching the barrier- or they enter in the brain hidden within some of the immune cells that are allowed to pass through (see text).

Unfortunately, the barrier that isolates the brain from the bloodstream is vulnerable. Several tricks have been developed by pathogens to circumvent this defense. Some viruses have the capacity to directly cross the barrier, like the polio and Zika viruses. Some others use a "Trojan horse" strategy, infecting immune cells of the bloodstream: this is the case for example of the measles virus and varicella virus. These immune cells then carry the enemy into the brain after they leave the blood vessels to enter brain tissue...

(6)
Called Blood Brain Barrier.

E – NEURONAL RAILROADS

In addition, the brain has another characteristic that differentiates it from other organs: one of the main categories of cells that make up the brain, the neurons, have a highly specialized structure that allows the elaboration and transmission of electrical messages throughout the network, sometimes over long distances. Neurons are elongated and polarized cells: they generate electrical signals at one end, integrate them in the so-called "cell body" (like a head) and then propagate the resulting signal down to the other end of the neuron. During this process, incoming information (electrical, chemical, etc) activates branch-like ramifications of the neuron (called dendrites, see Figure 8), leading to electrical signals which are conducted towards the cell body (green arrows Fig.8). Following integration of excitatory and inhibitory inputs, the signals propagate in a thin cable with some bifurcations (the axon), reaching terminals that impinge on the downstream neurons. There, the carried information activates the next neuron via a specific connection site (called synapse) which is a zone of junction between one terminal of neuron 1 and one dendritic branch of neuron 2. It should be noted that information in the human brain is never coded by a single neuron, but always by a group of neurons called "cell assembly". Therefore, information propagates through the brain by sequential activation of different connected cell assemblies.



<<< **Figure 8**

Neurons are ramified cells in which electrical signals arising in upper ramifications (dendrites) propagate (green arrow) down to a cell body. The integrated signal then goes down (blue arrow) through a long and thin cable, the axon, surrounded by a protective sheath (myelin). The signal further propagates in the ramified axon down to the terminals (synapses).

Although the length of an axon remains limited within the brain, it can be remarkable in other regions of the nervous system: for example, neurons contained in the sciatic nerve can reach a length (between upper and lower ramifications) of almost 1 meter. There is an obvious need, under these conditions, for specialized systems within a neuron to ensure the transport of materials (most of which are manufactured in the cell body) down to the terminals. Such transport structures exist in neurons and may be compared to a network of railroad tracks in the city. There is bi-directional transport on these tracks: some molecules move from upstream to downstream and vice versa, thanks to the energy produced by the neuron. A permanent traffic allows

(7)
Thus, there are viruses attracted by the nervous system (called "neurotropic" viruses), and by neurons in particular (called "neuronotropic" viruses).

exchanges from one end of the cell to the other, notably in order to ensure the necessary presence of all the constituents in the different zones of the neuron.

Unfortunately, some viruses have developed the ability to exploit the "railroads" within neurons[7] (Figure 9). This is the case, for example, with rabies viruses, whose inexorable effect can be fatal: it can cause paralysis, dementia and death (like for undiagnosed rabies patients for whom it is too late when they have symptoms, as the rabies virus can incubate more than a year after a bite by an infected animal). This virus penetrates the neuronal endings present in the muscles and then, it moves upwards within the neuron via so-called "retrograde transport". For it is there that the heart of the city is located, whose functionalities it will use to reproduce itself, before continuing its journey, crossing synapses in order to penetrate further neurons upstream. This virus thus follows a path through several consecutive connected neurons to/in the brain. The polio virus, for its part, is able to enter both from bloodstream and by traveling into neurons.

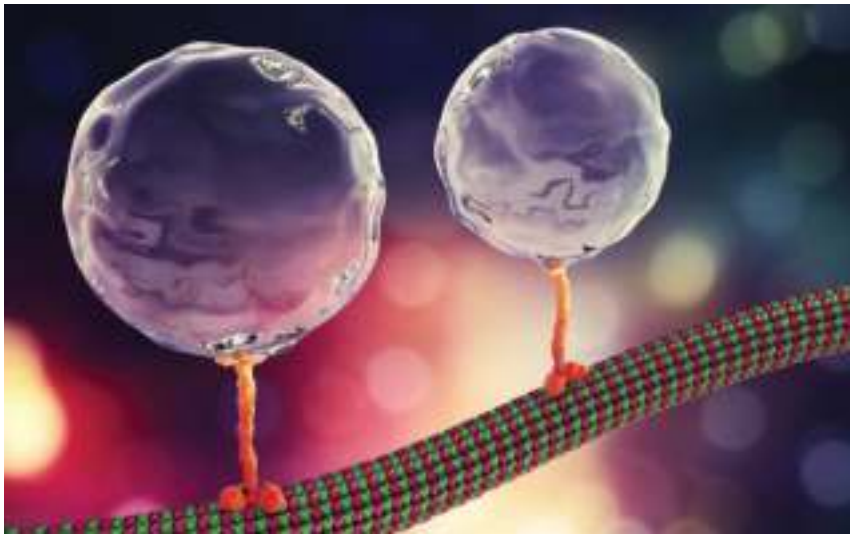


Figure 9 >>>
Living cells are equipped with specialized systems of transport, which, like railroads, carry particles from one place of the cell to the other. Some viruses strategically use this system as a cargo to travel between the different zones of a neuron. They enter the terminals of the neurons in the periphery (skin, muscle, etc) and begin a long journey, travelling back from the terminals to the cell body and crossing the junctions between neurons. They end up in the brain, having bypassed the blood barrier that protects the brain.

F – WAITING IN THE BRAIN...

While some viruses can cause considerable brain damage, and even death, some others have developed the capacity to persist in a latent, even silent, state in the nervous system as we will see below. Latent viruses are hidden and do not reproduce; instead, only a few of their proteins are reproduced once in the cell. Like if, in our comparison, robots would make only some of their parts in the line assembly. These parts restrict the reading of the genetic handbook of the robot, containing the production of new robots... We shall see that this latency seems acceptable for the brain; however, not only this latency may occasionally reverse, but it turns out that the long-term effects could be a time bomb, at least in some at-risk patients. What about the virus that caused the Covid19 pandemic?

§2 CORONAVIRUSES & SARS-CoV2

The SARS-CoV2 virus which triggered the worldwide Covid19 pandemic at the end of year 2019 belongs to the family of coronaviruses, the genetic material of which consists of RNA. Some coronaviruses primarily infect birds, while some others infect mammals, including humans. The very first coronavirus discovered in humans was isolated in 1966 from a boy with common cold (see Annex 1 page 36).

A – THE FIRST 2 CORONAVIRUS PANDEMICS

Apart from SARS-CoV2, there are 6 other coronaviruses known as being able to infect human[8]. While 4 of them generally induce common cold, 2 coronaviruses have however been associated with severe lung disease. The first of them arose in China and triggered the first pandemics of the 21st century (2002 - 2003): because it elicited a Severe Acute Respiratory Syndrome, it was called SARS-CoV[9]. The second coronavirus, which triggered a serious epidemic in humans, emerged in Saudi Arabia (2012 - 2013), from where its name: MERS-CoV1[10].

With a fatality rate of almost 10%, the SARS-CoV was highly lethal and spread over 26 countries, killing 774 people (for 8098 reported cases). Most cases

(8) And apart from the aforementioned first known coronavirus of human origin, B814 (see Annex 1 page 36).

(9) Severe Acute Respiratory Syndrome Coronavirus. Sometimes referred to SARS-CoV1, to differentiate it from the SARS-Cov2 virus associated to Covid19 pandemics.

(10) Middle East Respiratory Syndrome Coronavirus.

//

were however nosocomial[11] infections and faded out after intense public health mitigation measures.

In comparison, the MERS-CoV has caused 858 deaths for 2494 reported cases in 27 countries. Despite this high case fatality rate of 34%, MERS-CoV is not currently presenting a pandemic threat. Although possible, human-to-human MERS-CoV transmission is quite inefficient as it requires extended close contact with an infected individual. Thus, most transmission has occurred within patients' families and between healthcare workers. The new coronavirus SARS-CoV2 is less deadly but far more transmissible than MERS-CoV or SARS-CoV1.

B – ZOONOTIC DISEASES

All three viruses – SARS-CoV1, MERS-CoV and SARS-CoV2 – have been suggested to originate in bats. Bats might indeed be the natural host of these coronaviruses: they represent a tremendous reservoir of zoonotic diseases because these mammals live in high concentration at the same place. Coronaviruses have a great ability to mutate which facilitates their transmission from animals to humans. The transmission of SARS-CoV1 is thought to have been mediated by civets but was eradicated from this intermediate reservoir following drastic measures. The transmission of MERS-CoV has been attributed to dromedary camels: because it is widespread in these animals, zoonotic[12] cases are still observed, unlike SARS-CoV1. Finally, SARS-CoV2, which apparently emerged from the wet animal market in Wuhan, might have been transmitted by the intermediate host pangolin, although this is not really established.

Some variants of SARS-CoV2 have been identified as soon as June 2020 in mink farms in Denmark; the minks were probably contaminated by the farm workers, offering a huge reservoir in which the virus developed several important mutations. Then, minks might have contaminated the farm workers back, thus spreading a new variant. Since then, zoonotic transfer of a SARS-Cov2 variant has also been observed from mink farms in Netherlands, Spain and USA, and suspected in France. This reminds us that Covid19 is a zoonotic disease and that places where farm animals live in high concentrations are conducive to the development and appearance of new viral variants. Several specimens of the following animal species have been found infected by SARS-CoV2 up till now: cats, dogs, minks, lions, tigers and gorillas. The wild animals in this list were infected in zoos following human transmission. Because it occurred in a short time window (2 decades) following the SARS and MERS epidemics, the Covid19 pandemic has "benefited" from the basic knowledge accumulated during the previous pandemics, accelerating research on SARS-CoV2.

(11)
Is said from an infection that is acquired in a certain location such as an hospital.

(12)
Zoonotic diseases (zoonoses) are diseases that spread between animals and people.

(13)
Acute inflammation of the brain.

§3 SARS-COV2: MUCH MORE THAN A RESPIRATORY VIRUS...

SARS-CoV2 exerts a broad array of effects in humans, ranging from no symptoms at all (affected people are then called "asymptomatic") to death. The major clinical signs of SARS-CoV2 infection are respiratory-related, ranging from limited shortness of breath and cough to pneumonia and a severe condition called "Acute Respiratory Distress Syndrome" in the most serious cases. Moreover, some patients develop additional cardiac problems and multiorgan failure. Of note, SARS-CoV2 causes the formation of blood clots, which confers some of its dangerosity in vulnerable patients. It has however been observed from the beginning of the pandemic that some patients with Covid19 also suffered from headache, nausea, and vomiting, suggesting neurological dysfunction. Moreover, loss – or modification – of smell and loss of taste have been observed in more than 70% of patients, again pointing at a possible effect on nerves and/or brain.

NEUROLOGICAL AND PSYCHIATRIC EFFECTS OF SARS-CoV2

Importantly, observations have accumulated which indicate that SARS-CoV2 infection may also be associated with neurological and neuropsychiatric illness. Since March 2020, many neurological complications suspected to result from Covid19 infection have been reported, including epilepsy, stroke, unconsciousness, encephalitis[13] and brain haemorrhagies. As a general rule, neurological complications

are more likely to be observed in severe forms of Covid19 than in mild forms (45.5% versus 30%). Some Covid19 patients have developed some symptoms typical of Parkinson's disease[14] (parkinsonism). Transient paralysis – with possible sequelles – ("Guillain Barré Syndrom") has also been observed in some patients following Covid19 infection. Moreover, psychiatric problems have been observed, including memory disorders, anxiety, depression, irritability, confusion, insomnia, and delirium[15]. Some cases of psychosis (voice hearing, hallucinations, delusions[15]) relating to Covid19 have been reported: they were generally transient but occurred in people with no previous history of psychiatric disease.

Last but not least, many Covid19 patients experience long-term illness and residual symptoms even after the virus is no longer detectable: this condition, which persists after 12 weeks, is called "Long Covid". One of the most common long-term complaints is "brain fog", which is characterized by debilitating severe fatigue, analogous to the so-called «Chronic Fatigue Syndrome». This condition can severely affect memory, cognition, the ability to concentrate. Some patients are even unable to work 13–36 months after the acute infection. Interestingly, chronic fatigue has also been reported in previous coronavirus and flu epidemics. Long covid is also associated to the emergence in about 6% of people of a new psychiatric illness, including depression, anxiety, dementia or insomnia. The list of long-term sequelae does not end there and also includes headaches and muscle pain. Thus, SARS-CoV2 turns out to be able to alter brain function. In order to clarify how it might do this, let's go back to the history of medicine to learn what is known regarding previous pandemics, viruses and effects on brain function... Did other respiratory viruses do the same and can we draw lessons for Covid19?

(14)
See page 25
for definition of
Parkinson's Disease.

(15)
A wrong belief or impression
maintained despite being
contradicted by the reality
or by rational argument.

§4 VIRUSES & NERVOUS SYSTEM DISORDERS: INSIGHTS FROM OTHER PANDEMICS

A – THE RUSSIAN FLU (1889 - 1892)

So-called because it had broken out in St Petersburg, the Russian flu had several recurrences between 1889 and 1892. This viral pandemic, which has been estimated to have killed one million people worldwide, left many people with "post-flu" symptoms, suggestive of long-term neurological effects. These symptoms included an extreme fatigue, psychosis, prostration, anxiety, paranoia, neuralgia, etc. Such symptoms were also observed during the next flu pandemics (see below).

B – THE SPANISH FLU (1918 - 1919)

Everyone has heard about the terrible Spanish flu that killed an estimated toll of 17 to 50 million people worldwide after the First World War. Contrarily to what its name suggests, the Spanish flu probably originated in Kansas, USA, in March 1918. Rapidly propagated by soldiers, it spread across USA and Europe, where the Spanish media were the first to describe this new disease. Soon, the situation worsened, leading in September 1918 to an unusual mortality rate, 10 to 30 times higher than the usual flu epidemics. Even though questions remain on the exact identity of the virus(es) which triggered the Spanish flu, autopsy studies performed on victims buried in permafrost (Figure 10) have led to the identification of a so-called H1N1 strain of influenza virus. Brain complications were observed during the Spanish flu pandemics, including reversible psychosis (strange thoughts, hallucinations, etc), altered cognition ("brain fog") and chronic fatigue.

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Dr Johan Hultin

© Dr J. Hultin

<<< **Figure 10**

This picture illustrates Dr Johan Hultin, a Swedish microbiologist, excavating a body from the Brevig Mission burial ground. Brevig Mission was a small ocean-side village in Alaska: 80 adults, mostly Inuit Natives, lived there in the fall of 1918. However, during the five-day period from November 15-20, 1918, the 1918 pandemic of Spanish flu claimed the lives of 72 of the villages' 80 inhabitants. Dr Hultin made a first attempt to obtain the virus from human tissues in 1951: however, he was unable to retrieve the virus. It wouldn't be until 46 years later, in 1997, that J. Hultin would have another opportunity to pursue the 1918 virus. That year, a young molecular pathologist, Dr. Taubenberger was able to determine the sequence of some fragments of the virus. He claimed that the 1918 virus was a novel influenza A (H1N1) virus. This convinced J. Hultin to make another attempt to isolate the virus. Back to Brevig Mission, he excavated the body of a 20 years old Inuit woman called Lucy. Her lungs were perfectly preserved in the Alaskan permafrost, about 7 feet deep.

(16)
Perpetually frozen ground in the Arctic regions.

C – THE H1N1 PANDEMIC (2009 - 2010)

Baron Constantin von Economo

Constantin von Economo, whose full name is "Constantin Alexander Economo Freiherr (Baron) von San Serff", served during the First World War on the Tyrolean front. He was called back to Vienna in 1916 to take part in the care of head trauma patients, where he discovered the first cases of lethargic encephalitis, also known as "von Economo-Cruchet disease". Nominated in 1926, 1930 and 1932 for the Nobel Prize in Physiology or Medicine, he never received this prize and died in 1931 at the age of 55 of a heart attack.

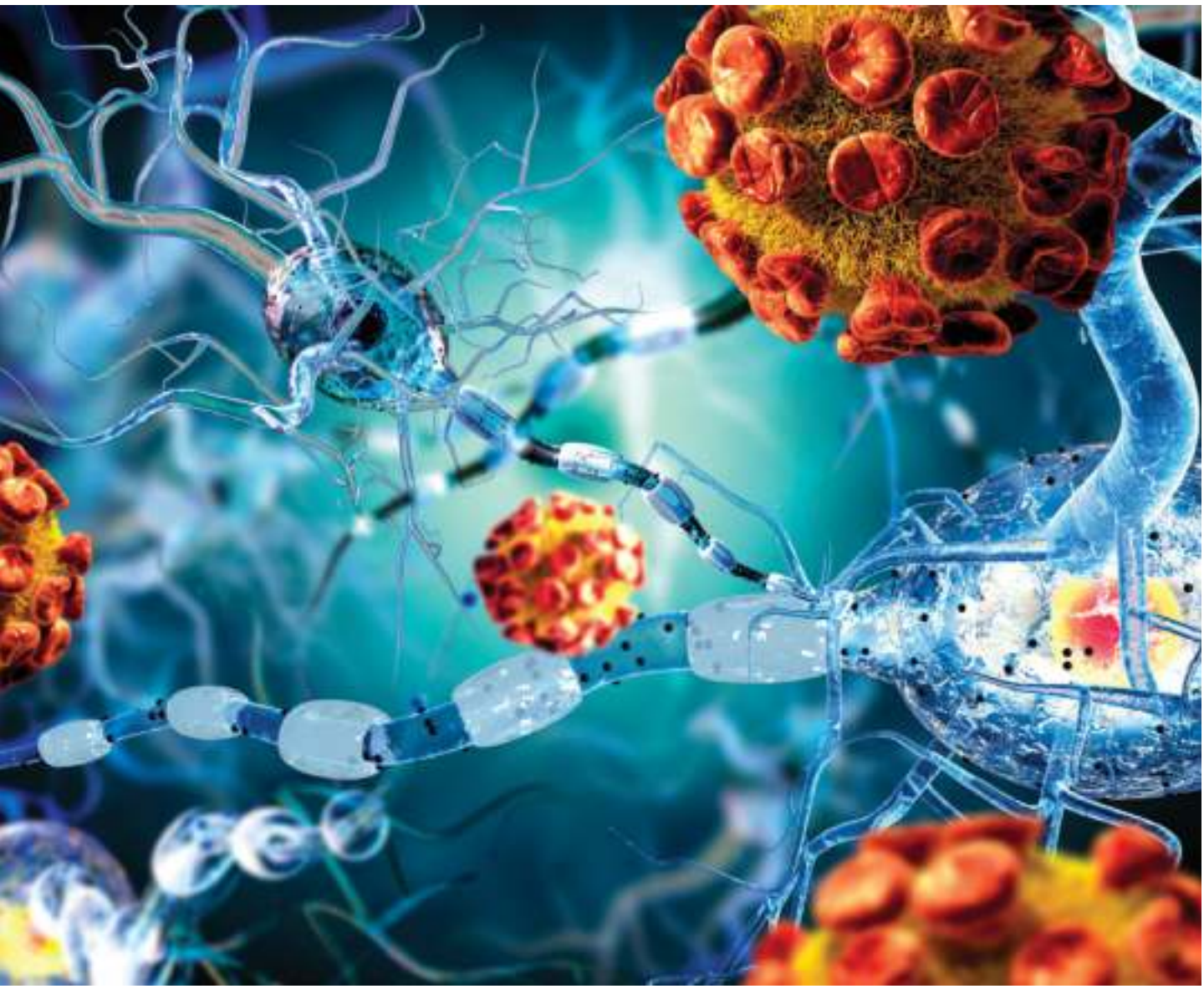
The much more recent H1N1 influenza pandemic killed about 20 000 people with diagnosed H1N1 infections worldwide, with 80% of the deaths in people younger than 65 years[17]. It was provoked by a novel virus that emerged in Spring 2009: the influenza A (H1N1) pdm09 virus. An episode late in this pandemic has highlighted potential links between this respiratory virus and subsequent brain lesions. An unexpected vague of narcolepsy in children and adolescents was observed following vaccination with one of the vaccines, the H1N1 Pandemrix vaccine. Narcolepsy is a chronic sleep disorder characterized by overwhelming daytime drowsiness and sudden attacks of brief sleep episodes. Because narcolepsy attacks arise without warning, (for example while driving or in the middle of a sentence), the disease is very debilitating. The risk to develop narcolepsy was increased by a factor of 12.7 following Pandemrix vaccination in this young population. Narcolepsy was found to result from the lesion of some neurons within a specific brain region that controls sleep.

Interestingly, these neurons are part of a path connected to the nose, suggesting again the possibility for the virus to travel backward from neurons in the nose to the connected (sleep) neurons located farther in the brain. Several hypotheses have been raised to explain the lesion of the sleep neurons: some have suggested that, if the neurons had previously been infected by the virus [in people who got the flu before vaccination], then the inflammation triggered by vaccine could have inadvertently targeted and lesioned the previously-infected neurons. The question remains unanswered; it however illustrates the potential effects of a respiratory virus on brain function, in this case, sleep. This is reminiscent of a large (and much older) pandemic that was also found to profoundly affect sleep.

Much remains mysterious about the *"Encephalitis Lethargica"* (E.L.) pandemic that spread at the same time as the Spanish flu. That is in the late 1916s that Baron Constantin von Economo, soon followed by a French physician, René Cruchet, examined at the Psychiatric-Neurological Clinic of the University of Vienna several patients who presented unusual neurological symptoms. Interestingly, the early phase of E.L. was quite similar to early flu: however, it was soon obvious, from the signs and symptoms of affected patients, that the brain was involved. Many patients in particular exhibited marked lethargy[18], which led Von Economo to design this set as a distinct disease entity, which he called *Encephalitis Lethargica*. Beginning in the winter 1916–17, this neurological syndrome spread across Europe and then the world, up into the 1930s. Although the exact number of victims of E.L. during the pandemic is unknown, it has been estimated to reach more than one million worldwide and be associated to a mortality of around 20%. Following the initial phase of E.L., many patients developed a chronic form of the disease after a period ranging from 6 months to 1 year (but sometimes after several decades). A majority of the patients, who were nearly unable to move, were diagnosed as suffering from a form of Parkinson's

(17)
The 2009 pandemic followed the Asian flu pandemic (1957 - 1958) due to an influenza A virus H2N2 (thought to have caused the death of one to four million people worldwide) and the Hong Kong flu pandemic (1968 - 1969) due to a viral influenza strain H3N2 which killed about the same number of people.

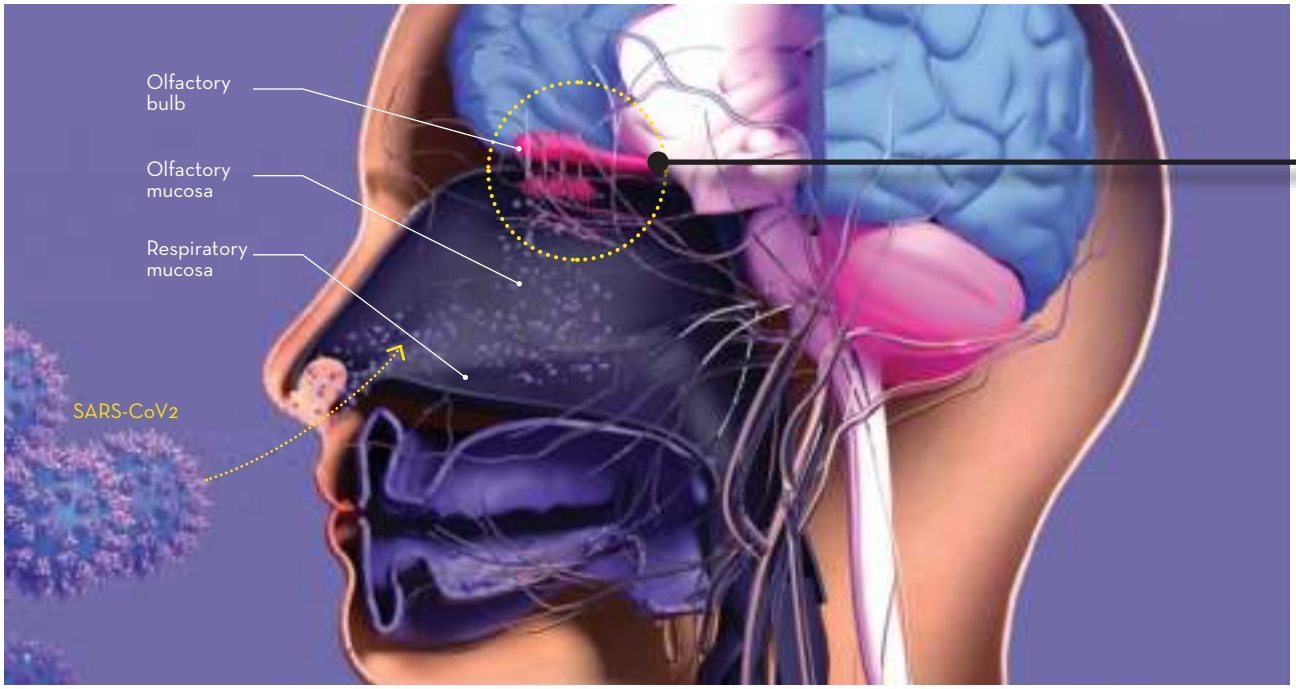
(18)
Abnormal lack of energy or sleepiness.



disease (PD). In the 1960s, the young doctor Oliver Sacks met EL patients in a nursing home. For the first time he administered the later Parkinson medication L-DOPA and described his experiences in the book "Awakenings". Despite a lack of recurrence of this epidemic, a few putative cases have been reported, even though it is not possible to claim that it is the same disease. After more than a century of research, the cause of E.L. is still unknown but the hypothesis of a viral infection prevailed and could not be discarded.

The exact link between the viruses that induced the aforementioned pandemics and the neurological effects that were observed is not firmly confirmed up till now. There are many difficulties and obstacles: the presence of viruses into human brain is better investigated by autopsy. Yet, the brain rapidly deteriorates after death, decreasing the chance for usable anatomical findings. Moreover, viruses are tiny particles, which may be disseminated in many places, diluting the signal. But these historical observations draw attention on the fact that some pathogens known to induce respiratory diseases may also exert effects on the brain, at least under certain conditions.

§5 HOW CORONAVIRUSES ENTER THE BRAIN?



The main "key" that allows SARS-CoV2 to enter target cells is the so-called spike protein. This protein sticks out of the envelope, which covers the rest of the virus hiding most of its content from the immune system. The receptors (the "lock") that fit this key, the angiotensin converting enzyme 2 (ACE2) is present only on some target cells in the body. A third protein[19] has been suggested to act like a tool (a pair of scissors) that modifies the shape of both keys & locks. By doing that, it increases the entry of the virus into the cell. In humans, the ACE2 receptors for SARS-CoV2 are numerous in human blood vessels. Since there are also blood vessels that irrigate the brain, this importantly constitutes a potential entrance door for the virus into the brain (and a potential explanation why SARS-CoV2 induced stroke in many patients, as stroke results from clots in blood vessels). The receptors for the virus have been found in the brain as well, but in smaller quantities. We have seen that the brain is in a way comparable to a fortress isolated from the rest of the body, thanks to the blood-brain barrier, a protective shield that separates the blood from the brain tissue.

Is SARS-CoV2 able to reach and cross this barrier? In order to do so, however, it requires that the virus enters via brain blood vessels. The genetic material of SARS-CoV2 has been found in the blood vessels of about 30% of hospitalized patients, and the strength of the virus load correlated with severity of the illness. However, genetic material is only part of the virus and this does not prove that whole viruses circulate in blood vessels. This has not been shown yet. Therefore, it is not known yet in what proportion of patients the virus might use this path of entrance.

(19) Called TMPRSS2.

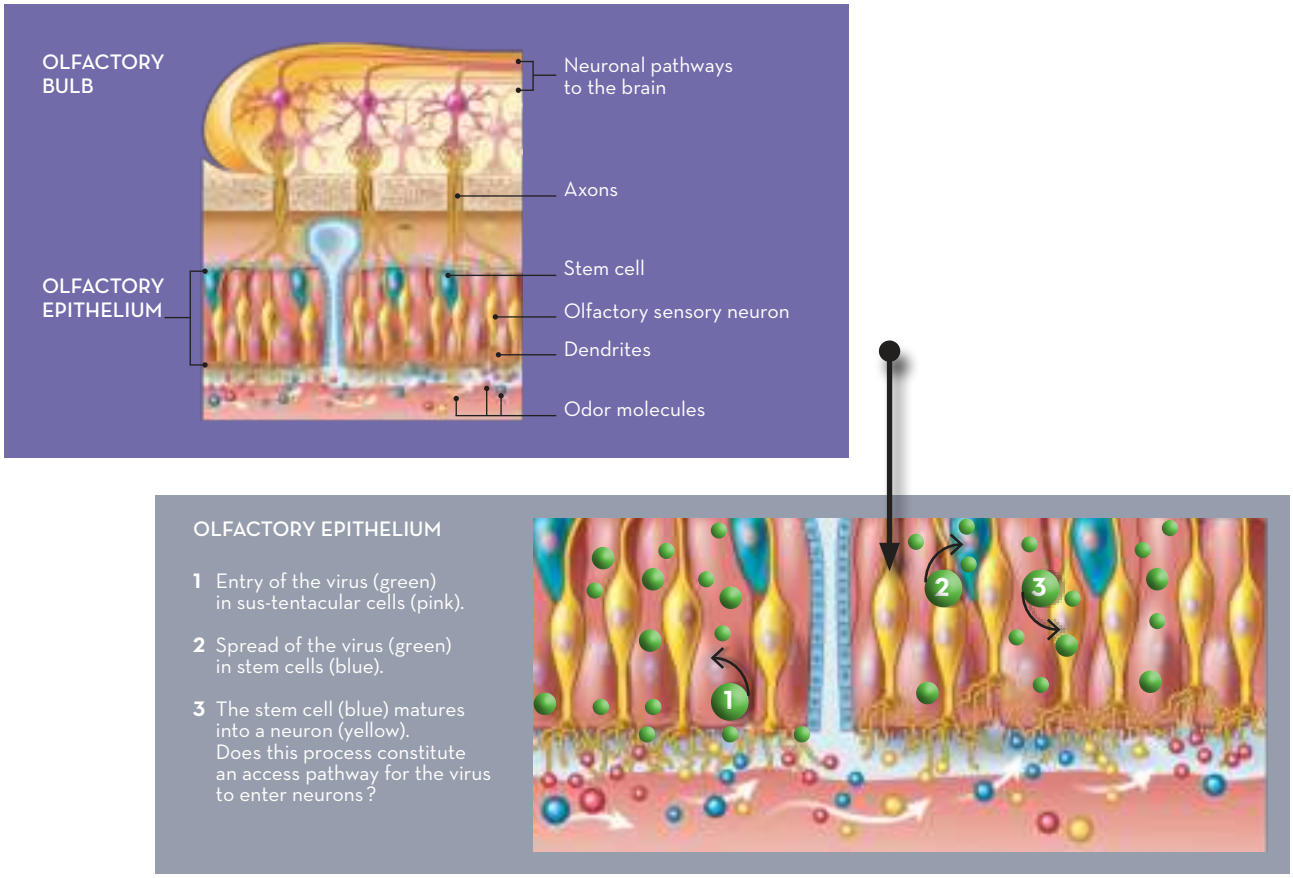


Figure 11

This diagram illustrates some of the potential pathways that SARS-CoV2 could use to enter the human brain. The virus (green beads) enters into the cells of the nasal mucosa (supra-tentacular cells, in pink) which, unlike the adjacent olfactory neurons (yellow) have receptors for SARS-CoV2. However, the receptors are also thought to be present on stem cells (in blue) which will give rise to neurons via a slower mechanism. It has been proposed that the virus could thus indirectly infect neurons by entering stem cells that will in turn become neurons. The virus could then move up into the olfactory neurons and from there reach neuroanatomically connected neurons, allowing entry into the brain.

Interestingly, the nose (nasal mucosa) can constitute another doorway to the brain. The nose ceiling contains the dendrites (sensing ramifications) of neurons that are activated by odor molecules, generating smell (Figure 11). These neurons project up in the brain. There are indeed receptors for SARS-CoV2 in the nasal mucosa: this has been proposed to explain why Covid19 is associated with loss of smell in most of the patients, as the virus is able to target some cells there. Nevertheless, the receptors (locks) for the virus are not present on the neurons themselves, but on neighboring non-neuronal supporting cells, called sustentacular cells (in pink, Figure 11). Therefore, the loss of sustentacular cells might lead to a secondary degeneration of the sensory neurons, leading to anosmia – the loss of smell. In most cases this is followed by rapid regeneration of the sense of smell within 2-3 weeks. This is possible because olfactory sensory neurons can regenerate form neural stem cells also located deep in the nasal mucosa. In some cases, however the loss of smell is more prolonged, which might be due to the fact that the stem cells are also compromised by virus, because they also possess the locks for SARS-CoV2. Furthermore, some have suggested that SARS-CoV2 might enter neurons by first invading some immature stem cells which survive and subsequently develop into mature neurons. Does SARS-CoV2 exploit the neuronal railroads after entering the nose, continuing its journey into the brain by going up a chain of interconnected neurons? Importantly, the presence of SARS-CoV2 has been found in the nasal mucosa and in the anatomically-connected paths that enter the brain: to come back to our robot comparison, both whole robots (whole viral particles) and robot parts (RNA and proteins) have been observed in autopsied patients.

§5 HOW CORONAVIRUSES ENTER THE BRAIN?

Some deep brain regions involved in breathing were also infected. Of note, lower levels of viral RNA were found in the eye and oral mucosa, highlighting additional potential sites of SARS-CoV2 CNS entry into the brain via the eyes and mouth...

The human coronaviruses SARS-CoV1 and MERS-CoV can also invade neurons, which they are able to weaken or kill. Gaining access to the nervous system is not a privilege of coronaviruses: other human viruses are known to possess this property, including the influenza virus and measles virus. It is thus well established that many viruses may reach the brain using several distinct doorways. This draws the attention on the fact that SARS-CoV2 could add to the list of viruses that might endanger the brain of some people, potentially many years after the first infection.

Several common viruses have been suspected to play a role in the common brain disorders that affect our memory, motricity or cognition, like Alzheimer's Disease, Parkinson's Disease or schizophrenia. But an important point is that the viruses in question are generally considered as harmless, often because the symptoms during acute infection are not serious. If correct, these hypotheses imply that an unsuspected infectious cause might underlie the late effects of serious chronic diseases. This raises the problem of assessing the role of ancient infections – including Covid19, into late chronic disorders.

The following paragraphs illustrate some of the avenues currently being explored regarding a possible link between viruses and common brain diseases. They mention the current known effects of the coronavirus on cerebral functions (memory, motor skills, etc.) affected in these diseases, raising the question of possible long-term consequences of Covid19.

§6 BRAIN DISEASES: LATE EFFECTS OF VIRAL INFECTIONS?

A – THE INITIAL (ACUTE) EFFECT OF VIRUS INFECTION...

Acute infection of the brain by a virus may cause acute inflammation within the brain, called "encephalitis". Both a first infection or viral reactivation may cause viral encephalitis. It is always a case of medical emergency. For example, the measles virus may cause encephalitis.

B – ... ARE MUCH EASIER TO DETECT THAN LATE EFFECTS.

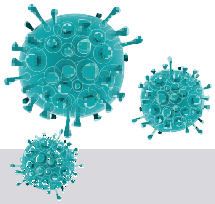
Although the viral etiology (cause) of acute encephalitis has quite some chance to be rapidly identified & diagnosed, it is not the same with the chronic effects of viral infections. Indeed, viruses may induce lesions in the nervous system following a –sometimes long– delay after the infection, and the identification of the causative agent may be very challenging. What about the common brain diseases that affect our motricity, memory and thoughts?

C – VIRUSES & PARKINSON'S DISEASE

Parkinson's disease (PD) is a neurodegenerative disorder that progressively affects motricity (how a person moves, speaks and write). It generally begins in mid-life, develops slowly over years and get worse over time, and is accompanied by tremor, stiffness, slow movements as well as various nonmotor symptoms.

There is a long history of associations between PD and viral infections, like with the influenza virus. The association of Parkinsonism[20] with influenza dates back from the outbreak of *Encephalitis Lethargica* and the postencephalitic Parkinsonism that took place after 1918. Even though the link between E.L. and influenza remains a matter of debate, an increased incidence of PD was observed following the 1918 H1N1 influenza A pandemic (Spanish flu). Other viruses have been suggested to induce Parkinsonism, like the so-called West Nile virus. Even more strikingly, the flu viruses H1N1 and H5N1 experimentally induce parkinsonism in mice: the influenza virus H5N1 has been found to cross the protective brain barrier and to destroy the same brain region as the one that is involved in human PD. The H1N1 virus, for its part, was not able to cross the barrier but still indirectly induced death of neurons by triggering a strong immune attack. In mice, one coronavirus has been reported as well to induce parkinsonism and destroy the brain region concerned with PD.

The *neuronal* path of entrance of viruses into the brain –the railroads– are highly suspect in PD. Like in the nose, the neurons that innervate the gut have been suspected as potential doors of entry. Oddly enough, PD patients experience changes in smell and/or gastrointestinal symptoms long (sometimes by decades) before the clinical



The loss of smell, taste and the gastrointestinal disorders which have been repeatedly described in Covid19 patients raise concern on the impact that SARS-CoV2 infection might have in terms of PD. Indeed, several cases of acute parkinsonism have been observed following COVID19 infection. This concern is strengthened by the fact that the 2 other human coronaviruses SARS-CoV and MERS-CoV have been detected in the brain of PD patients, raising the question of a potential link between PD and these viruses... It is however too early to conclude on the nature of this putative link.

(20)
i.e. movement problems analogous to the ones seen on PD.

onset of PD. Last but not least, the brain regions that are successively deteriorated during the progression of the disease are anatomically connected, beginning with neurons in the gut. One famous hypothesis suggests that the progression of a pathogen (virus?) from the gut to the brain might kill the neurons in a corresponding order (like a falling raw of dominos). Could the properties of SARS-CoV2 lead to an increased risk of Parkinsonism in infected patients? See box on previous page.

D – VIRUSES & ALZHEIMER'S DISEASE

Alzheimer's disease (AD), the most common form of dementia, usually starts in middle age or later in life, and is characterized by memory loss, impaired thinking, disorientation and changes in personality and mood. AD is a neurodegenerative disorder characterized – as its name says – by the degeneration of neurons leading to atrophy[21] of the brain. AD is in most cases a disorder of aging but some familial cases (in about 5% of affected patients) begin much earlier in life.

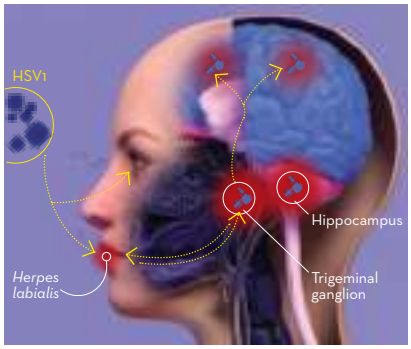
The most common hypothesis is that AD results from the toxicity of certain deposits in the brains of AD patients (which are commonly used to diagnose AD). However, after more than 100 years of AD research – which has more or less led to a dead end in terms of therapy – divergent hypotheses have emerged. For example, it has also been suggested that AD may be – in susceptible patients – a response to viral infections. Among the viruses incriminated – in particular, but not only – HSV1: *Herpes Simplex* Virus 1...

1 ////////// A SEEMINGLY HARMLESS VIRUS...

Everyone knows about the cold sore, or *Herpes labialis*, so called because it is due to an infection by a Herpes virus, HSV1 (*Herpes Simplex* Virus 1). This widely distributed human pathogen is transmitted mainly by intimate contact (saliva) between infected and susceptible individuals. Primary infection generally occurs during childhood and it is thought that over 60 to 80% of individuals under 50 years of age worldwide are infected with HSV1. After infection of the mouth epithelium, HSV1 goes up into the (touch-sensitive) neuron that innervates the mouth region. It then establishes a latent (asymptomatic) infection in the cell body of the neuron (located in a ganglion close to, but out of the brain, Figure 12). A range of stimuli such as emotional stress, UV exposure or immune weakening can however reactivate the virus within the cell body of the neuron. When this happens, a new cycle of replication takes place and the newly-replicated viruses travel back to the lip, where they are released, contaminating other individuals by physical contact.

Figure 12

This picture illustrates how the HSV1 virus that causes the common cold sores enters neurons from the lips, and then moves back into the sensory neuron that innervates the infected region (yellow nerve with dotted line). It then establishes latency within neurons located in a ganglion out of the brain (blue dots in the so-called "trigeminal" ganglion). The virus may however occasionally travel back in the other branch of the neurons that goes from the ganglion into the brain. It may reach several brain regions, and in particular the so-called hippocampus involved in memory.



(21) Shrinking.

(22) Estimated worldwide incidence: 2.5–12 cases/million/year.

Clive Wearing,
a British former musicologist, is a sadly famous victim of HSE. Also known as "the man with the seven second memory", this musician contracted HSE when he was 47 years old, leaving him with a memory capacity not exceeding 30 seconds. After which all his memories are gone, leaving him prisoner of an endless present... The picture on the right illustrates a piece of his diary: Clive is in a perpetual state of momentary standby. He still can play the piano and enjoys listening music. But his entire awareness is limited to a tiny window of time.

>>>

Since several decades he is trying to write a diary. However, he is still busy with writing the first line. Because he doesn't remember anything happened before, every moment feels as a moment of first awakening. Therefore, he is crossing out the previous mention of anything he had just written a few minutes ago and adds a new "first" line to start with.

2 /////////// ... THAT MAY DEVASTATE THE BRAIN

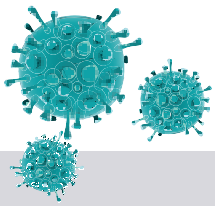
Because touch-sensitive neurons need to transmit sensory signals from skin to the central nervous system, there is also a branch of the axon entering the brain. The replicated virus may also engage into this branch of the neuron (Figure 12). . HSV1 infection of the brain may cause encephalitis (HSE, *Herpes Simplex* Encephalitis), a rare[22] but severe inflammation of the brain. This disease causes 70% mortality in untreated patients, and has a high incidence of neurological sequelae in surviving patients. Some milder forms of HSE have also been described, and even the presence of HSV1 into the brain without symptoms.

What about the link between HSV1 and AD? A number of research teams have suggested that AD may result – in susceptible patients – from the slow degeneration of brain memory regions in response to HSV1. Several arguments have been raised in support of this hypothesis: HSV1 has the potential capability to move into the brain regions most affected in AD. The genetic material and proteins of HSV1 have been found specifically within the brain deposits suspected to induce the disease. In a large cohort of patients treated with medications against the herpes virus, the risk of AD was decreased by a factor of 10; moreover, the ratio of AD in the HSV-infected population was 2.5 higher than the non-infected one. Interestingly, the deposits used to diagnose AD are also found in some people who have no cognitive or memory deficit. New hypotheses now suggest that these deposits could be part of an immune response, engulfing microbes in an attempt to control an infection: this further strengthens a potential role for viruses in AD.

Other pathogens have been suggested to be potentially associated to the development of AD, including the CMV (cytomegalovirus), human *herpes* virus 6A and 7, and even some bacteria. This raises the question of whether the *response* to a pathogen, rather than one specific pathogen, could be a determining factor in the development of the disease... Let's note that the scenario of infection-associated AD has been suggested to take place in *susceptible* patients who carry some genes that are risk factors to develop the disease. This highlights the importance of vulnerability in the development of diseases (see Box 2).

E – VIRUSES & MULTIPLE SCLEROSIS

Multiple Sclerosis (MS) is a disabling disease of the brain and spinal cord that generally affects people between the ages of 20 and 50 years. It is characterized by abnormal entry of immune cells into the brain, by a destruction of the protective myelin that, like a sheath around an electrical cable, covers nerve fibers, and by the degeneration of some axons, causing communication problems between the brain and the rest of the body. Signs and symptoms of MS vary widely between affected patients. Some people with severe MS may lose the ability to walk, but symptoms may include numbness, vertigo, pain, double vision, fatigue, blurred speech etc. There's no cure that allows to eradicate MS.

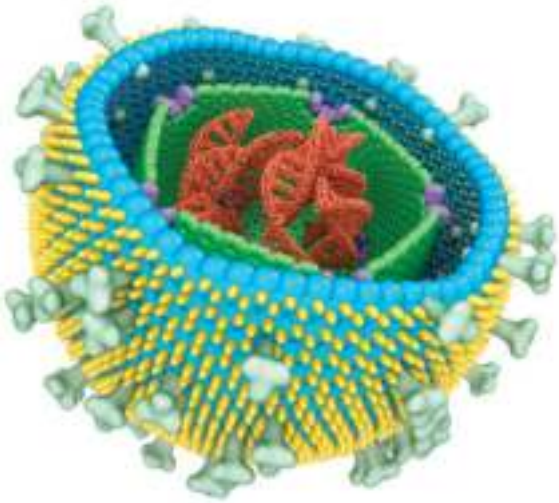


It is of course much too early to assess the impact of SARS-CoV2 on AD. However, a significant proportion of Covid19 patients –especially having suffered from severe Covid– displays memory impairment, sometimes persisting in Long Covid. Interestingly, there is common point of vulnerability between AD, infectious diseases and Covid19: the severity of Covid19 is increased in people who carry a gene of vulnerability to AD.

BOX 2 / SOME PATIENTS ARE MORE AT RISK...

*Individuals do not present the same **vulnerability** to disease. Clearly, the outcome of viral infections in humans (susceptibility to infection, extent of damage) differs from person to person, and is determined by **risk factors**. For example, immunosuppression (inhibition of the immune system) is a risk factor to develop serious infections. Some gene mutations increase vulnerability, for example by modifying the extent of damage. Stress is an important risk factor that is known to trigger many deleterious effects. Many brain diseases have been reported to develop after a stressful event. The outcome of a viral attack can thus range from non infected, asymptomatic to severe illness and death. This range of different human vulnerabilities towards disease (infectious, in particular) further complicates the problem of identifying dormant viruses as possible causes of brain disease...*

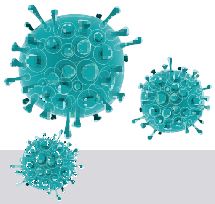
Under normal conditions, there is very limited access of immune cells into the brain: as we know, this strategy is protective as it preserves brain cells from the defensive inflammation that could kill not only the enemy but also the neurons themselves. However, in MS, there is an abnormal infiltration of immune cells and presence of antibodies in the brain. The mainstream hypothesis states that MS is an attack (in particular by antibodies) against the self, with inflammation and destruction of the protective sheath around neurons.



A history of virus infection is considered a key contributor that increases the risk for developing MS. Importantly, some environmental conditioning before the age of 15 confers predisposition to disease. Thus, a considerable amount of time may pass between the initial exposure to the environmental factor (such as a hypothetical viral infection) and first clinical manifestation of MS. Several viruses have been suspected to play a role in the disease, and in particular the Epstein Barr virus (EBV). EBV is a (herpes) virus, transmitted by saliva, which infects more than 90% of humans worldwide. EBV infection generally occurs during childhood and is often asymptomatic, or induces mild symptoms. In contrast, delayed primary infection during adolescence or young adulthood can lead to infectious mononucleosis (IM), resulting in fever, fatigue, headache, sore throat and swollen lymph nodes. The EBV targets a specific type of immune cells, where it remains latent, persisting lifelong in individuals. Previous exposure to the EBV is virtually a prerequisite for developing MS: more than 99% of MS patients are positive for the virus. Moreover, patients who had infectious mononucleosis carry a higher risk (more than doubled) to develop MS. Last but not least, the EBV has been found in the brain of MS patients, yet it is not its usual target organ.

Many viruses have been suggested to be associated to MS, including Epstein–Barr virus, human herpesvirus 6, varicella–zoster virus, cytomegalovirus, John Cunningham virus, human endogenous retroviruses, measles, mumps and canine distemper virus.

How could viruses trigger MS? It has been suggested that a virus might take profit of the immaturity of the immune system (in early age) to enter the brain and remain silent there. A second infection with a resembling virus –later in life– could trigger an immune response and the production of antibodies. If the first and the second virus are relatively close –in terms of structure–, then the antibodies might attack the brain cells which host the first virus that was silent up till then. Such a scenario has been proven possible in mice. The currently available treatments –which target the immune response– are quite efficient in alleviating the symptoms, yet they do not prevent the progression of the disease.

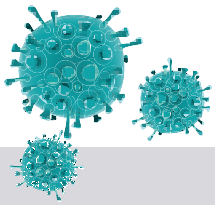


Some human coronaviruses have been found in the brain of patients suffering from MS while some coronaviruses have been shown to elicit a disease resembling MS in mice. Nevertheless, this does not mean that they play any role in the disease. Only one patient has been reported to develop MS following Covid19 infection; however, it was concluded that SARS-CoV2 did not induce the disease but rather precipitated its occurrence. Thus, it is much too early to speculate about any potential effect of SARS-CoV2 in MS; some hindsight will be necessary.

§6 BRAIN DISEASES: LATE EFFECTS OF VIRAL INFECTIONS?

F – VIRUSES & SCHIZOPHRENIA

Schizophrenia is a psychotic disorder that affects the way how a person thinks, feels and behaves. It is an early onset mental dysfunction that generally appears between 16 and 25 years old in average, despite some rare cases of childhood onset. Schizophrenia is a heterogenous disorder with a broad range of clinical expression, and probably causes as well.



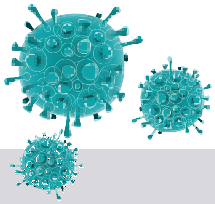
Some episodes of acute psychosis (schizophrenia-like) associated to COVID19 have been reported in a few patients. However, again, it is too early to evaluate the late psychiatric effects. Since they have been shown to possibly occur some years, not to say decades, after a primary infection, a detailed follow-up of the population, including children born from infected mothers, will be important in future generations.

Several epidemiological studies have described a link between maternal infections and risk of schizophrenia in the offspring in a subtype of schizophrenic patients. Several pathogens are suspected to exert potential deleterious effects following an infection during pregnancy, including the *herpes simplex* and the influenza virus. Despite global similar infection rates, the mothers of schizophrenic patients have reported more infections during the second trimester, especially during the fifth month of gestation. Influenza and respiratory infections are the most frequent, accounting for up to 70% of the second-trimester infections. Other studies on the 1957 type A2 influenza epidemic have reported some association between exposure to the epidemics during the second trimester of fetal life and schizophrenia. However, again, one should emphasize the importance of vulnerability: thus, the relationship between infections and psychosis probably remains limited to a subset of susceptible individuals.

G – VIRUSES & CHRONIC FATIGUE

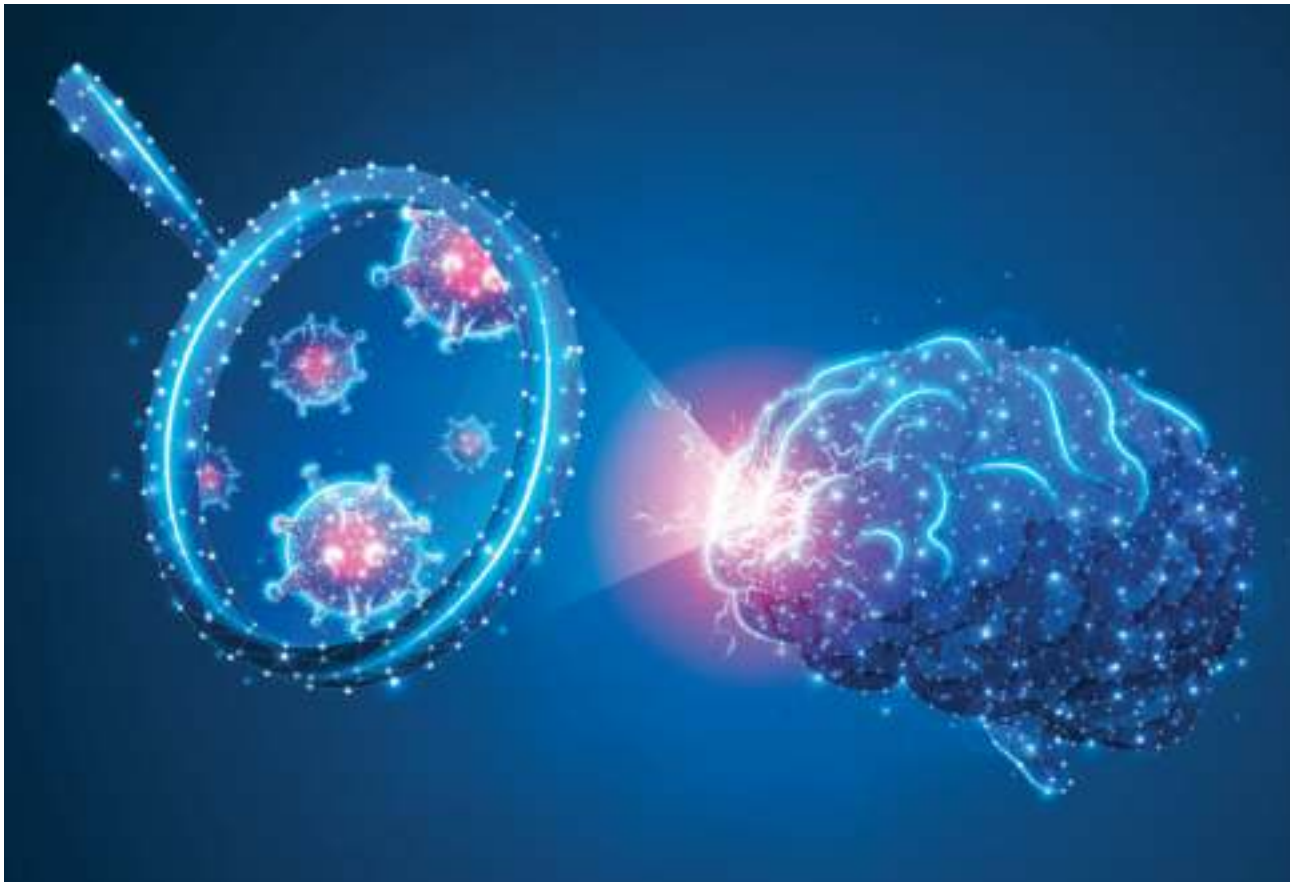
Severe disabling fatigue is a feature of the so-called "Chronic Fatigue Syndrom" (CFS), a condition which is often precipitated following infection, viral in particular. Among others, it is characterized by disturbed circadian (day and night) rhythms: while there is marked lethargy during the day, sleep is very irregular at night. Moreover, there is an overall and important lack of energy.

Inflammation has been suggested to underlie chronic fatigue: it is known that some cytokines (the distress signals) act on sleep neurons and modulate the genes (the region of the genetic handbook) that control day & night rhythms. Many convergent observations suggest a link between infection, inflammation and fatigue.



SARS-CoV2 infection is associated with strong inflammation, linked to the release and circulation of many distress signals. The severe fatigue observed in some Covid19 individuals, in particular in victims of Long Covid, is reminiscent of the fatigue observed in CFS.
Even though the exact mechanism underlying fatigue in Covid19 is not known yet, inflammation is a main suspect, and in particular the inflammation targeting brain cells. Inflammation in the brain may persist for months after an insult, even when the trigger has disappeared, suggesting some self-feeding mechanism. This could be one explanation for the debilitating fatigue associated to "long Covid" but the exact mechanisms remain unknown at the moment.

§7 WHAT MYSTERIOUS SCENARIO(S) COULD LINK(S) – EVEN HARMLESS – VIRUSES TO BRAIN DISEASE?



In summary, Covid19 produces neurological deficits in a significant percentage of patients. Moreover, there is some evidence of links between viral infections and common neurodegenerative or psychiatric diseases. This raises the concern that some vulnerable Covid19 patients might be at higher risk to develop brain diseases later. What possible common features might characterize the effects on brain function of SARS-CoV2 and other viruses?

A – DISTRESS SIGNAL NAVIGATE IN BLOOD

Viral infections (at any place in the body) are associated to local inflammation, which can spread into blood circulation. This phenomenon is particularly important in Covid19: SARS-CoV2 induces the release of distress signals, an effect which is particularly exaggerated in some vulnerable patients (the "cytokine storm"). Importantly, the distress signals which are released **out of** the brain during an infection in the periphery (lungs, for example) are able to inform the brain about the situation. They can propagate the alarm into the brain even if the virus that triggered the distress signals does not enter the brain.

(23) Except in MS where they invade the brain, creating symptoms.

Apart from the classical immune cells which have restricted access to the nervous system[23], there is a type of immune cells specific to the brain, called microglia, which are in charge of immune surveillance. These cells release distress signals in response to a local invader (virus, for example), but *also when they detect an alarm*. The distress signals sent by microglia may last for months even when the primary reason that caused it has disappeared... Thus, like during a war, inflammation is analogous to the weapons used to kill the enemy, it may cause collateral damage... This possibility is a plausible mechanism that probably explains –even without entry of SARS-CoV2 into the brain– at least some of the neurological and psychiatric effects that have already been observed during Covid19. For example, the release of some distress signals in critically ill patients predicts deterioration of hippocampus, a region involved in memory, while it is associated to a decline in cognitive capacities. This effect might unfortunately result from the dual role played by cytokines..

Indeed, there is a phenomenon that is very important during brain development. Called "synaptic pruning", this process –which takes place in particular between childhood and adolescence– consists in the refinement and elimination of synapses. Like sculpturing, synaptic pruning sharpens up a final piece by gradually removing some material (synapses), contributing to the maturity of the brain network[24]. Thus, importantly, development is a phase when the elimination (« pruning ») of some synaptic contacts is as important as the creation of new ones. The capacity of microglia to ingest particles plays a very important role in this process: microglia are able to prune synapses within neural circuits. Even after circuit's maturation, synaptic pruning continues to maintain brain plasticity in adulthood – particularly in relation to learning and memory, which are associated with microglia-dependent plasticity of synapses. And, interestingly, cytokines at low levels are some of the "molecular tools" used by microglia to modulate neurodevelopment. One can easily suspect the potential deleterious role of a chronic increase of these same distress signals later in life... From useful tools during the brain development period, the distress signals might turn into dangerous weapons later in life, engendering the cognitive and memory problems characteristic of brain fog or even some of the psychotic symptoms seen in Covid19... Therefore, a cytokine storm could potentially promote the development of chronic fatigue in vulnerable Covid19 patients.

(24)
For more information on synaptic pruning, refer to "L'axe intestin cerveau: les pistes actuelles", downloadable on www.neurex.org

§7 WHAT MYSTERIOUS SCENARIO(S) COULD LINK(S) – EVEN HARMLESS – VIRUSES TO BRAIN DISEASE?

Figure 13

is chronic low-level inflammation the culprit for the neuronal damage observed in neurodegenerative diseases? Whereas a little oxidation might not create significant dysfunction, the rust accumulated after years or decades of inflammation might turn out to be devastating for brain function...

B –WHY SO MANY YEARS BEFORE THE FIRST SYMPTOMS OF COMMON NEURODEGENERATIVE DISEASES?

Viruses can induce acute and/or chronic inflammation. However, in many cases, viral presence in the nervous system is associated to a moderate immune surveillance, often silent in terms of symptoms. The strategic compromise that consists of diminishing the immune response in the brain in order to protect neurons might unfortunately be a double-edge sword. This might have conferred an evolutionary advantage to many viruses which use this protected environment to establish **latent** infections in the brain, undergoing occasional reactivation. This is true both for some RNA and DNA viruses.

Because this latency is relatively silent in terms of symptoms, the dormancy of a virus may be misleadingly considered as harmless. However, the immune surveillance generates some low-grade inflammation, elicited in order to maintain some pressure on infectious agents. Thus, the common point between different pathogens and late neurodegenerative brain diseases might be the chronic low-level inflammation. The effects of the low-level signals in the brain might become observable many years after infection. A little bit like a little oxidation seems innocuous, whereas the rust accumulated over a long time turns out to be very destructive (Figure 13)...

Thus, in a way, some of the common neurological and psychiatric diseases could be the price to pay for a never-ending immune surveillance of viruses. Indeed, brain diseases such as PD, AD, or schizophrenia are thought to start years, and even decades before they produce visible symptoms, and are associated to inflammation.

CONCLUSION

SARS-COV2, A TIME BOMB FOR NEUROLOGICAL AND PSYCHIATRIC DISEASE?

A close look at common brain diseases affecting important brain functions such as memory, cognition or motricity thus suggests that viruses considered as harmless might potentially be involved in deleterious events years after the initial infection.

Even though only hindsight will reveal the potential late effects of the virus, several features of Covid19 disease place SARS-CoV2 in a position to join this growing list of viruses suspected to potentially play a role in common brain diseases. These features include the fact that (i) SARS-CoV2 has been observed to elicit (memory, motor, etc) problems demonstrating that it can influence brain function in some individuals (ii) SARS-CoV2 is able to enter the brain, at least in some patients (iii) and some display lasting sequelae, even months after the infection, raising the question of a continuous detrimental effect in the brain.

Several important questions remain concerning the Covid19 pandemic: what is the percentage of patients in which SARS-CoV2 might enter the brain? Which brain regions could it reach? What direct effects could it exert (for example directly killing neurons)? What indirect effects (immune response)? Is SARS-CoV2 entirely eliminated after infection or is it able to persist dormant? Is it under immune surveillance in the brain and if yes, will this «quiet fight» be potentially deleterious for the brain? What about infected but asymptomatic patients? Is the virus able to wake up under specific conditions (like immunosuppression) and if yes, what will the consequences be? How do the genetic and environmental backgrounds of infected people influence these effects? Will the long Covid reverse after a while or could it predispose people to late brain diseases?

Importantly, the outcome of infections is not the same in everyone: it depends on genetic background, environmental factors (stress, in particular) but also many other risk factors. Thus, susceptibility will be important to evaluate and it is important to emphasize that a past Covid infection does not predict of course the emergence of future brain diseases. However, even though the long-term effects of SARS-CoV2 infection are highly speculative at the moment, several hints constitute a significant warning for the clinical and scientific community to assess (1) the middle term and late effects of Covid19 and (2) the links between viruses and nervous system function in general.

All these fascinating questions call for interdisciplinary research, where neuroscience and virology will undoubtedly gain from an increase in interactions to decipher the pathophysiological mechanisms of neurological and psychiatric diseases. Furthermore, it raises the importance of assessing the late effects of – even seemingly harmless – viruses.

ANNEX 1

JUNE ALMEIRA, A PIONEER OF ELECTRON MICROSCOPY, IDENTIFIES THE FIRST CORONAVIRUS

The first known coronavirus in humans was isolated in 1961 from a nasal swab obtained from a school boy with a typical common cold. It was however not before 1965 that the pathogen present in this specimen, called B814, was identified as being a novel type of virus. That's one year later that June Almeira, a Scottish scientist, improving electron microscopy techniques, was able to observe virus particles in the B814 specimen. And the beautiful pictures she observed revealed that the virus was surrounded by a kind of halo, like a solar corona. The coronaviruses were born and named as such in 1968. The B814 virus could not however be propagated in laboratory and was exhausted during experiments in 1968. It was thus excluded from further classifications. June Almeira's death in 2007 went unreported despite a tremendous scientific legacy in the field of electron microscopy.

ANNEX 2

WHY THE DEFINITION OF DISEASES FLUCTUATES AND ERRONEOUS DIAGNOSIS MAY TAKE PLACE...

A disease is defined on 3 hierarchical levels: first, by its primary cause, for example, infection by a (specific and identified) virus. Then, by the pathological consequences resulting from this cause, for example, anatomical lesions in one organ (such as the degeneration of some neurons). Finally, by its third level, i.e. the signs and symptoms of the affected patient (like fever and pain). The problem with most neurodegenerative and psychiatric diseases is that their primary cause remains unidentified. Thus, neurodegenerative diseases such as Alzheimer's or Parkinson's disease are characterized – as their name indicates – by the degeneration of certain neurons, but it is not known what causes their destruction. Moreover, the extent and nature of the lesions can be accurately characterized only after autopsy. The diagnosis of these brain disorders is therefore mainly – even though not uniquely – based on symptoms. For psychiatric disorders, the problem is even more complex: in a significant number of cases, even the second-level criteria (brain lesions for example) are often very difficult to identify.

The result is that the criteria used to define many brain disorders are not 100% sensitive or specific : clinical experience demonstrates that the border between diseases is not so clear-cut because symptoms may overlap. Patients suspected to suffer from the same disorder do not always have the same anatomical lesions. Thus, not identifying the cause of a disease implies that there will be people diagnosed as having a disease when they don't have, or that asymptomatic individuals may have it. Two separate causes might also lead to one disease. Identifying the primary cause (and not only the secondary lesions) is therefore of primary importance. This remains a challenge for disorders such as the well-known Alzheimer's Disease, Parkinson's Disease, Multiple Sclerosis or Schizophrenia.

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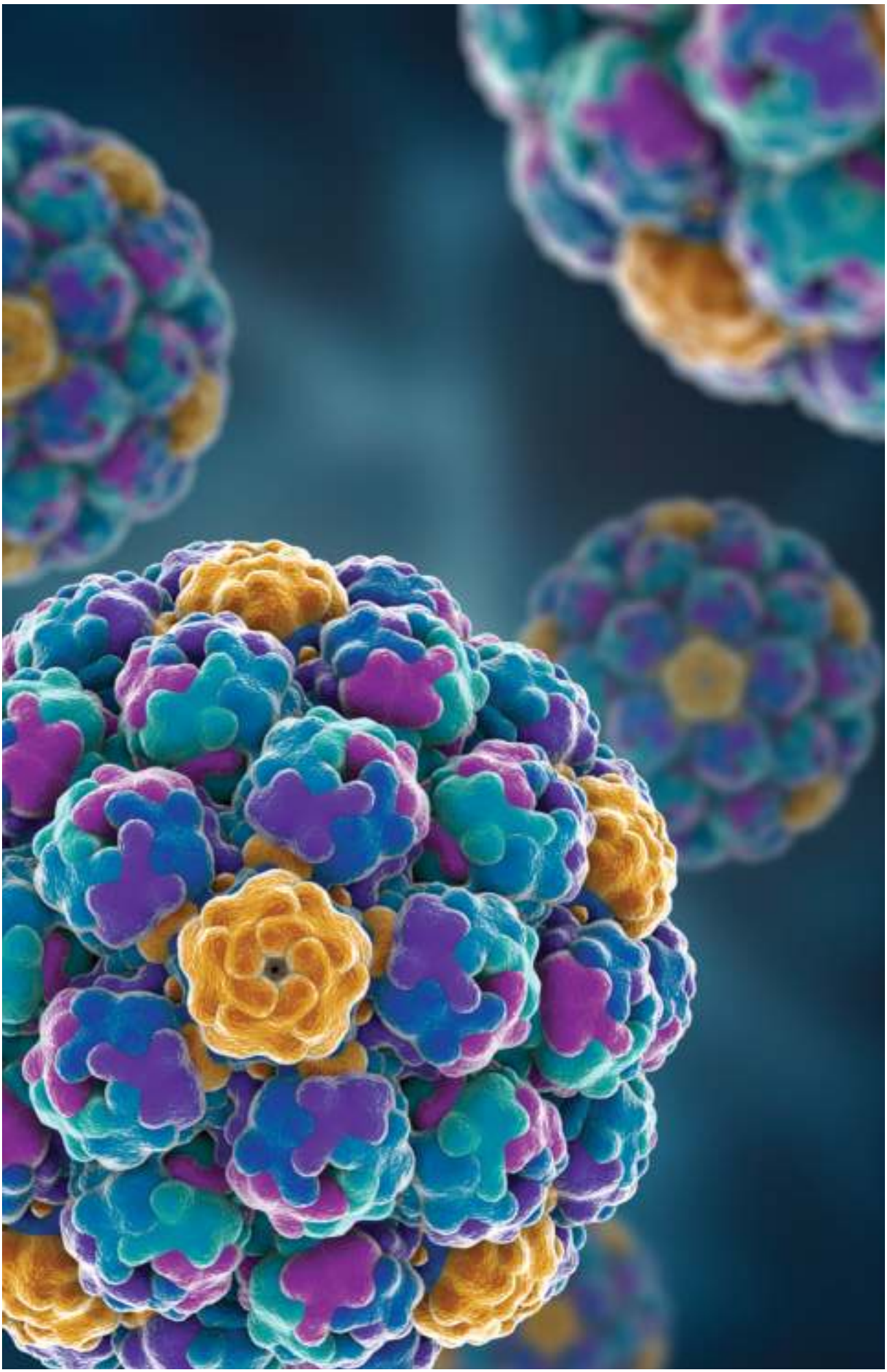

BROCHURE NEUREX

« NEUROSCIENCES & GENERAL PUBLIC » N°3

COVID19,
VIRUSES AND BRAIN DISEASES

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