T he human brain is the most complex biological structure known. Indeed, our brain generates all our thoughts and behaviours, and when it malfunctions it causes hundreds of disorders at any age. In strictly economic terms, this represents a greater burden on society than cancer, cardiovascular disease and diabetes together. Moreover, according to available data, the number of Europeans affected by brain disorders more than double those infected by SARS-CoV-2, meaning that brain diseases constitute an unchecked pandemic, and calling for urgent brain research. To paraphrase Cajal, we will not understand the basis of thought or brain disease until we discover the fundamental principles underlying the structural and functional complexity of the brain. As with all fundamental scientific discoveries, we should expect from further knowledge of the brain not only treatments for brain disorders, but also conceptual changes in the way we understand ourselves and our place in nature.

With the exception of the Institute for Neuroscience in Alicante and the CNIC (Cajal International Neuroscience Centre) in Madrid, neuroscience research at the CSIC is generally carried out by small groups scattered throughout university departments, hospitals and bio-medical research institutes (such as IBiS, CBM, among others). The same could be said of neuroscience outside the CSIC. In the European scenario, things are a little different. In France, serious efforts have been made to foster multidisciplinary centres with a neuroscientific focus, particularly in Oxford (225 groups in neuroscience, neurology and psychiatry), and at University College London. Similar actions are being taken in other countries such as Germany (multiple Max Planck institutes with a neuroscientific focus and high budgets), Finland, etc., together with the creation of new neuroscience centres and programmes in the USA, Japan, China, Australia, among others.

Despite the clear progress that we have witnessed during the 20th century in this field of study, thanks to the adoption of modern disciplines by neuroscience, such as molecular, cellular, systems and computational biology, etc., understanding the causes underlying neurological and psychiatric disorders continues to pose a real challenge. The CSIC’s recent White Paper Volume 5 highlights the institution’s many strengths in this field of study. To tackle the challenges that will lead to determining the causalities of brain disorders and identifying targets for new therapeutic strategies we must answer questions to discover the basic mechanisms of learning and memory, the forces that organise neurons during development to form functional and coherent nuclei and circuits, what principles make the computational mechanisms of neuronal circuits possible, etc. This White Paper also identifies a number of weaknesses, mostly related to organisational aspects of research in our institution. Therefore, it is worth reflecting on the future with more imaginative organisational ideas. We must prepare for the battle to acquire neuroscientific knowledge, because the future is already here.

**Our quest for neuroscientific knowledge**

by **Juan Lerma**

**TERMINOLOGÍA Y ACRÓNIMOS**

- **CNS** (Central Nervous System). The human body’s control system. It is composed of the brain and the spinal cord.
- **NPO** (Neurociencias de la Pyramidal). The main neuron is pyramidal because of its shape. It is located in the cortex and is responsible for motor function.
- **GBR** (Glia Basis for Repair). It encompasses the repair of the central nervous system and it is related to processes of neuroplasticity.

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Neurona piramidal de la corteza cerebral (1904), de Santiago Ramón y Cajal. (Instituto Cajal)

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Céulas gliales de la médula espinal de ratón (1899), de Santiago Ramón y Cajal.

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Teams from the CSIC study how human-built material structures have contributed to cognitive development throughout history.

Biochemists Jesús Ávila and Manuel Serrano and their team have managed to rejuvenate mouse brains.

The company Inbrain, co-founded by CSIC researchers, is developing graphene sensors to decode brain signals.

María Llorens-Martín’s team reveals stem cells in the hippocampus that generate neurons throughout life.

CSIC teams develop devices to enhance neurorehabilitation therapies in adults and children.

Aixa Morales’ team reveals a mechanism reactivating brain stem cells and generating new neurons in mice.

Mind-shaping artefacts

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Reversing brain ageing

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Restoring synapses, a new strategy against Alzheimer’s disease

Tackling the loss of neuron connections could pave the way to drug development.

The obstacle to cerebral irrigation that aggravates Alzheimer’s disease

Blood vessel formation is impaired, hindering oxygen delivery to the brain.

CINC, the new national beacon in neuroscience

The Cajal International Centre for Neuroscience was created to undertake cutting-edge research.

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Exoskeletons help the brain to walk

CSIC teams develop devices to enhance neurorehabilitation therapies in adults and children.
We are witnessing remarkable advances in nervous system regeneration. In Alicante, and José Antonio Esteban, from the CBMSO (Centre for Molecular Biology Severo Ochoa, CSIC-UAM) in Madrid are the coordinators of White Paper on the Brain, and they tell us about the challenges facing neuroscience.

Question: What are the objectives of the White Paper on Brain, Mind and Behaviour?

Answer: One of the main objectives of the White Paper addressing the brain has been to try to predict the main challenges we are going to face in the next ten years in the field of neuroscience so as to place greater emphasis on resolving these issues. We also set ourselves the vital goal of fostering and facilitating collaborations between CSIC researchers who work in different fields but who can contribute highly diverse visions to research into the nervous system.

Q. Does the fact that our brain is studying itself make it more difficult to understand how it works?

A. This is a very interesting and exciting moment in time for a number of reasons. One of them is purely technical. In the last decade, technology has enabled us to carry out experiments that we could only dream about before. For example, techniques such as lithography let us visualise structures, molecular pathways, circuits and processes that were previously invisible to us. In addition, the fact that society is more aware of issues related to mental health and neuroscience certainly helps to make government policies more sensitive to our research.

Q. Where are we in brain research?

A. Research on the brain has been and remains a great challenge because of its extreme complexity and also because its accessibility for manipulation is limited. However, although we may find it curious, the fact that it is studying itself need not be any more difficult than research into any other organ or biological process. After all, brain function is the result of biology, and sooner or later we will be able to unravel the mechanisms that make it tick.
Q. One of the great challenges facing society today, with increasing life expectancy, is to find treatments for neurodegenerative diseases such as Alzheimer’s. What does the White Paper contribute on this point? Will we manage to curb diseases like Alzheimer’s?
A. The integrative approach proposed in the White Paper may be fundamental to tackling this problem. For example, although more and more people are reaching older ages, observations show that the percentage of people with Alzheimer’s is actually decreasing. This may have to do with factors that lead to healthier ageing, such as better eating habits, physical exercise, etc. We may never be able to cure Alzheimer’s, but we may be able to slow the disease down, through a deeper understanding of its mechanisms and the relationship between the brain to the rest of the body.

Q. Mental and neurological disorders are another major challenge for neuroscience, as few have curative treatment. How have we progressed so far and what is the goal? A. We certainly need a better understanding of the mechanisms that generate our cognitive functions. For example, diseases such as schizophrenia or autism spectrum disorders are so difficult to treat because we still do not fully understand how we perceive the outside world and how we interpret it. Nonetheless, we have come a long way. Thanks to remarkable progress in bioinformatics and genomics techniques, we know thousands of genetic alterations that contribute to these diseases. Now the challenge is to integrate all this information and understand the neural circuits responsible for these disorders. Only then can we hope to find effective therapies.

Q. The 14 strategic themes chosen by the CSIC set out to broaden our knowledge with multidisciplinary teams to tackle global challenges. In the specific case of the brain, how important is such an approach, one addressing different perspectives? A. Related to the previous point, it is essential to tackle these problems with multidisciplinary teams. We need experts in biology, chemistry and physics to understand the mechanisms at work in the brain; computer experts to integrate all the molecular, genetic, anatomical and functional information that is being generated; medical personnel who can relate this information to the mental disorders they see in the clinic; engineers to develop new devices that interact with our brains accurately and can restore lost or damaged functions. No one can be an expert in everything, but a national initiative must aspire to be one.

Q. One of the challenges investigates the influence of the microbiome on the body-brain interaction. Can the microbiome condition our behaviour?
A. It certainly can. In behaviours related to autism spectrum disorders or in diseases such as amyotrophic lateral sclerosis, there is already evidence in this respect, which is even guiding the first clinical trials. But this should not lead us to simplify the problem. There is never going to be an antibiotic, a vaccine or a food supplement that will cure autism or make us smarter. The mechanisms being discovered are complex and multifactorial. We have to avoid pseudo-scientific explanations and magical solutions.

Q. Another relevant field is spinal-cord regeneration, where we have seen significant progress in terms of regaining mobility. Will spinal-cord repair be accomplished? A. Indeed, we are seeing spectacular progress in terms of regaining mobility. On the one hand, different electrical stimulation protocols are being developed and, on the other hand, a wide variety of robotic devices are being designed, which are giving very good results. In other words, we are moving in the right direction, but we still do not know enough about the biological mechanisms underlying the function and regeneration of spinal neurons to be able to say whether or not spinal cord repair will be achieved.

Q. Where do you stand in each of the fields in which you are experts? José A. Esteban (CBM): My field is the study of the mechanisms of learning and memory. Traditionally we have studied this from the point of view of individual neurons, i.e., looking into how neurons change when we learn something. Now we are integrating this knowledge to understand how specific neural circuits change, depending on the type of learning or behaviour we are considering. And here, not only are neurons involved, but also glia cells and even the cerebral vasculature that provides energy for all these mechanisms. We certainly need a better understanding of some of the mechanisms leading to the generation of neurons and how they start to connect with each other. But to prevent neurodevelopmental diseases we will require a much deeper and more comprehensive understanding of these processes of neurogenesis and circuit formation. It will also be a huge challenge in the coming years to understand the biological translation of events during childhood, be they either positive or traumatic. In other words, we know that the experiences we have as children have a huge impact on shaping our personality, but at the physiological and molecular level, we do not fully understand how this happens. We still have a long way to go.

Eloisa Herrera (IN): I work on how the nervous system is formed in the embryo and during the first postnatal stages. We have a rough understanding of some of the mechanisms leading to the generation of neurons and how they start to connect with each other. But to prevent neurodevelopmental diseases we will require a much deeper and more comprehensive understanding of these processes of neurogenesis and circuit formation. It will also be a huge challenge in the coming years to understand the biological translation of events during childhood, be they either positive or traumatic. In other words, we know that the experiences we have as children have a huge impact on shaping our personality, but at the physiological and molecular level, we do not fully understand how this happens. We still have a long way to go.

There is never going to be an antibiotic, a vaccine or a food supplement that will cure autism or make us smarter.”

José A. Esteban (CBM)
Throughout history, mankind has dreamed of reversing ageing. For hundreds of years this pipe dream was only in the context of magic. But not anymore. Today, science has fully engaged in undertaking such research. More importantly, scientific groups around the world are making momentous progress. One of the leading companies dedicated to the quest for eternal youth is Alto Labs. This company, fostered by Amazon owner Jeff Bezos, and other billionaires, has already signed up some of the most important scientists in this research area, such as the Spaniards Manuel Serrano and Juan Carlos Izpisúa and the Japanese researcher Shinya Yamanaka. But they are not the only ones achieving results. At the CMBSO (Centre for Molecular Biology Severo Ochoa, UAM-CSIC), the team led by biochemist Jesús Ávila (Madrid, 1945) has managed to rejuvenate the brains of mice through cellular reprogramming in a study that this CBMSO researcher co-directed with Manuel Serrano.

Jesús Ávila, who retired three years ago but is still linked to the CSIC as an honorary professor, explains what led him from his almost exclusive dedication to Alzheimer’s research to brain rejuvenation: “We work on Alzheimer’s disease, which is very complex. And we focus mainly, but not exclusively, on two aspects. On the one hand, we investigate a theoretically modifiable risk factor and, on the other hand, a biomarker that enables us to follow the course of the disease. This modifiable risk factor is ageing.

Considering ageing as a modifiable factor is revolutionary. Throughout the history of biology it was a dogma, until very recently, that life goes from a pluripotent embryonic cell (which can potentially develop into any of the two hundred cell types of the organism) to differentiated cells (which are mature, specialised cells) in that direction only. But in 2006, Japanese scientist Shinya Yamanaka succeeded in creating what have since become known as IPS (induced pluripotent stem cells). The IPS are stem cells with the capacity to become any type of cell, but whose origin lies in a reversion from already specialised adult cells. In other words, this is the start of reverse biology.

To achieve this, Yamanaka reprogrammed cells by genetically engineering four proteins to express genes that act as de-differentiators. These proteins have since become known as Yamanaka factors.

At the same time that research groups were trying to rejuvenate various tissues in the body using Yamanaka’s factors, Jesús Ávila’s group focused on achieving the same in the brain. In the hippocampus there is an area called the dentate gyrus, which is linked to episodic memory (related to biographical moments), which is lost in Alzheimer’s disease. “We think that this area is one of the first to be affected by the disease” Jesús Ávila explains, “and what we have done is to see if we could rejuvenate the brain while slowing down Alzheimer’s disease in genetically modified mice. What we have found is that we can indeed rejuvenate cognitive faculties in this animal model.”

Old becomes new

The results of this work on cell reversion with the cyclic application of Yamanaka’s factors carried out by Ávila’s group have been published in the journal Stem Cell Reports, but it is only the start of a much more ambitious project: “What we would like to do now, and this is the future, is to see how we can replace those factors that we cannot express in humans, because genetic modifications are not allowed, with something simple. When I talk about something simpler, I mean compounds that would be better if...”
natural, cheap and could be given to a person orally or nasally in a very simple way, rather than by genetic modifications. We have already found some things that work. And that’s where we are at. We have already patented something with the CSIC,” explains the researcher.

“That is one part of the work,” Jesús Ávila continues. But we also have another part that is more focused on the mechanics of the process: how and why does it happen? That is where we are designing these theoretically cheap and simple products that can replace Yamanaka’s factors while exerting the same effect. The first part of the work, which was published in Stem Cell Reports, was undertaken together with Manuel Serrano. And we are working on the second one with Juan Carlos Izpisúa.”

While Jesús Ávila’s group has achieved this spectacular progress in the part of research dealing with the possible modification of the risk factor for Alzheimer’s that is ageing, it is also not far behind in the other point of interest in this research area, namely, the biomarker that makes it possible to follow the course of the disease. “We have been working all our lives on a protein called tau, which is linked to the development of Alzheimer’s disease,” explains Ávila.

Jesús Ávila’s group has discovered two new isoforms of tau. Isoforms are versions of a protein with some slight differences from other isoforms of the same protein. These isoforms are produced from related genes or from the same gene by what is known in genetics as alternative splicing. The function of the tau protein is to bind to microtubules, which are cellular structures involved in numerous biological processes, and to promote the cytoskeleton formation of neurons. In people with Alzheimer’s disease and other types of dementia, the tau protein is altered. In these cases, tau forms what are known as neurofibrillary tangles, abnormal protein clumps that break down the cytoskeleton and cause neuronal death.

“Our work has shown us,” explains Ávila, “that not only does at least one of these two new tau isoforms, which we have called good tau, not aggregate but it also impedes the aggregation of the other isoforms.”

Jesús Ávila came up with the idea of how to search for these new isoforms during a meal. “Sometimes we go out to lunch with other researchers,” Avila recalls, “and, naturally, we keep talking about science. At one of these meals, JJ Lucas was there (José Javier Lucas, who studies the molecular basis of Huntington’s disease, is also a researcher at the CBMSO and he recounted research reporting that Huntington’s disease was due to intronic retention problems. It occurred to us to look for tau isoforms that had been produced by alternative splicing. And so far, we have found these two.”
Neurodegenerative diseases hinder the birth of new neurons

Neuroscientist María Llorens-Martín leads a study revealing that stem cells in the hippocampus can produce neurons throughout life and how they can be altered by various disorders.

“We analyse brains of patients at various stages of Alzheimer’s and saw that neurogenesis was affected very early on, even before neurological symptoms became apparent”.

María Llorens-Martín (CBM)

We investigate a process called adult neurogenesis, which involves the birth of new neurons in the adult mammal brain,” explains neurobiologist María Llorens-Martín (Badajoz, 1981) from the CBMSO (Centre for Molecular Biology Severo Ochoa, UAM-CSIC), who received the 2022 Gabriela Morreale National Research Award for young investigators in the area of Medicine and Health Sciences. Llorens-Martín’s group specifically studies “the relationship between the birth of new neurons and various neurodegenerative and psychiatric diseases,” in the researcher’s own words. This is a very new field of study, so much so that we did not even know adult neurogenesis took place in humans until just over twenty years ago.

During many years of research, it was assumed that a person was born with a certain number of neurons, which decreased over the course of life due to ageing and other pathological processes. In other words, the opposite of adult neurogenesis. But at the end of the last century, a different reality was revealed. Specific regions of the adult brain did appear to produce new neurons. And this could have important implications for many neurological processes, which is the research area targeted by Llorens-Martín’s team.

“The birth of new neurons in the hippocampus,” says Llorens, “is related to memory and mood regulation. As these processes are disrupted in neurodegenerative and psychiatric diseases, it has long been thought that there may be a link between alterations in the birth of new neurons and the appearance of some of these disease symptoms. Everything that has to do with brain research is especially difficult, but this is even more so for the research carried out by Llorens-Martín’s group at the CBMSO, and the work currently underway. “The most complicated part has been the construction of a collection of human samples that would allow us to study this process in the brain of our species,” explains the researcher.

Adult neurogenesis in humans was discovered back in 1998 and immediately stirred up enormous interest, but in 2018 a paper was published that seriously questioned the finding. The group behind that research found no markers to prove the existence of newborn neurons in adult brains. Following that publication, and amid international bewilderment at the results “our group showed that such markers are indeed present in some regions of the adult brain”.

Dividing neural progenitors (red) and cell nuclei in the adult human hippocampus.

By Victoria Toro

January 2023 · CSIC INVESTIGA
Llorens-Martín, winner of the National Research Award, leads the European Human project to study in depth the mechanisms that regulate neurogenesis in humans during physiological and pathological ageing.

The importance of sample preparation

Llorens-Martín noticed that the duration of the protocol used to fix the brain samples in the biobanks was over 24 hours. And what happened then was that the antibodies used were unable to detect the proteins identifying the newborn neurons. We obtained the brains of several subjects, divided them into several small fragments and fixed each fragment for a different length of time,” explains Llorens-Martín about this previous work. What we saw then is that, in the same subject, when we fixed the brain sample for a short time, we did see immature neurons, but if we fixed the fragment next to it for a longer time, as is commonly used in other biobanks, the markers for new neurons disappeared. In this work, Llorens-Martín’s group demonstrated that the way in which brain samples are usually prepared is incompatible with the observation of neurogenesis markers. That is, neurogenesis was indeed there but we still don’t know how,” she says. “Right now, we have a very ambitious project called Human, an ERC Consolidator Grant project, funded by the European Research Council, which tries to go one step further in how neurogenesis occurs in humans during physiological and pathological ageing. We are creating a unique collection of samples, with which we are applying high-resolution microscopy methodologies to find out how the new neurons are integrated into the circuit, whether it is possible to detect whether they are functional and whether they are different from mature neurons. We also want to know at the intracellular level what is going wrong in these pathologies, in order to understand the molecular processes, once, at the moment, we know what is going wrong, but we don’t know why it is going wrong. That is the first step, and then we will go back and try to reverse these degenerative processes in rodents”.

That explains the first part of the project, the second is to study these same processes in psychiatric diseases, which receive much less research attention. “We don’t know what these neurons do in the human brain, but we do know what they do in the mouse brain. We have genetic mouse models where we can knock out neurogenesis and see how this negatively affects the mouse. And what we have seen is that they are related to episodic memory, specifically to the separation of very similar information, which is called pattern separation. And, also, with mood regulation. We know that when we suppress neurogenesis, the mouse seems to be more or less normal, but if you make it learn very similar things, it is not able to learn them, moreover, it shows anxiety and depression-like behaviours.” Regarding the potential future applications of her research, Llorens-Martín is very cautious: “We cannot think that our discovery is going to open a therapeutic door immediately, but it is also true that, if this knowledge did not exist, there would be no possibility of a therapeutic avenue that could be explored. Nonetheless, the discovery itself is important in that it provides new knowledge about the functioning of the human brain, information that was previously unknown.”
The mechanisms of neurogenesis envisaged by Ramon y Cajal

By Belén Remacha

Neurobiologist Aixa V. Morales resorts to a quote by Santiago Ramón y Cajal whenever she can, to introduce the studies that have occupied her for over six years. It was uttered by the Aragonese scientist at the time he won the Nobel Prize, in 1906, and reads as follows: “Nervous circuits are something fixed, closed and immutable. Everything can die, but nothing can regenerate. It is the task of future science to modify this cruel decree.”

What the father of neuroscience was saying is that, once the human brain has completed its development in infancy, it stays the same throughout adult life. Until the moment we die, not a single new cell, or a single new neuron is generated in the nervous system. This is not trivial, and embodied our knowledge at the beginning of the 20th century, becoming the dogma for decades. But what Morales, a researcher at the CSIC, finds interesting is the second part of the quote: the Nobel laureate was not pessimistic and predicted with certain humility that science might perhaps one day, when he was no longer around, be able to challenge this cruel decree.

Challenging this dogma stirred in the late 1960s, when some scientists started exploring the possibility that stem cells with the potential to generate new neurons could exist in the animal brain. The dogma was such that many of these findings remained isolated until the 1990s. But the research field was progressing. Brain stem cells have been found in two regions of the mammalian brain: in the lateral ventricles and in the hippocampus. Confirmation that the human brain, and not just some animal brains, has the capacity to generate new cells too, is very recent, and is still shrouded in controversy. It was achieved by several scientific groups between 2019 and 2021, including another CSIC team led by María Llorens, whom Aixa V. Morales usually mentions immediately after Ramón y Cajal.

Aixa V. Morales’ contribution to this puzzle, which already forms part of the history of science, is the work she leads at the CSIC institute named after the Nobel Prize winner: the IC (Cajal Institute) in Madrid. Her team has carried out research in mice. In February 2022, they presented the discovery of a mechanism that serves to activate the brain stem cells of these rodents, enabling them to generate new neurons. In other words, it promotes neurogenesis throughout life, not just in the embryonic phase or in infancy. This finding made it onto the cover of the prestigious journal Cell Reports. “The novelty is that we have discovered how to activate adult mouse stem cells, the stem cells that are normally silent, dormant. They have the capacity to generate neurons, but most of them are dormant,” she explains.

The stem cells they have managed to activate are in the hippocampus, which is responsible for memory and learning. The mechanism for new neuron formation was discovered using transgenic mice. It is based on two transcription factors, Sox5 and Sox6, which are found in these stem cells, which are located in the hippocampus. Transcription factors are like sort of signals sent to cells via DNA to instruct “which programmes to turn on in the cell,” as Morales puts it. On observing that losing Sox5 and Sox6 decreases the capacity for neurogenesis, the researchers found that by altering the levels of these transcription factors they could get stalled stem cells to divide, and thus generate new neurons. “The new neurons mature progressively, forming an axon and dendrites, with which they communicate with the rest of the neurons in the hippocampus,” she explains.

So, what is the point of generating new cells in the brain? When gene editing - such as...
CRIS-PR - and the use of neural stem cells in regenerative therapy is more developed in humans, we think it can be very powerful. Especially for patients with neurodegenerative diseases,” Morales responds. What they believe is that activating stem cells and promoting neurogenesis could compensate for the death of neurons, resulting from neurodegenerative diseases. Alzheimer’s, the second leading cause of death in most European countries, immediately comes to mind. A disease about which little is known yet, but about which “we already have evidence that these patients have altered neural stem cells. It’s a puzzle we are still putting together, but we think it makes sense to try to intervene with neural stem cells to remedy the loss of cognitive ability caused by Alzheimer’s.

Applications in cancer treatment

The researchers are also interested in its application in glioblastomas, a highly invasive and incurable tumour, and Lam-Schaffer syndrome, a neurodevelopmental disorder affecting children. Both appear to be linked to the Sox5 mutation. Part of the team that has worked with her is already meeting with patient associations to see how to move forward on that front. They also seek to understand, in greater depth, the genetic keys to adult neurogenesis: “We want to understand how neural stem cells that last a lifetime are formed in the brain, their development in the hippocampus; at what point they are generated and acquire the capacity to be almost dormant afterwards. And with greater ambition: to discover why these cells that last a lifetime are formed in some areas of the brain and not in others. Why for example, new neurons are not formed in the cerebral cortex but they are formed in the hippocampus,” adds Morales.

Her research project has been funded by the Ministry of Science and Innovation and the Alicia Koplowitz private foundation.

Brain science progresses more slowly than others. Morales points out two main reasons for this: firstly, “the brain has thousands of different types of neurons and cells; it is the most complex part of the human body and therefore the one we know the least about. We know more about many types of tumours than we do about the brain,” and secondly, “brain research involves a series of ethical requirements and exhaustive controls, exceeding those requires for any other disease in humans.” For this reason, such neurogenesis research will continue before reaching patients. When it does, it will be through gene therapy: for example, with adenovirus vectors, such as those that exist in the form of vaccines, which are transported to a particular molecule. In this case, to the brain stem cells they want to activate. Morales does not believe that this type of gene therapy can be used “safely” within the next 10 years. Projecting even further in the future, Morales is considering another possible application: the implantation in patients of stem cells previously prepared in laboratory culture. There are still many tests to be done, but progress is promising.

As always in the history of science and the brain, Morales has not been alone. This project was born of international cooperation and, moreover, young researchers: it began with the PhD thesis of Ling Ling Li, who obtained a grant from the Chinese government to pursue research at the CINC. Morales supervised Li’s thesis, with subsequent work continued by Cristina Medina, another doctoral student, from Jaén. In addition to these two researchers, dozens of students have been involved in this project: “Many young people, most of them PhD candidates, but also some studying the Masters in Neurosciences and Molecular Biosciences at the UAM”, and staff from the IBV (Institute of Biomedicine of Valencia, CSIC-UPV). Morales remembers to acknowledge them all for their contribution to the work, “and also of senior researchers, who have advised us on techniques, researchers from the United States...”. She calls it “laborious lab work” referring to hours and hours spent in the lab. Many other groups around the world are doing this hard work and have identified, among other systems, transcription factors other than Sox5 and Sox6, which also cause neurogenesis when altered. Science scholars around the world are looking for what Ramón y Cajal dreamed of: that future science will modify the cruel laws we believed in.
She did her doctoral thesis at the IN (Institute for Neuroscience, CSIC-UMH) with Alfonso Fairén and Rafael Luján, studying the expression of two of the main neurotransmitters (glutamate and GABA) during development of the cerebral cortex and hippocampus, the part of the brain that plays important roles in memory and space management.

Afterward, she began her postdoc at the laboratory Professor Zoltán Molnár, Developmental Neuroscientist at the University of Oxford. There she learned about the development of neural connections and, specifically, of the thalamocortical system, the nucleus through which we process all the sensory information that we receive from the world around us (except smell).

After four years at Oxford, she returned to the IN (Institute for Neuroscience) with a Ramón y Cajal contract. She joined the

By Isidoro García Cano

Curiosity is the mother of science, as the popular saying goes. Her curiosity to discover how things work is what led Guillermina López-Bendito (Santo Domingo, Dominican Republic, 1975) to study one of human beings’ greatest enigmas: the brain. Born in the Dominican Republic during hurricane season (hence her middle name, Eloísa), she studied biology at the University of Alicante, to which her parents returned so she could pursue her professional career. As she previously related in Las científicas cuentan, a project focusing on women scientists, “one day a professor from the Institute for Neuroscience came looking for minds and I jumped on the bandwagon.”

Her team has shown that astrocytes can be reprogrammed in mice to become specific neurons to replace those damaged in sensory circuits of sight or hearing.
Regarding sensory pathways, we know a lot, but we know very little if we ever want to answer that question, we have to start by asking smaller, less encompassing questions, which are realistic in the context of today’s methods but ambitious at the same time.

Q. Do we perceive the world as it is or as we recreate it in our brains?
A. That question echoes back to classical philosophy. The debate continues despite tons of books and articles. There are many examples that tip the balance towards the second option, for example, the rubber hand illusion [an experiment where someone was placed at a table with their left hand hidden by a panel and only a rubber hand was left in view; on stroking the same areas on both hands with a brush, the participant, who could only see this action on the rubber hand, later claimed that they had felt the rubber hand being caressed].

Q. Your lab has shown that astrocytes (nervous system cells important for brain function) in mice can be reprogrammed to become specific neurons to replace those damaged in sensory circuits of sight or hearing... Will we be able to reverse certain types of blindness or other sensory diseases?
A. That is the objective, and having a clear goal is an important part of the research. Now, the results obtained by our group and others are positive, but they are also preliminary. Translating basic research results into clinical applications takes years, with many attempts, many failures and some successes.

Q. What would be the key breakthrough or breakthroughs to achieve this?
A. The key breakthrough would be for the astrocyte to become the type of neuron we are looking for, and for this neuron to integrate and function normally in the existing damaged circuit.

Q. You are leading the European Research Council’s Spontsense project to understand the mechanisms of sensory circuit specification in the developing brain. Will we see this brain function deciphered in the 21st century?
A. I don’t know, but what I do know is that if we ever want to answer that question, we have to start by asking smaller, less encompassing questions, which are realistic in the context of today’s methods but ambitious at the same time.

Q. In the time you’ve been researching neuroscience, which advances have impressed you most?
A. There are several to choose from. For example, brain implants of small technological devices that enable a person who is totally paralysed by amyotrophic lateral sclerosis (ALS) to speak again. There are two important facets working in tandem here. First, the technological advances that have led to the development of these devices, which can capture how a large population of neurons is activated and is able to translate that activity into words. And second, the brain’s extraordinary ability to adapt to extreme situations. Patients train their brains to activate the implants to produce the desired sounds.

Q. Your research focuses on the study of the system by which we perceive the world through our senses such as sight, hearing and touch. Specifically in the thalamus, the organ that receives information from outside, and the cerebral cortex, which processes it... What is known and what is unknown about this system?
A. We know a lot, but we know very little if we consider all that we could know. This is true for almost any field of neuroscience. Regarding sensory pathways, we know quite well how sensory receptors capture information from the environment. The tricky part is when we ask how this information is represented in more complex brain structures downstream of the sensory receptors, such as the thalamus or the sensory cortex. It is difficult to reconstruct a sensory stimulus just by looking at the neuronal activity in the thalamus or cortex, and much more difficult to know what that stimulus represents to the organism at that place and time.

Q. Over 100 years ago Santiago Ramón y Cajal won the Nobel Prize for Medicine for his work on the structure of the nervous system... Will the next Spanish Nobel Prize also be for research on the brain?
A. It is likely that our next Nobel Prize in science will go to a Spanish researcher carrying out their work abroad.
Restoring synapses, a new strategy to tackle Alzheimer’s

By Mónica Lara del Vigo

By 2030, around 78 million people will suffer from Alzheimer’s disease, according to the World Health Organisation. The huge impact it has on patients and their families, as well as its growth due to demographic ageing, has led to this pathology being labelled the 21st century pandemic. Since the first drugs became available in the 1980s to slow down the cognitive deterioration of those affected, the scientific community has been working hard to make therapeutic progress. The CSIC has several institutes and research groups dedicated to this task. One of them is the IC (Cajal Institute), where biologist Alberto Ferrús led the team that published a study in the journal Molecular Biology of the Cell in 2020, which could open up new avenues for developing drugs against Alzheimer’s disease.

The research, which had to be halted mid-pandemic, identified a mechanism to slow down the loss of synapses (connections between neurons to transmit the nerve impulse between them), which occurs during the disease. “We wanted to test the effect that an artificial increase in the amount of PI3K protein could have on the number of synapses,” says Ferrús. That idea did not come out of the blue. In previous studies, his team had already seen that the PI3K molecule is responsible for instructing neurons on how many connections to make. “Our premise was: if the number of synapses increases when the amount of PI3K goes up, we could apply this to cases of Alzheimer’s disease, where we know that neuronal connections deteriorate and decrease,” he adds.

To explain his thesis, the biologist stresses the importance of a gene, the amyloid precursor protein (APP), which is found in virtually all organisms, including humans, and whose function, although not well understood, is involved in the good health of many cell types. “APP undergoes two types of cleavage by two different enzymes: one cleavage generates a fragment, called a peptide, which is 40 amino acids long (Abeta40); the other cleavage generates another very similar fragment that is 42 amino acids long (Abeta42).” He continues: “Normally, all cells have both Abeta40 and Abeta42 fragments, and as long as the ratio of the two remains stable, we are talking about normal biology. But for various reasons, the balance between Abeta40 and 42 becomes unbalanced in favour of the latter. When that happens, Alzheimer’s ensues. In other words, these patients’ brains show an accumulation of toxic levels of this molecule, which is caused by diverse genetic mutations associated with ageing.

Abeta42 peptides would therefore be the “bad guys”, although with certain nuances. As independent molecules (monomers), they are not very toxic, but they can join in the form of two or more molecules and form dimers, trimers, etc. This can lead to a large formation called a beta-amyloid plaque. “Monomers are not very toxic, dimers start to become toxic, trimers more so, and so on. However, a beta-amyloid plaque is not toxic per se, it is a monster formed by so many mo
that it has no chemical activity whatsoever," explains Ferrús. Until recently, scientists were mistaken when they looked at a slice of brain tissue affected by Alzheimer's disease under the microscope. "Seeing these clumps, we thought they were toxic. But then 10-15 years ago we discovered that the toxicity came from the smaller formations (the oligomers, which range from dimers to pentamers)," he clarifies.

On that basis, they began a series of experiments in which the protagonist was the fruit fly, namely Drosophila, an organism that can be genetically manipulated simply. Ferrús' team decided to make "tailor-made bugs" that had an excess of PI3K protein and also an abnormally high amount of the peptide Abeta42. "They knew that this would trigger the loss of synapses, but they also wanted to see if this could be compensated for by increasing the amount of PI3K."

The hypothesis was confirmed. But they also found that Abeta42 toxicity manifested itself at many levels, not only did it cause the loss of synapses, but also the dismantling of certain cellular structures (microtubules), the reduction of the flies' half-life, and their mobility. "We tested everything in these insects. The surprise was that all the parameters were improved compared to the Abeta42-expressing specimens alone," he says.

However, his team had another surprise in store, which they had not counted on. The researchers thought that in flies whose synaptic symptoms had subsided, they would also see fewer amyloid-beta plaques, but the opposite was true. How was this possible? "This increase in the plaques fitted in with the idea I explained earlier: the plaques themselves are not the cause, but are actually a strategy of the cell to free itself from the truly harmful agents, the oligomers," he explains. So, what is the mechanism that drives an increase in beta-amyloid plaques? The key lies precisely in the introduction of PI3K, a kinase that, when phosphorylated, alters the pathological molecule Abeta42, forcing it to precipitate in the form of plaques. This reduces the amount of Abeta42 monomers and oligomers, which are the ones causing toxicity in the cell. As a result, neurons do not lose synapses. "What we did with this experiment was to restore the amount of PI3K in the cells, which had been reduced due to the toxicity of Abeta42," adds Ferrús.

After experimenting with flies, the team did the same with human cell lines (groups of neural cells grown in the laboratory) and obtained identical results. For Angel Acebes, co-author of the study and currently a researcher at the University of La Laguna, the novelty is that they demonstrated that "the increase in synaptic contacts has a beneficial and neuroprotective effect in a context of neurodegeneration," both in a genetic model of Alzheimer's disease, using Drosophila flies, and in human cells in which toxicity was induced to create a pathological environment similar to that of the disease. From this perspective, the research could be the springboard for the development of new drugs, as it is based on the restoration of synapses as a therapeutic strategy. "Alzheimer's disease is neurodegenerative, but in the early stages of the disease, before neurons die, they begin to lose synapses, i.e., the close connections between them. If a drug could reverse or stop that early synapse loss, we would be in a better position to protect them before they degenerate," Acebes explains.

Seeking early detection of Alzheimer's disease

When, in 1901, Dr Alois Alzheimer examined Auguste Deter, the first patient diagnosed with what he called the "forgetfulness disease," he concluded that he was demented and had no doubt that it was a brain pathology. Later, when millions of patients had been diagnosed with Alzheimer's, researchers "discovered that there were beta-amyloid plaques not only in this organ, but also in the liver and other tissues," highlights Ferrús. The researcher believes that little attention has been paid to this fact because a neural defect is far more striking.

A previous study in which the biologist also participated, published in 2017, focused on this question. "We wanted to find out whether other non-neural cells expressing Abeta42 also suffered toxicity. We found that they did. In the epithelial cells of the Drosophila fly's wing, we saw tremendous disturbances affecting the expression of a whole family of genes. We found a kind of metabolic signature of expressing Abeta42 in non-neural cells."

Ferrús believes that this finding, beyond its academic interest, could have a practical utility that has not yet been explored. "It would be a very cheap system, and above all very fast, to test existing or new pharmacological products and find out if the toxicity of Abeta42 can be prevented or reduced in other cells. Doing this in the nervous system takes time and is more complicated, but doing it in fly wings is easy and can be done in huge quantities," he says. Although now and again the media report advances in early diagnostic tests, they are generally not statistically supported. Ferrús gives an example: "It is known that a type of neuronal cell, those of the olfactory bulb, are very sensitive to Alzheimer's and also to Parkinson's. Defects in olfactory perception have been correlated with future defects associated with these diseases, but the existing database is too small for the correlation to be statistically reliable. In contrast, our proposed method would work with specific molecules that we know have a causal relationship with Alzheimer's disease. When Abeta42 increases, that metabolic signature I was talking about appears. It would be a matter of extracting a very accessible sample and analysing it. No one has done it yet and it would be worthy of investigation."

Ferrús has retired now, but his message is clear and so is his audience: "I would tell the pharmaceutical companies to take note; there is an avenue here that could lead to the discovery of new drugs. I would be happy to tell them our ideas," he concludes.
Obstructed brain blood supply aggravates Alzheimer’s

The dreaded neurodegenerative disease alters the generation of new blood vessels and thus hampers the arrival of oxygen and nutrients to the brain, according to a study co-led by the CSIC.

By 2030, in just seven years’ time, one in five people living in Europe and the United States will have turned 65 years of age. And in 2035, for the first time, people over the age of 65 will outnumber those under the age of 18. As a result, the prevention of age-related diseases such as Alzheimer’s, an invisible pandemic, is of growing importance for quality of life, public health and the economy.

Aging is the main risk factor for developing Alzheimer’s disease. The disease, which begins several decades before the first symptoms appear, affects one in 10 people over the age of 65, a figure that rises to three in 10 over the age of 85.

Without effective medication to at least slow down the progression of this devastating pathology, prevention is our best bet, for the time being, to reduce the incidence of the disease. In 1906 Alois Alzheimer first described this condition, for which there is still no effective medication, and which is one of the greatest challenges facing medicine today.

Beyond focusing on the two proteins characteristically associated with Alzheimer’s, beta-amyloid and tau, so far with little success, there are other modifiable factors that can be targeted. Indeed, a recent paper published in the journal PNAS reported a 30% decrease in the number of elderly people with dementia in less
described how the brains of Alzheimer’s patients accumulate markers that are associated with poor oxygenation. To explore this finding further, the researchers set out to discover whether this neurodegenerative disease could directly affect the brain’s blood vessels, which would explain the comorbidity with peripheral vascular deterioration factors and the lack of oxygen observed in the brain of Alzheimer’s patients,” explains Pascual.

After an analysis of previous studies on cerebral vasculature in Alzheimer’s patients, the researchers realized that there were signals in the brain for the creation of new blood vessels, by a process called angiogenesis, but at the same time there was a decrease in the number of functional vessels observed near the beta-amloid (Aβ) plaques, characteristic of this neurodegenerative pathology. “All this was paradoxical: the brain was demanding the generation of new vessels but the net result was their absence,” Pascual points out.

Research groups from the University of Malaga (Prof. Antonia Gutiérrez), the CIEN Foundation (Dr. Alberto Rábano), the Cajal Institute (Dr. Fernando de Castro), Alcante’s Institute for Neuroscience (Dr. Eloisa Herrera), the University Medical Centre Hamburg-Eppendorf (Dr. Jakob Körbelin) and IBIS (Prof. Javier Vitorica, Javier Villadiego and Miriam Echevarría) collaborated in this study published in Nature Communications.

They focused on a possible dysfunction of angiogenesis. This mechanism is important during embryonic development to form brain vessels and in adult life to recover from damage to pre-existing vessels. The work showed that Alzheimer’s disease induces dysfunctional angiogenesis that leads to vessel loss rather than vessel formation, which undoubtedly aggravates this neurodegenerative pathology.

Blood vessel disruption

Published in Nature Communications, this study led by the Pascual lab at the IBIS Neuroscience (Dr. Eloisa Herrera), a joint centre of the CSIC, the University of Seville and the Virgen del Rocío and Macarena University Hospitals.

A hallmark of Alzheimer’s is the accumulation of highly toxic substances in the brain in what are known as senile plaques. Transport through the blood is one of the mechanisms by which these toxic substances from the brain. “The fact that the plaques cause the loss of blood vessels leads to a vicious circle: new blood vessels mean decreased brain cleansing and so more toxic substances accumulate, which in turn continues to destroy the blood vessels and aggravate the situation in the Alzheimer patient’s brain,” says Pascual.

Moreover, as the brain takes up a large part of the body’s oxygen (20 %) and nutrients, the local reduction in the supply of these substances through the blood is an added stressful situation to the already existing accumulation of toxic substances in Alzheimer’s disease.

The data provided by this research also linked familial Alzheimer’s, which has a genetic origin, to problems in the vascular component in this pathology, affecting over 1,200,000 people in Spain.

As a proof of concept, researchers led by Pascual showed that there are significant improvements in memory capacity in models of Alzheimer’s disease on administering anti-angiogenic treatments used to treat cancer.

They are currently working on demonstrating the importance of restoring cerebral blood vessels to improve cognitive function in people affected by the disease. “Once the molecular pathways involved in this destructive process of the blood vessels associated with Alzheimer’s disease have been identified, new therapeutic strategies can be rationally designed to alleviate the effects of this disease on the brain’s blood vessels,” concludes Alberto Pascual.
CINC: new internationally ambitious beacon of neuroscience

The Cajal International Centre for Neuroscience was created to undertake cutting-edge research on the brain and provide knowledge for the prevention and treatment of diseases such as Alzheimer’s, Parkinson’s, addictions, depression and schizophrenia.

The CSIC has launched what is perhaps its most far-reaching brain research project, the Cajal International Neuroscience Centre (CINC) in Alcalá de Henares, which aims to become the new beacon of Spanish neuroscience with international ambition. It is located at the CIC biomaGUNE, the new interdisciplinary research centre in Alcalá, housed in a modern 28,000 m² building on the Alcalá de Henares University campus, which will be equipped with the most advanced technologies and complete scientific and technical support services.

With this large research complex, the CSIC aims to undertake cutting-edge multidisciplinary research to unravel the basic workings of the nervous system, attract the best talent from around the world and achieve a more dynamic and flexible organisational model.

The CINC has a vital mission: "To provide basic knowledge for understanding the brain and behaviour, and to make this knowledge available for prevention programmes and the design of therapies for the most devastat-
ing diseases, such as Alzheimer’s, Parkinson’s, addictive behaviours, depression, or schizophrenia, thus fulfilling the general objective of conducting translational research,” according to its director, neuroscientist Juan Lerma.

The CINC is committed to carrying out excellent, competitive and innovative research, fostering collaboration between the best national and international groups in new projects, which are also capable of attracting both the private and public sectors so the results achieved have great impact on society.

**Cutting-edge research**

The lines of research proposed for the CINC are organised along five main lines, ranging from brain development and maturation to computational and systems neuroscience, including research into brain ageing and brain physiology and plasticity, with a high level of translational neuroscience, i.e., clinical applications.

These guidelines are based on the recommendations for priority topics set out in the Consensus Statement on European Brain Research developed by the European Brain Council (the network of key members in the field of neuroscience bringing together research centres, professional societies, patients and industrial partners) for the understanding of the brain, as well as those set out in the CSIC’s White Paper on the Brain, Mind and Behaviour, addressing the scientific challenges of 2030.

**Flexible organisational model**

The CINC is a CSIC centre aiming to attract talent and excellence based on a modern and flexible management model, both in terms of its cutting-edge scientific-technical services and its staff. “We hope that in the future it can become a public foundation sponsored mainly by the CSIC, which would give it the flexibility and autonomy to attract talent and excellence,” says its director.

**Attracting the best talent**

In 2021, the CINC issued a call for expressions of interest in this project from groups inside and outside Spain. A total of 141 expressions of interest were received, 77 of which corresponded to groups established in institutions both in Spain and abroad. The Scientific Advisory Board (SAB) of the CINC evaluated these expressions of interest and made a selection, which served as a basis for the CSIC to put out a call for 16 positions at different levels for the CINC within the Public Employment Offer of 2021. Groups have already been recruited from Portugal, the United States, Australia and the United Kingdom, in a clear action of talent return and recruitment.
Flames’ team, at the IBV (Institute of Biomedicine of Valencia, CSIC-UPV), is studying in depth how the genetic mechanisms of this specific cell specialisation develop. To do this, they are combining mouse models and a type of millimetric worm (the nematode Caenorhabditis elegans), which contains a regulatory genome (one bearing the information that tells each cell what type it has to be) that is 50 times smaller than that of humans. Despite its simplicity, this nematode generates more than 100 different types of neurons during development.

“We want to understand how a single genome that is shared by all cells in the organism is specifically decoded to give rise to the different types of neurons present in our brain,” Flames explains. “In other words, how during embryonic development, a neuron that is going to mature knows specifically which genes in the genome to activate,” she explains. “Fundamental to this process are the so-called transcription factors, proteins that bind to non-coding DNA (the regulatory genome) and which can regulate the expression of specific genes.

In the lab headed by Flames, researchers seek to understand the fundamental rules, or principles, that organisms use to generate neural diversity. “Because these are such basic processes, we expect that many of these principles are conserved between nematodes and mammals,” she says. In order to do this, they need to understand which transcription factors are involved in this function and the mechanisms used to decode the regulatory DNA sequences.

It is vital to understand how non-coding DNA works. “In fact, most disease-associated mutations, including those in the nervous system, are found in non-coding regions of the genome, probably affecting gene expression levels. However, because we don’t fully understand how
the regulatory genome works, we cannot assign biological significance to most of these mutations,” she says.

Circuits regulating aggression

Researcher Félix Leroy’s team is investigating the neural origin of social behaviour. Specifically, he studies two regions that could play a key role in social aggression. On the one hand, Leroy found that an area of the hippocampus called CA2, which is involved in encoding social memory, exerts an intense pro-aggression. On the one hand, he studies two regions that

- leroy has focused on the lateral septum area because it is a prime candidate for playing a key role in regulating motivated behaviours, such as the satisfaction of physiological and social needs. “It is very likely that it integrates cortical signals to regulate the activity of the hypothalamus and subcortical nuclei controlling motivated behaviours,” says Leroy. “Knowing these signals are integrated is vital because any dysfunction of the circuitry between the septum and the cortex can lead to altered social behaviour, a feature indicative of many psychiatric disorders.

Cerebellum: an up-and-coming secondary player

The cerebellum is a region of the encephalon at the back of the brain that has traditionally been associated with motor functions such as coordination and precision of movements. But the cerebellum may have other functions associated with cognition, language and emotion, and its dysfunctions may lead to neurodevelopmental disorders. The cerebellum is targeted by the team led by Juan Antonio Moreno-Bravo, a researcher at Alicante’s IN (Institute for Neuroscience). “We study the basic regulatory mechanisms underlying the formation and function of cerebellar circuits,” he explains. For this investigation, researchers are developing animal models with alterations in the development of the cerebellum to observe how they affect the global function of the brain.

“We hope to understand whether such lesions in the cerebellum alter the cerebral cortex during development and whether abnormal functioning of this region leads to some of the major impairments associated with disorders such as autism spectrum disorders, among others,” he adds.

“Ultimately, we want to understand the contribution of the cerebellum to overall brain functioning, both in normal development and in the context of neurodevelopmental disorders,” concludes Moreno-Bravo.”
Thiamine treatment may help combat Huntington’s disease

A team led by CSIC and CIBERNED has identified a molecular mechanism that explains low levels of thiamine (vitamin B1) in the brain of people with this serious disease characterised by progressive nerve-cell degradation, for which there is still no cure.

By Aser García Rada

Huntington’s disease is a rare, severe, inherited neurological disorder causing progressive degradation or degeneration of nerve cells in the basal ganglia, at the base of the brain. Sufferers of this condition are born with a genetic mutation located on chromosome 4; however, symptoms do not commonly appear until after the age of 30 or 40 and can develop very differently, even among family members. They include alterations in movement, thinking and behaviour that can be very incapacitating. Although there are treatments that help to control some of the symptoms, there is no cure that slows down or stops the disease.

In the search for such a therapy, a therapeutic target that could guide new treatments has been identified by a team under José Javier Lucas, a researcher at the CSIC and the CIBERNED (Network Centre for Biomedical Research in Neurodegenerative Diseases) at the CSIC-UAM joint research centre CBMSO (Centre for Molecular Biology Severo Ochoa). Although the underlying mutation causing Huntington’s disease is already known and gene silencing therapies preventing its development are being tested, the molecular mechanisms involved must be explored more deeply so that specific treatment targets can be identified. “There are no curative treatments for most neurodegenerative diseases. Although some are being developed based on gene therapy or antibodies they have the drawback, in addition to their high costs, that they are based on molecules whose large size hinders accessibility to the affected brain areas. That is why it is important to identify new therapeutic targets that can be addressed using drugs that are easily administered,” says Lucas.

Their research, published in the journal Science Translational Medicine, suggests a new molecular mechanism causing Huntington’s disease, which would cause levels of thiamine, or vitamin B1, essential in several bodily chemical reactions, to malfunction in the brain, which could be playing a role in the disease.

Vitamins as a potential treatment

Specifically, the researchers point out that a process involved in the correct production of certain proteins inside cells, called polyadenylation of messenger RNA (mRNA), undergoes changes in neurodegenerative diseases, which directly links this mechanism to these pathologies. These are cytoplasmic polyadenylation element-binding proteins (CPEBs), which regulate the expression of certain genes. As Lucas observes, “one of the genes most affected by the alteration in CPEBs is SLC19A3, which contains the information to generate a protein that acts as thiamine transporter”, which reduces the levels of this vitamin in the brains of these patients.
Thiamine is essential for brain function and, when it is lacking, neurological conditions such as Wernicke-Korsakoff syndrome or Biotin- and Thiamine-responsive Basal Ganglia Disease (BTBGD), which affects the same brain structure as Huntington’s disease, i.e., the striatum, says Sara Picó, researcher at the CBMSO and first author of this work, which has shaped her PhD studies.

The research team led by Lucas has studied this process in Huntington’s disease, the most prevalent of the hereditary neurodegenerative diseases, which affects around 4,000 people in Spain. Their research has shown that these alterations reduce the transport of thiamine into the brain, and that these changes can improve in individuals with BTBGD. Consequently, his study suggests new therapeutic options.

**A ghost in the family**

The disease is named after George Huntington, an American physician who described it in 1872 and identified its hereditary nature. Although its symptoms can crop up at any time, they usually appear in adulthood. They involve psychiatric and motor disorders that develop slowly over years or decades. Severe psychiatric disorders often precede motor disorders, including depression, concentration difficulties and eventually dementia.

Charactertistically, the disease is evidenced by abrupt jerky limb movements known as chorea, which is why its original name was Huntington’s chorea, and uncontrollable facial grimacing. In advanced stages, it impairs speech, thinking and memory. It can also lead to complex and painful body positions that last for hours. All this can also lead to frequent suicidal tendencies, having a major negative impact on family members and caregivers.

**This hereditary disease usually manifests itself in adulthood, after the age of 30 or 40, through involuntary jerky movements, psychiatric disorders and dementia.**
Protein **CPEB4**, key to developing autism, sheds light on the biological basis of this disorder

A team co-led by the CSIC demonstrations that a protein exerts a regulatory function on the risk genes responsible for autism spectrum disorders, paving the way towards therapeutic developments.

In 2018, an international team co-led by José Javier Lucas, CSIC researcher at CBM-BSO (Centre for Molecular Biology Severo Ochoa, CSIC-UAM) and CIBERNED (Network Centre for Biomedical Research in Neurodegenerative Diseases), together with Raúl Méndez, researcher at the IRB Barcelona (Institute for Research in Biomedicine), identified that a protein synthesis regulator, CPEB4, was affected in most cases of autism. The researchers observed that CPEB4 defects trigger the expression of the majority of the 200 risk genes that are dysregulated.

The work, which was published in the journal Nature and led to Lucas being awarded the 15th Health Sciences Award (Fundación Caja Rural Granada) in 2019, contributed to shedding light on a previously unknown aspect of the genetic basis of autism, shedding light on a previously unknown aspect of the genetic basis of autism, paving the way towards therapeutic developments.

**By Azucena López Márquez**

Asperger’s syndrome, also known as autism spectrum disorder (ASD), opened a promising path towards the therapeutic development of autism. Risk genes, responsible for the nervous system configuration and brain function. Autism spectrum disorders are estimated to affect one in every 100 people in Spain. There are about 200 genes that, when mutated, increase the risk of developing ASD, but there was scant knowledge about the molecular mechanism linking these risk factors with each other, and with other environmental factors playing a potentially important role in triggering these disorders.

The researchers discovered that a protein called CPEB4 may be the link regulating the expression of most ASD risk genes.

Since 2018, and the subsequent four years, new works have appeared that have searched deeper into what Lucas, Méndez and Alberto Parras, first author and CBM-BSO researcher, discovered. Some studies identify new genes regulating gene expression that have the same type of alteration in autism that they saw in CPEB4. In addition, his research group has shown that the CPEB4 dysfunction also appears in schizophrenia. Regarding the potential as a therapeutic target suggested by their 2018 study, they have proven that a technique other than gene editing can be used to correct the imbalance in CPEB4.

So far, they have only been able to test it on cells in vitro, but they are studying ways to explore its potential in vivo and have patented the new tool that has been developed in collaboration with a group from CBM-BSO, led by Lourdes Ruiz Desviat, and another from the Danish University of Syddansk, led by Brage And someone. “It is also possible that at some point gene editing may be used to tackle the CPEB4 gene so as to correct its dysfunction in autism. But it is not easy, because above all this technique enables us to correct a gene whose sequence is altered, but in the case of autism it is a matter of correcting the imbalance between two forms of the CPEB4 protein, without the gene harbouring any mutation,” says José Lucas.

In recent years, important progress has been achieved thanks to genetic analysis of thousands of patients, but a paradigm shift is still needed. “We are probably in a similar situation with respect to autism as we were for cancer a few decades ago. In the beginning, cancer was considered a single disease, characterised by uncontrolled cell division. Significant advances in the understanding and treatment of cancer have come later on when it became clear that there is not one cancer but many types of cancer. Categorising patients according to their cancer type has allowed us to understand specific causes of each subtype and to develop specific therapies for many of them,” says Lucas.

Therefore, for the scientific community, a current challenge facing autism research is to identify biomarkers, diagnostic tests by neuroimaging, or analyses of cerebrospinal fluid, blood, urine or faeces or genetics, which help classify cases into subcategories that may have common molecular origins and for which specific therapies can be tested.

Most cases of ASD are manifest in the first months or years of life by signs of patients’ limited interest in certain activities and
difficulties in relating and communicating or by the appearance of behavioural anomalies. Moreover, these symptoms are common to many individuals who are very different from each other in other ways. "It is highly likely that this common symptomatic presentation is caused by different molecular dysfunctions," highlights Lucas.

Humans have around 22,000 genes that contain the information to generate as many proteins, which are the nanomachines carrying out the specialized functions taking place inside cells. The functions performed by a neuron differ from those performed by other cell types, such as hepatocytes, and the functional needs of the cells also change according to their activity state at any given moment. Thus, neurons specifically generate the proteins that make them neurons and function as such at each physiological stage. These are the genes expressed by neurons, while the others are silenced. "There are specialised proteins controlling which genes are expressed more or less in each cell type and according to the physiological moment. One of these regulators is CPEB4, the protein that we found to be altered in autism, which leads to a lower expression of many of the genes that it controls, and which are implicated in the altered state of neuron functioning in autism," concludes Lucas.

This chronic neurological dysfunction has a strong genetic basis. Knowing its biological origin will facilitate the design of experimental therapies and tools to improve diagnosis. Lucas and his team’s work contributes to our molecular understanding of these disorders and to knowledge of the complexity of gene regulation of the associated risk genes. Their research is crucial to gain an understanding of how this originates and thus enable us to design corrective therapies, which were previously unattainable.

There are about 200 genes whose expression and/or functional defects are linked with a predisposition to autism.
Alcohol can damage your brain even after you quit drinking

A CSIC study shows that drink increases its addictive capacity by changing brain geometry and that these alterations endure for the first six weeks of abstinence.

The research, published in the journal *JAMA Psychiatry*, showed that six weeks after giving up alcohol consumption, changes in the white matter of the brain were still occurring in a sample of 91 volunteers, average age 46, hospitalised in Germany for rehabilitation treatment for alcohol use disorder. A control group, consisting of 36 men with an average age of 41 years without drinking problems, was used to compare the brain MRI scans of controls with those of the aforementioned patients.

“An important aspect of the work is that this patient group took part in a detox programme, and their consumption of addictive substances was controlled, which guaranteed the absence of alcohol consumption. Therefore, the abstinence phase, a critical period, can be faithfully monitored, because relapses lead to chronic alcohol consumption,” says Canals. More recently, this team of researchers has been able to reproduce these results in an independent cohort of patients, which validates the results obtained in 2019.

Another distinguishing feature of this study is that it was conducted in parallel in a model with alcohol-preferring Marchigian Sardinian rats. On the one hand, this makes it possible to assign a causal role to alcohol consumption in the deterioration of the white matter, as opposed to studies using patients only. The latter usually have confounding factors due to the comorbidities associated with the disease, such as the consumption of other substances and the patients’ own medication, which make it difficult to establish cause-effect relationships, says CSIC researcher at the Institute for Neuroscience Silvia De Santis, first author of the article.

On the other hand, studies with animal models make it possible to monitor the transition from a normal, healthy state to alcohol dependence in the brain, “a process that is not possible to see in humans, because the studies involve healthy volunteers and people who already have an alcohol abuse disorder,” explains De Santis. In this case, he adds, “the same patterns of alterations observed in humans could be reproduced in rats through alcohol intake alone, which supports the causal role of alcohol in the alterations observed in the brain.”

The researchers hypothesised that the progression of damage is maintained because a runaway inflammatory process is set in motion in the brain, which continues even in the absence of alcohol. “We believe that this is also related to the ease of relapse that occurs after quitting drinking, during the critical period of abstinence,” Canals said.

The immune system may promote relapse

Although the direct effect that had not even been imagined hitherto.

“Before our research work, no one could believe that during alcohol abstinence the damage in the brain would continue. Although the direct toxicity of alcohol ceases when you stop drinking, we saw that the changes in the brain caused by alcohol carry on,” explains CSIC researcher Santiago Canals, head of the Neural Network Plasticity group at the IN, who led the research.

The detrimental effects of alcohol on the brain are widely known, but the structural changes observed are very heterogeneous. Moreover, there are few diagnostic markers to characterise alcohol-induced brain damage, especially in early abstinence, a critical period due to the high relapse rate.

However, in 2019, a joint study by the IN (Institute for Neuroscience, CSIC-UMH) in Alicante and the Central Institute of Mental Health at the University of Heidelberg in Germany set a milestone in this field. These researchers used magnetic resonance imaging to reveal that the damage caused by alcohol in the brain does not stop on quitting drinking, as previously thought. On the contrary, damage goes on at least for the first six weeks of abstinence from alcohol; a delayed effect that had not even been imagined hitherto.

Research, published in the journal *Science Advances*, showed that six weeks after giving up alcohol consumption, changes in the white matter of the brain were still occurring in a sample of 91 volunteers, average age 46, hospitalised in Germany for rehabilitation treatment for alcohol use disorder. A control group, consisting of 36 men with an average age of 41 years without drinking problems, was used to compare the brain MRI scans of controls with those of the aforementioned patients.

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Grey matter is made up of a body of neurons and forms the cerebral cortex, cerebellum and spinal cord. Grey matter is involved in muscle control and sensory perception, such as vision and hearing, memory, emotions, speech, decision-making and self-control; these functions are impaired by alcohol intake.

The cells of the immune system residing in the brain, called microglia, are responsible for the change in the geometry of the grey matter, as demonstrated in the second study by Canals and De Santis’ workgroups. Alcohol, like any other harmful substance, triggers the defensive activation of microglia, leading to a change in their biochemical characteristics and also in their shape. This change in shape reshapes the extracellular space and opens up routes for the diffusion of substances that would be limited in the absence of alcohol.

The extracellular space consists of the gaps and channels left free by cell bodies and their dense cytoplasmic ramifications, such as the dendrites and axons of neurons and other glial cells, and is occupied by fluid and proteins. Substances essential for many physiological processes, such as neurotransmitters, circulate in the extracellular fluid.

"What we saw in this work was that the reactivation of microglia removed barriers to diffusion in the extracellular space, or in other words, it enabled pathways that were blocked in the absence of alcohol. Based on the results of a mathematical model simulating diffusion in the alcoholic brain, we proposed that this change facilitates the diffusion of neurotransmitters such as dopamine, involved in motivation and addiction, which increases the addictive power of alcohol.

This translational study was again carried out in rats and humans and was also coordinated by Santiago Canals of the Institute for Neuroscience and Wolfgang Sommer of the Central Institute of Mental Health at the University of Heidelberg (Germany).

“The next step in our research will be to find out whether this effect is produced by the direct action of alcohol on microglia, or indirectly, through intermediaries such as the liver or the intestinal microbiota,” concludes Canals.
Researchers at the IN (Institute for Neuroscience) have succeeded in preventing neuropathic discomfort associated with colon cancer treatment in trials.

By Pilar Quijada Garaballu

Chemotherapy, which is increasingly personalised and effective, is first-choice treatment for many types of cancer. However, despite the considerable increase in survival rates achieved by chemo, it does have side effects. Between 30-40% of people undergoing cancer treatment develop peripheral neuropathy, induced by various chemotherapeutic agents. This adverse effect of anticancer drugs can damage the peripheral nerves (those outside the brain and spinal cord) and can lead to a reduction in chemotherapy dosage or even the withdrawal of cancer treatment due to the intensity of the discomfort it can sometimes cause. The main symptoms of peripheral neuropathy, one of the most difficult types of pain to treat, include tingling, numbness, burning, weakness, inability to feel hot and cold, cramping or even severe pain in the hands and feet, especially when exposed to the cold.

Both pharmacological and non-pharmacological therapeutic approaches have been tested to tackle this problem arising from the pharmacological fight against cancer; however, there is as yet no standardised treatment to alleviate peripheral neuropathy induced by chemotherapeutic agents. “These chemotherapy-associated discomforts, arising from the development of peripheral neuropathy, can be highly disabling and affect normal daily activities, such as getting dressed, buttoning or unbuttoning clothes, going outside in cold weather, or even just walking. Often, these adverse effects lead to the need to reduce or stop cancer treatment early, compromising the tumour-fighting effectiveness of the chemotherapeutic agent and, therefore, having a negative impact on patient survival,” explains Dr Félix Viana, a CSIC researcher at the IN (Institute for Neuroscience, CSIC-UMH) in Alicante. However, adds Viana, “a few years ago a new molecular target was discovered to treat these symptoms, known as the sigma-1
A group of researchers led by Félix Viana and Elvira de la Peña, both from the IN, continue to search for solutions to peripheral neuropathy derived from chemotherapy.

Another starting point in their research was the fact that tactile and thermal hypersensitivity was previously known to be associated with changes in a molecular sensor known as the TRP A1 ion channel, discovered by Armenian molecular biologist Ardem Patapoutian, winner of the 2021 Nobel Prize for Physiology or Medicine, shared with US biochemist David Julius for his findings on temperature and touch receptors.

With a view to these previous discoveries, the Alicante researchers have resorted to biochemical, imaging and electrophysiological techniques to reveal that this TRP A1 channel needs to interact with the sigma-1 receptor, forming a molecular complex, for its correct expression on the neuronal surface. "Sigma-1 receptor antagonists prevent the formation of these molecular complexes, removing the sensor from the membrane of neurons capable of detecting painful stimuli. As a result, the sigma receptor antagonist is able to normalise the painful stimuli caused by the neuropathy," De la Peña tells us.

This work, spanning several years and recently published in the journal Brain, shows that modulation of TRP A1 by the sigma-1 receptor can prevent painful peripheral neuropathy induced by one of the most widely used therapeutic agents, oxaliplatin. And therefore, there is a way to alleviate the irritating adverse effects of peripheral neuropathy associated with chemotherapy, affecting a large number of patients and originating in the peripheral nerves, which are responsible for conducting sensations from the external environment to the brain.

In order to arrive at this conclusion, the team led by Félix Viana and Elvira de la Peña decided to administer an antagonist of the sigma-1 receptor, a key pain control protein before chemotherapy in a mouse model, which reproduces the treatment-related neuropathy described by patients. Treatment with the antagonist could largely prevent the development of neuropathic symptoms associated with the administration of oxaliplatin, a drug used in the treatment of colorectal cancer and other solid tumours.

In particular, a high percentage of patients with colon cancer, the second most commonly diagnosed cancer, may develop chronic, uncomfortable sensations in response to cold and touch in their extremities and oral cavity as a consequence of oxaliplatin treatment. In these cases, development of this painful peripheral neuropathy restricts the maximum dose of chemotherapy they can receive, compromising its efficacy and patient survival.

"As the chemotherapy sessions are scheduled, the chemotherapeutic agent can be administered together with the sigma-1 antagonist and thus prevent the development of neuropathy, so that patients can prolong treatment and not have to withdraw due to pain," says de la Peña.

This breakthrough, which was recently published in the journal Brain, is the result of several years of research by the IN-based Sensory Transduction and Noiception Working Group, of which de la Peña and Viana are principal investigators, and carried out in collaboration with pharmacologists from Esteve Pharmaceuticals.

"The first objective of our work was to use an experimental mouse model to replicate the adverse sensory effects produced by oxaliplatin in oncology patients in order to verify that the mice developed the painful symptoms common in many patients treated with this drug, i.e., an overblown response to tactile stimuli," Peña explains.

The second step was to administer a sigma-1 receptor antagonist to alter the formation of the molecular complex formed by the TRP A1 ion channel and the sigma-1 receptor. This strategy showed that mice treated with the sigma-1 antagonist during oxaliplatin administration normalised their response to painful stimuli, no longer experiencing the effects associated with chemotherapy-induced peripheral neuropathy.

"These results are an important step forward in our understanding of this pathology, and offer hope that in the future they can be used as a new therapy for the treatment and prevention of these disabling side effects of anticancer treatments," says Viana.

However, although hopeful, Viana warns us that it will not be applicable immediately, because "as in any basic research carried out on experimental animals, it must later be validated by performing clinical trials on patients".

Oxaliplatin is one of the agents used in chemotherapy, but there are more chemotherapeutic agents and each gives rise to a somewhat varied spectrum of symptoms, so the next step for this IN research team will be to determine whether what they have discovered for oxaliplatin can be generalised to other anticancer drugs used to treat different tumours.
Working out improves your children’s intelligence

A study in mice reveals that parents who keep up moderate physical activity have offspring with better cognitive function.

By Victor Lloret Blackburn

ow and then, genetic research can also bring joy. Not only does José Luis Trejo make this statement, he is also the bearer of good news. He is one of the researchers at the IC (Cajal Institute), the centre that has led a study that does indeed bring us good news. Or at least it is good for those of us whose parents practised sport before bringing us into the world because, according to the results of a study in which this CSIC centre participated, laboratory mice whose parents who did moderate physical exercise have better cognitive brain function. In other words, if the parents had corpore sano, their sons and daughters would inherit mens sana.

Trejo is a leading researcher, who has spent years studying the role played by various hormones in both neuronal production and the formation of the part of the brain known as the hippocampus in adult brains. For years he has been leading the Neurogenesis in the Adult Animal workgroup at the IC in Madrid, whose research targets the role played by these new neurons in memory, and their possible application in therapies for various diseases or stress. He currently forms part of the team that has studied how exercise affects the brains of mice. Not just the direct benefit to the exerciser, but also the benefit that their offspring will inherit.

As Trejo explains, neuroscientists have long known that the effects of stress are inherited, and not just among rodents. “The children - and even the grandchildren - of those who lived through...”
famine or war can still suffer the effects of these traumatic experiences. This does not mean that a genetic change has taken place in that family; rather, it is an epigenetic factor. What does that mean? Well, in the researcher’s own words: “Genes are like a book: even if the pages themselves don’t change, you may be paying more attention to some pages, giving more emphasis to others”. That emphasis or focus would be the epigenetic factor, which literally means on or near the genes. These factors affect the gene without being part of the gene itself. Trauma would make us tend to go to the darkest pages of this genetic book. Moderate physical exercise would have the opposite effect.

We have known for decades that our physical activity has a positive effect on our neurons. More recently, research has shown that new neurons continue to be created in adult individuals, and particularly in the area of the brain known as the hippocampus. “The fact that the increase in neurons in this brain area can be inherited is of utmost importance, because the neurons in the hippocampus are associated with conditions such as depression or anxiety,” explains Trejo. It is also this brain area that is responsible for memorisation, and thus plays a crucial role in memory and the long-term retention of what we learn. What is more, the hippocampus is also responsible for spatial orientation, so we could say that a sporty dad will help us park the car better.

According to studies by the IC, the benefits would go beyond our own organism, improving the quality of life of our descendants. In order to prove this inherited benefit, it may be necessary for parents to follow a moderate exercise plan while their offspring were not physically active, in order to make it clear that their improved mental functioning is entirely due to the previous exercise carried out by the male parent mouse. Not only were the offspring of sedentary mice compared with those of mice doing physical exercise, but also an exercise regime was applied to previously sedentary mice, which parented new offspring. Again, the same benefit was observed for the offspring.

So far, the study has focused on the male parents, finding that mice with a lifestyle that included a moderate exercise regimen passed on this epigenetic improvement to their offspring through their sperm. In the future, they plan to also explore the possible transmission of these epigenetic determinants from the mother to her sons and daughters.

Researchers also plan further investigation to determine whether the effects extend beyond the first generation and, if so, how strong the benefits are for the grandchildren of the active mice.

More exercise does not mean better health

Another important conclusion of the study conducted by Trejo is that the bodily benefits of exercise do not increase exponentially. More sport does not mean better health, at least when it comes to the effects of physical exercise on our brain. Not only will it not keep getting better, but rather it will have negative consequences. “Unlike what happens with the heart muscle, for example, where the more exercise you do the better, until you reach a point where no matter how much more you do it will not improve, this is not so with the brain. In the brain there is a turning point at which if you continue to exercise you start to lose the positive effects due to stress, because blood cortisol levels rise and what you gain on the one hand, you lose on the other. According to this IC researcher’s description, it is as if the different epigenetic factors “compete with each other”. The benefits of sport would be on one side of the scale, while the mental stress of too much exercise would be on the other. Our goal should be a balance, a middle path that allows our brains to get the most out of exercise. Our brain activity will improve and our descendants will thank us for it.

Can we define that optimum point above which we should not go? According to Trejo we can. Specifically, there are two methods to find out. One is by measuring the lactate threshold in the blood, which would indicate when that tipping point is reached, turning the effects of exercise on the brain negative. At the moment, this is not a viable methodology for most athletes. Another simpler method is to measure your heart rate - through a professional - and mark an intensity curve that should not be exceeded.

Trejo also has some general advice for people who want to keep fit: do not look for generic exercise (or diet) plans, but look for your own threshold and regulate your physical activity accordingly. Bearing in mind that it will vary as you get fitter. This would also apply to diet.

This study was fruit of collaboration between the Cajal Institute and CNB (National Biotechnology Centre), also part of the CSIC, as well as CNAG (National Centre for Genomic Analysis), INIA (National Institute of Agricultural and Food Technology), and the Universities of Valencia, Seville, and Cambridge (UK).
Graphene, with its high conductivity, flexibility, and biocompatibility, is the perfect ally for deciphering the brain’s electrical activity and exploring therapies for neurological diseases, as researchers at the IMB (Institute of Microelectronics of Barcelona, CNM-CSIC), together with other research centres, have demonstrated in recent years. Researchers are getting closer to applying these advances to the diagnosis and treatment of diseases such as epilepsy and Parkinson’s, as the technologic-based company Inbrain Neuroelectronics, co-founded by CSIC researchers, is now developing graphene transistors in the IMB’s Micro- and Nanofabrication Clean Room. The company has already been selected by the European Innovation Council (the European Commission’s body for boosting innovation in the EU), which has allocated it Accelerator funding of €17.5 million.

For years, the scientific community has been developing materials to advance our understanding of the brain and the signals involved in diseases such as epilepsy and Parkinson’s disease, which cannot be understood using previously employed electrode technology.

“... using the same sensor array,” explains Anton Guimerà, IMB scientist.

European projects such as Graphene Flagship and Brain-Com have shaped the international collaboration of leading research institutions to deepen this knowledge and the application of graphene. These consortia bring together IMB, ICN2 (Catalan institute of Nanoscience and Nanotechnology) and CIBER...
Public-private development

More than a third of the European population suffers from some form of brain disease, implying high social and health costs. New diagnostic tools and more efficient therapies are needed. Graphene implants pave the way to providing a therapeutic response adapted to each patient’s clinical condition. Setting up Inbrain and its current technological development is an example to the success of CSIC’s knowledge transfer, which has transferred technology in order to make the most of it. Identification, protection and licensing of the technology has been done by technical staff specialised in technology transfer from several institutions, including CSIC and ICN2. This research is a joint endeavour of both centres. On the one hand, the IMB and CIBER team is in charge of the characterisation and design of the chip - making sure that all the elements fit together - while the ICN2 is responsible for the basic knowledge of the material and its synthesis - providing the elements.

Kostarelos. In 2021 it became one of the companies with the largest amount of funding in Spain in the techno-medical industry, with an investment of €15.8 million led by Asabys Partners and Alta Life Sciences. Currently, the company is manufacturing graphene transistors in the CSIC’s Micro and Nanofabrication Clean Room.

With reference to the company’s upcoming goals, director of Inbrain Neuroelectronics Carolina Aguilar tell us: “We want to carry out the first clinical trial in humans in 2023 so as to achieve brain mapping for the resection of tumours and epileptic foci,” which has already been tested on mice and larger animals. “The tests will be carried out at a centre associated with the University of Manchester, with whom we are collaborating, and it will be the first time that graphene has been used in a human being’s brain,” she adds. Subsequently, “we will focus on developing the platform for decoding and treating brain diseases”.

Graphene microtransistors in direct contact with brain tissue

Existing brain interfaces are based on metals, such as platinum or iridium, and can have multiple side effects. The technology developed consists of nanostructured graphene electrodes with micrometric dimensions and, due to their properties, provide several advantages over metal electrodes. The microtransistors are a sheet of graphene in direct contact with brain tissue connected by two metal tracks to the recording electronics. These devices “take advantage of the field-effect property of graphene to implement local amplification of neuronal signals,” says Guimerà. The electrical activity of the brain thus modulates the conductivity of the two-dimensional material, enabling the recording of brain activity. Graphene, which began to be developed little more than a decade ago, thus enables interfaces with fewer restrictions in terms of miniaturisation and resolution of brain signals. In addition, multiplexing techniques (combining two or more signals and transmitting them on a single medium) make it easier to increase the number of recording channels, without increasing the number of connections, and to simplify handling. Capturing these signals is based on integrated circuits or chips designed at the IMB, making it possible to process the large volume of information extracted from brain activity. “Thanks to its biocompatibility and electrochemical stability, the transistor records a wide range of frequencies, including ultra-slow ones, with the same fidelity as glass micropipettes, overcoming their limitations of use and allowing these signals to be recorded at multiple points in the brain simultaneously, for the first time. This facilitates the study of ultra-slow signals in the functioning of the brain and its pathologies,” explains the IMB researcher, adding: “The goal is to exceed the current standard.”

Simulated composition showing the adaptation of a neural interface based on graphene transistors with the brain convolutions. / INBRAIN

Example of the flexibility of substrates and materials for fabricating neural interfaces with microelectronic technology. / INBRAIN
When a child suffers from cerebral palsy, the damage he or she has experienced leads to huge difficulties in controlling his or her muscles. Depending on the severity of the brain damage, they may be able to stand up and walk on their own better or worse or with the help of physical aids, but the consequences on their cognitive and motor development will require multidisciplinary rehabilitation, with the involvement of traumatólogists, educational psychologists, occupational therapists and physiotherapists.

Infant cerebral palsy, the most common cause of motor disability in children, affects almost one in every 500 children born in Spain, according to data from the ASFACE (Spanish Confederation of Associations for the Care of People with Cerebral Palsy). Not only does it modify motor response, but it is also often accompanied by epilepsy, visual, auditory and intellectual disorders and learning difficulties. In 75% of cases, spasticity (a disorder involving an abnormal increase in muscle tone) is the most frequent clinical symptom and the main cause of gait disturbance.

The brain can suffer these injuries during gestation, birth or the first three years of a child’s life due to a variety of causes, such as bacterial infections or lack of oxygen during birth. The damage occurs at a time when their central nervous system is maturing, which means that the innate impulses to stand up and start walking do not happen properly.

Therefore, their brain is unable to make the necessary connections to properly control movement, posture and balance. Researcher Eduardo Rocon asks: “What if we put these children through the experience of starting to walk and evaluate the potential that walking has on their cognitive development?”

Rocon is head of CSIC’s Neural and Cognitive Engineering Group at CAR (Centro de Automática Robótica, CSIC-UPM), in Arganda del Rey, Madrid. He shows us his latest prototype and explains its purpose: a flexible exoskeleton designed to rehabilitate the lower limbs of young children, aged between one and three years old, with infant cerebral palsy. This kind of portable muscle-building device consists of a metal platform attached to the feet by cables and to the hips and pelvis by a device worn like a pair of pants. Several motors exert the necessary force for the patient to start walking.

In the last century, treatments have been revolutionised by the emergence of technologies capable of compensating for motor disorders and recovering functions forgotten or not acquired by the nervous system. These include neurorobotics, based on wearable exoskeletons that attach to the body, neuroprosthetics, which aims to stimulate muscles using low levels of electric current, and virtual reality, used to facilitate the learning of new devices.

The CAR’s Neural and Cognitive Engineering Group has spent over 15 years working on exoskeletons that complement traditional neurorehabilitation therapies, a field aimed at treating people who have suffered a neurological disorder and are unable to carry out everyday activities such as walking, moving around, feeding and dressing. These devices are beneficial for patients because their involvement is active during therapy. “We know from scientific
The best quality of Discover2Walk, says Rocon, and his team have named this baby robot, is its flexible design, which is adaptable to various weights and heights. When it is tested in a hospital in a few months’ time, doctors and physiotherapists will be able to assess whether it is useful to complement their patients’ rehabilitation. “It also incorporates sensors that measure and program the force applied to the system. This makes it possible to monitor the patient’s progress more accurately and fine-tune his or her treatment,” the CSIC scientist tells us.

In 2010, the team decided to apply their knowledge of automation to develop technical aids for the disabled. The very same year they presented a neuroprosthesis capable of compensating and even eliminating the tremors caused by Parkinson’s disease. Later, in 2015, their progress led to the creation of the CSIC spin-off Werium Solutions, which has transferred some of the technologies emerging in their labs to society.

**Personalised neurorehabilitation**

The CP Walker 2.0 is an exoskeleton that promotes active therapy for posture correction during walking in children with cerebral palsy. This robot, designed for use by older patients than the Discover2Walk, allows more personalised strategies to be applied.

After being validated in 2019 in a trial with ten patients at the Niño Jesús Hospital in Madrid, the efficacy of this exoskeleton is being evaluated in a multicentre study involving nearly 50 patients at the Shirley Ryan Ability Lab Hospital in Chicago (United States).

“Robots are machines suitable for making repetitive movements in a very intensive way and we have always tried to take advantage of this capacity to recover mobility”, says Rocon, after stressing that he would not have been able to integrate his developments into clinical practice without the vision and contributions of the professionals involved in neurorehabilitation.

**Exoskeleton test environment**

The same opinion is expressed by Diego Torricelli, CSIC researcher at the IC (Cajal Institute, CSIC) and coordinator of the European Eurobench project, which aims to create the first European centre for testing, standardisation and research in robotic exoskeletons for rehabilitation. “Although engineers are aware of the problems, our technologies would be useless if we did not consult physicians, who tell us why a certain device is necessary or not. Our work is also key because we provide on-the-fly data that they don’t have,” says Torricelli.

Thanks to the collaboration of over 80 companies, universities and research centres from 15 European countries, funded under the European Horizon 2020 programme, Eurobench selected the Centre for Clinical Neuroscience at Los Madroños Hospital in Brunete (Madrid) as a test centre. “The aim is to provide a test environment for exoskeletons that replicate everyday life. Companies and researchers in the sector will have an ideal space to test their technologies’ performance at any stage of development,” explains Torricelli.

One of the exoskeletons that will be tested at the centre is the Exo-4i3 by Technaid, a technology-based company created in 2004 within the CSIC’s Neurorehabilitation Group. This wearable robot, which adjusts to feet, legs and hips, can fully emulate walking and assist people who have partially lost their ability to walk after suffering a stroke or partial spinal-cord injury.

A mannequin robotic leg

Torricelli’s laboratory at the Cajal Institute has also seen the birth of a prototype that simulates knee movement. This robot, part of the Exosave project, will allow scientists to study the interaction of exoskeletons with patients before starting neurorehabilitation therapy.

“The little white balls on the robotic leg are physical interaction sensors for force, kinematics and movements,” explains Stefano Massardi, postdoctoral researcher. Fellow graduate student David Rodríguez adds: “It’s a device that enables us to do a lot of replicable tests and eliminate variability. In the future, our idea is to design a mannequin robot that replicates the whole body. The project will serve to establish protocols and safety indicators”.

**Hybrid robots**

Juan Camilo Moreno, leader of the Neurorehabilitation Group at the IC-CSIC together with Torricelli, knows how well to transfer these technologies to the clinical environment. One of his latest developments is the Tailor device, designed in collaboration with the Hospital Nacional de Parapléjicos de Toledo, the UPH (Polytechnic University of Catalonia), the URJC (Rey Juan Carlos I University) and the Guttman Institute. It is a hybrid gait training robot that combines robotic systems, which provide strength, with a neuroprosthesis that artificially activates the lower limb muscles. One advantage of Tailor, which has already been tested on patients with spinal cord injury and stroke, is its modular design.

“The rehabilitator can configure the modules so that the robot adapts to the patient and activates some muscles more than others during assisted walking,” says the CSIC researcher. He concludes: “The patients who have tested this prototype have been satisfied with the system’s configuration and adaptation capacity. Now we want to continue working to optimise the integration of all these technologies and bring them closer to the market.”
Moisture restoring drops for dry eyes

Researcher Carlos Belmonte, an expert in corneal sensitivity, plays a key role in the spinoff Avizorex, which develops therapies for dry eye syndrome.

Much of what is known today about corneal sensitivity and the molecular and cellular mechanisms underpinning this condition is due to Carlos Belmonte, who founded the IN (Institute for Neuroscience in Alicante, CSIC-UMH) in 1990. In 2009, he received the National Biomedical Research Award for “his brilliant scientific work and his important contribution to the promotion of biomedical research in Spain and internationally.”

His work on the neurobiological mechanisms of corneal sensitivity includes its dysfunction in patients with dry eye. Belmonte demonstrated that ocular surface moisture is regulated, in part by the corneal cold thermoreceptors and that dry eye disease may be the result of damage to these fibres.

This finding eventually led to the creation of a technology-based company, Avizorex, which may soon provide a solution to treat this condition, affecting millions of people worldwide. This is a clear demonstration that science is profitable. “But you have to take risks to make a profit, and in Europe that mentality is hard to find,” he says.

Professor Belmonte was a pioneer in bridging the large gap between basic scientific research and commercialising its results. “You shouldn’t do research for financial gain alone, but you should know how to recognise the opportunity when it presents itself,” he says referring to the patents that his research has yielded.

His group has focused on understanding how physical and chemical stimuli from the external environment are transformed into conscious sensations. “In recent years, one of the things we have been really interested in is finding out how a decrease in temperature is detected by studying the ion channels in the cold nerve endings, which are responsible for measuring them. We used the cornea of the eye as a model, which is a very simple tissue with a large number of cold nerve endings. Our experiments confirmed that cold detection is mediated by an ion channel called TRPM8 (Transient Receptor Potential Melastatin 8), discovered by David Julius and Ardem Patapoutian, winners of the 2021 Nobel Prize in Medicine.

“To our surprise, we observed that mice in which TRPM8 had been removed from the corneal nerves produced half as many tears as normal mice. In addition, we saw that the cold nerve fibres were silent and did not respond to temperature changes as they did in intact animals, where these nerves continuously send impulses to the brain, signalling changes in ambient temperature,” explains Belmonte.

They deduced that, conceivably, when the eye surface, which is wetted by tears, evaporates, the...
temperature drops and stimulates the cold nerve endings, which reflexively increases tearing, thus counteracting the drying of the ocular surface. "This appeared to be a nervous regulatory mechanism to adjust tear secretion to the degree of dryness of the eye surface," explains Belmonte, an idea that led to a patent registering the possibility of using TRPM8 channel-stimulating drugs to excite the cold nerve endings and increase tear production in dry eye syndrome.

These observations were published in Nature Medicine and another paper published in Nature Communications, this time in collaboration with English colleagues, showed that cold receptors not only regulate tear production, but also the frequency of blinking, which distributes tears evenly across the eye surface.

"The CSIC and the UMH were insistent that we should develop translational research and patent our discoveries, so I was very involved in issues related to patents as principal investigator of our group," with Félix Viana, researcher at the CSIC, and Juana Gallar, from the UMH, as my most senior colleagues. However, the patent was put on hold for a while, because scientists are not good at selling patents," says Belmonte.

When scientist meets maverick

It was at this point that Patrick Tresserras showed up. He was very young, 27 years old, but highly intelligent and with clear ideas. "He had done a search to identify CSIC patents and found ours, which in my opinion had great merit," says Belmonte. Tresserras told me: "I thought the idea of using a TRPM8 cold channel agonist as a possible therapeutic target to stimulate tear secretion, was great. I would like to set up a company with you!" I listened somewhat amused and said "go ahead".

That was how the company they called Avizorex was created, and Tresserras was in charge of the business side of things, starting with the search for funding, which he found immediately. "because he knew how to be convincing, was very well prepared and believed in the project". He set in motion the necessary steps to obtain a therapeutic target with great potential to treat dry eye.

Professor Belmonte helped him on the scientific side. In Alicante they were working with TRPM8 agonists and they had already identified a good candidate. Tresserras obtained the funds and organised the difficult process of approval by the official institutions: product safety, tolerance and potential clinical use, finally obtaining private funding to carry out a phase II clinical trial.

Both attended a meeting in San Francisco (USA) with major global companies and financial funds related to the eye. One of them was more receptive and months later they made them an offer to license the product. "Our company only had the TRPM8 agonist that we had selected and we preferred to suggest they make a purchase offer. They accepted it and sold for a substantial amount, partly linked to its future success. In mid-2022 they completed a very large clinical trial, which demonstrated the drug's effectiveness. Two phase III trials are now underway, aimed at marketing approval by the US Food and Drug Administration (FDA) and the European Medicines Agency (EMA)."

The future drug will be dispensed in the form of eyedrops to stimulate tear secretion in dry eye, a very common condition in which there is insufficient lubrication and wetting of the ocular surface, either due to scarse or poor-quality tears. Sufferers of dry eye syndrome experience itchy eyes, a gritty sensation, blurred vision and photosensitivity.

Despite his successful patent track record, Belmonte believes that scientific research should not be done with the idea of discovering something of applied value in mind, but rather to advance knowledge. Most research may not be immediately applicable (the Nobel Prizes are a clear example). But other research will build on it and that first finding may end up being something of applied value. That is why, he concludes, "I don't think you have to go looking for profit in research, you just have to recognise the opportunity when it presents itself," he concludes.

Business venture

In November 2010, the pharmaceutical company Aerie Pharma announced the acquisition of Avizorex Pharma, an ophthalmology startup company based in Barcelona's Science Park (PCB).

The deal, which is still pending closure, involves 5 million euros and additional payments subject to the accomplishment of certain milestones, plus royalties on net sales, which still benefit the CSIC, the UMH and the shareholders, Belmonte says. "Setting up a company is easier in the United States. The problem in Spain is funding in general. And for the record, we have raised Spanish funding and we are doing it again with three new successfully launched companies. However, when you want to launch a business in a big way, it's still better to do it in the US," he says.

What is wrong with Europe? Professor Belmonte gets straight to the point: "To a large extent, Spanish funders provide much less risk capital than their American counterparts. In the United States they risk more and earn more, here investors are more conservative, they invest less money in relation to the potential offered by the product."

Another important factor in getting companies like Avizorex going is "to have faith in young people's abilities; it's the only way to make it work. Nine out of ten investments are lost in the transition from the lab to the market, the so-called valley of death. But if you succeed, you come out winning. With Avizorex, for instance, you can make a hundred times what you invest. And that gives investors a lot of leeway. I believe that courageous entrepreneurs should be encouraged. That was the role of Patrick Tresserras, who had just finished his degree in economics and business. He started out with his own capital, some tiny savings," explains Belmonte. "Afterwards, we both put money into the company".

This future treatment will be dispensed in the form of drops, stimulating tear secretion in dry eyes, which is common when there is inadequate lubrication and moisture.
Research targeting the gut microbiota, defined as the set of microorganisms that live in our gut, has opened up a horizon of knowledge about the connection popularly known as the gut-brain axis, revealed to have a direct relationship with diseases such as depression or anxiety, among others. In other words, the brain and the gut are interconnected to an extent that enables us to tackle problems traditionally associated with psychiatric or psychological science from a completely innovative and complementary perspective.

Studies like those carried out by Yolanda Sanz, researcher leading the Microbial Ecology, Nutrition and Health group at IATA (Institute of Agrochemistry and Food Technology, CSIC), target explaining the role played by the gut microbiota in the transition from health to disease, through its interaction with diet and the immune and neuroendocrine systems of the human body. The pathologies investigated include a broad spectrum ranging from obesity to neurological conditions.

“The gut microbiota protects us from the impact of adverse environmental factors (poor diets, antibiotics, infectious agents, etc.) and interacts with various organs and systems, regulating a host of physiological functions (metabolic, immune, neural, etc.) that are key to our health,” explains Sanz.

Accordingly, numerous studies show that disruption of the gut microbiota can lead the symbiotic relationship to breakdown and contribute to the development of various diseases, ranging from gut disorders to many other metabolic, mental, autoimmune conditions, for instance,” she explains.

Motivated by the scientific, social and medical significance of diseases such as diabetes and obesity, and the social impact of mental health, the scientific

Protección mental via the gut-brain axis

Reseacher Yolanda Sanz’s team has patented an intestinal bacterium, licensed to the French biotech company LNC Therapeutics, potentially applicable to treat depression and anxiety.
community investigates the potential of the microbiota to treat neurodegenerative, metabolic and psychiatric diseases, including stress-related mood disorders like depression and anxiety.

Yolanda Sanz’s team is therefore working on the selection of key gut bacteria that could provide health benefits and may be used to design dietary strategies that reduce the risk of disease by modulating the microbiome. In 2020, Sanz’s group patented the bacterium Christensenella minuta, present in the gut of healthy individuals, for use to prevent or treat mood disorders such as depression and anxiety. The patent was licensed to LNC Therapeutics, a French biotech company specialising in research and drug development in the area of the gut microbiome.

“In the first trials we observed that Christensenella minuta was a good serotonin-producing strain in vitro; this was an interesting outcome because this neurotransmitter is found in low concentrations in people suffering from depression and stress, posing a risk for the development of depression, and it plays a crucial role in regulating emotions. It also plays an important role in cognitive ability,” says Sanz.

“What is more, when we evaluated its effects in vivo, in an animal model of depression induced by chronic social stress (a model resembling bullying in humans) we observed that this bacterium not only increased serotonin production, but also reduced stress-induced overproduction of corticosterone, likewise reducing vulnerability to stress and depressiveness behaviour,” she adds. The results are promising and open up an optimistic avenue for multidisciplinary research.

**Keys to the gut-brain axis**

The gut is considered the most important immune organ in the adult, as it contains most of the body’s immunocompetent cells, and has also been found to be the second most important organ relating to neurons. This discovery gave rise to the name gut-brain axis.

The two-way communication between the gut and the brain is based on the connection of endocrine, immune and neural networks, which serve as a channel for conveying information about the state of various organ functions and health status.

**Research fields targeting the microbiota**

Studies show that each individual has his or her own microbiota and shares only a small fraction of it with peers, thus it differentiates each person more than the genome itself. These data suggest that the microbiome may provide a better explanation for physiological variability and disease risk.

Numerous factors shape and alter the microbiota. The genome itself exerts some influence, but it is mainly environmental variables such as diet, medication and lifestyle that are the most important determinants. These external factors are able to modify the microbiota.

Several IATA studies have shown a cause-effect relationship between the restoration of microbiota and the prevention of obesity or reduced vulnerability to stress and depression, among others.

Yolanda Sanz coordinates the European Climb-Out project, which investigates whether the gut microbiome can help predict the risk of obesity in childhood. This knowledge would help determine how to modify diet and lifestyle for preventive purposes. She is also working on the European Early Cause project, which studies the relationship between microbiota and stress in childhood to understand its role in the development of psychiatric and cardiometabolic comorbidities. Sanz also leads the national Ineob project, studying the immune and neuroendocrine mechanisms by which intestinal bacteria can regulate inflammation associated with obesity and insulin resistance (leading to T2 diabetes), on the one hand, and reduce appetite and energy intake, on the other. Finally, her Biopred project, funded by the Valencian Innovation Agency, uses one of these bacteria aiming to prevent metabolic syndrome and diabetes.

Sanz explains that gut microorganisms and metabolites produced by the digestion of food (neurotransmitters or their precursors, short-chain fatty acids, etc.) are part of the biological and chemical stimuli involved in these signalling pathways. These can modify essential functions, such as the endocrine response to stress (cortisol production), the immune response (production of pro- or anti-inflammatory proteins) and emotions and behaviour in response to stress or trauma.

“If we can shed light on the communication processes between the gut and the central nervous system, we will be able to understand the reactions taking place in our organism as a result of traumatic or dysfunctional situations, and this will enable us to act more precisely on the specific problem,” the researcher predicts.
Mind-shaping artefacts

Research teams at CSIC study the existence of a universal model that demonstrates how human-built material structures have contributed to our cognitive development throughout history.

By Alejandro Parrilla García

Is the evolution of material culture related to the development of the human mind and rationality? This is the starting point of the Material Minds project. Researchers, backed by €10 million in funding granted by the European Research Council (ERC) Synergy Grant, have until 2027 to answer this ambitious research premise. That is, to demonstrate how the visual perception of the material environment around us influences our way of thinking and, therefore, how we understand the world and how we organise ourselves according to that perception.

Between 2014 and 2018, researchers from INCIPIT (Institute of Heritage Sciences, CSIC) and the IN (Institute for Neuroscience, CSIC-UMH), carried out a pilot study in which they investigated the visual response of 113 individuals to ceramics from Galician prehistory. These people’s cognitive response to the artefacts, pertaining to different styles and societies from 4,000 BC to the change of era, demonstrated that the construction of the world begins with how we see it. Different material forms trigger different ways of seeing and interacting, or as INCIPIT director Felipe Criado Boado points out: “Eye movements are the most objective proof that there is a parallel evolution between the cognitive process, material development and changes in society.”

On this basis, Felipe Criado Boado and IN researcher Luis M. Martínez Otero proposed this novel project, officially called Xscape ERC Synergy Grant Project. This initiative was joined by archaeologist Johannes Müller, director of the Institute of Prehistoric and Protohistoric Archaeology at the University of Kiel (Germany), and Andy Clark, cognitive philosopher at the University of Sussex (UK) and co-author of the Extended Mind, which places reasoning beyond the brain, specifically in the interaction of the brain and the body with the world.

After the pilot study using ceramic material from the northwest of the Iberian Peninsula, similar studies were begun in America and Europe with ceramics ranging from the Neolithic to the Iron Age (in Europe, from 5,000 to 500 BC). In February 2023, the experimental phase will begin in a laboratory (Material Minds Lab) purpose-built for this project, to analyse the interrelationship between material culture and cognitive development. This experimental phase should end, around 2025, with similar experiments carried out with great apes, in order to test whether they share perceptual biases with humans and whether their behaviour can be influenced by the surrounding materiality.

“This all stems from that first experiment in which researchers observed how, just as monumental Neolithic landscapes (such as the stone alignments of Carnac in France) direct our gaze horizontally, or just as the Egyptian pyramids of Giza raise our eyes vertically, the visual exploration of prehistoric ceramics generated statistical regularities and stereotyped behaviours. “In our brains there are neural maps that fix an internal pattern that determines the way we relate to the world. Our experiments show that there is a very close interaction between cultural changes and cognitive models, which provides a new perspective on how the mind can transmit cultural values, beliefs and customs,” explains Criado-Boado.

The world is full of artefacts that we, human beings, have built: ranging from small pieces of furniture to large cities. Interacting with these artefacts, such as...
counting on our fingers or a calculator, initiates a mental process which involves not only the brain, but rather the interaction between brain, body and environment; all artefacts are involved. Therefore, it is possible that the way in which the tools are used influences how we reason: “It may be that we internalise the process so much that it becomes part of us, that we have perfectly integrated mental maps of all the artefacts we use,” says Martínez Otero.

The relationship between material development and cognitive process through vision implicitly includes a third element in the equation: social complexity. Through 41 sub-projects spread over four continents (Europe, Asia, Africa and America), Material Minds attempts to correlate the way different material styles are perceived within particular social contexts. “Perception cannot be separated from form. The shape of objects and the pattern of visual exploration they produce have changed throughout history, and are connected to cognitive behaviour in the same way as they are to the social domain, including social complexity,” says the director of INCIPIT.

Therefore, the project starts from a premise: the way an individual thinks and reasons is influenced by his or her culturally-guided style of observing and interacting with the surrounding world. And it is directed towards a goal: to create an explanatory model that demonstrates the role of material culture in the construction of our cognitive capacities. However, as the researchers point out, the correlation between material, social conditions and thinking does not signify causation.

Predictive processing

The project’s conceptual framework is the paradigm of predictive processing, in other words, the idea that our perception of the world is not a passive capture of an objective external reality, but a process of active inference. “A kind of hallucination in which a circuit formed by perception, action and learning intervenes to analyse the sensory information we receive from the outside, and thus provide an explanation for what surrounds us,” explains the IN researcher.

As in the Platonic allegory of the cave, human beings initiate a cognitive process to make the world they see correspond to the world they know, and thus make it comprehensible. “This is a reciprocal relationship between the mind and the environment. Firstly, the world provides the brain with a catalogue of sensory impressions, which are stored in our memory to interpret our surroundings. Secondly, our mind intervenes in the world to match the flow of sensations it generates with our internal conception of it. “It’s a closed loop of action and perception: we look, we see, and we infer where to look next so that the world continues to seem comprehensible,” says the researchers.

Thus, human beings observe their surrounding environment with the aim of matching the world they perceive visually with the world they know mentally in such a way that, when there are incongruities, an alarm is triggered. “We use techniques to measure this discrepancy or error, such as eye tracking, electroencephalography or emotional recording techniques, because the error also sparks surprise, which is accompanied by fleeting but very specific changes in our physiology,” explains Martínez Otero.

This neurobiological theory has been successfully applied to the study of other cognitive functions, such as the construction of models of spatial planning, orientation and navigation, or decision-making under uncertainty.

Past, present and future

If we understand materiality as an element of anthropological communication, similar to that of language, its influence on cultural evolution throughout history must be acknowledged. That is to say, its role in the development of our internal model of the world and of the constructive styles acting as an imprint of our time and space. Every object is a cultural legacy, an impression of the mind at a particular moment in time, accessible to the present generation and capable of influencing future minds.

For this reason, researchers aim to get a glimpse of our ancestors’ minds through the objects they have left behind in order to re-evaluate, in the present, the influence of material culture on the development of the collective imagination. The first outcome would be to shed light on how our minds work in a given environment in order to correct deficits in cognitive development and develop automation devices with human-like behaviour. “It could also serve to improve vision in the blind, since one of the problems facing current prostheses is how to manage attention: how to encode the information we receive from the outside to generate a message that the brain can understand,” Martínez Otero explains.

In the event that the hypotheses put forward by the project are verified, “we should be very careful with how transform our natural environment and build our artificial world, as we are also building our mind. This, in times of pandemics and interaction with technological devices, does not seem at all trivial,” the researchers conclude.
By Marta García Gonzalo

To understand the signals recorded with these devices, a physics team at the French CNRS (National Centre for Scientific Research) is developing optical mathematical models of the light propagation through the probes and of the theory behind the Raman spectroscopy used. These simulations have enabled researchers to define the detection limits and support the precise interpretation of the signals obtained in animal models at the consortium’s experimental laboratories.

In Spain, the CSIC team led by neuroscientist Liset Menéndez de la Prida at the IC (Cajal Institute) collaborates with the Brain Metastasis Group led by Manuel Valiente at CNIO (Spanish National Cancer Research Centre) to apply the new probes to investigate brain metastasis. At the IC, they also apply the technology to cranioencephalic trauma diagnostics.

Nanobright develops fibre-optic probes capable of detecting the molecular changes surrounding tumours and brain trauma, identifying the presence of tumour cells or associated modifications.

Traumatic brain injury and cancer represent the most common causes of adult brain surgery. The incidence of brain cancers varies between two and 18 cases per 100,000 people, depending on whether they are primary tumours (those originating in the brain cells themselves) or the result of metastasis, originating from other affected organs. The incidence of traumatic brain injury is over 50 cases per 100,000 inhabitants, although this figure varies greatly depending on the geographic region.

In the case of both metastatic brain cancer and traumatic brain injury, the brain tissues surrounding the affected area are modified, altering their cellular and chemical composition. By precisely diagnosing and delineating the boundaries of these changes, scientists can help to improve their surgical treatment. This is the reasoning behind the European Nanobright project, which is developing fibre-optic probes capable of detecting the molecular changes surrounding tumours and brain trauma, identifying the presence of tumour cells or associated alterations, such as oxidative stress caused by strokes and contusions that accompany trauma.

Four institutions from three European countries, Italy, Spain and France, are involved in this initiative, which is funded by the European Commission with around €3.5 million. The IIT (Italian Institute of Technology), which leads the consortium, is responsible for the technological development of the device, which consists of integrating spectroscopic systems with brain activity sensors implemented on minimally invasive optical fibres.
"We have developed microscopic Raman spectroscopy strategies that we apply through sharp optic fibres. These probes are inserted into the brain tissue, where they accurately direct the light and set off a physical interaction with the cells and surrounding microenvironment in order to read their properties. In this way, by amplifying the light signal received we can infer whether there are indicators of cancer cells in that region, allowing much more precise surgery by delimiting the boundaries of the affected regions,” explains the director of the Neuronal Circuits Laboratory and specialist in Systems Neuroscience and Neurocomputing. To analyse these signals, the CSIC researchers use artificial intelligence techniques, enabling them to automatically classify the presence of reliable pathological markers.

The team led by Menéndez de la Prida comprises 11 people, three of whom are involved in Nanobright. In addition to this project, this laboratory seeks to apply the same artificial intelligence techniques to study electrical activity in the brain, a research area forming part of the CSIC’s Artificial Intelligence network, Conexión-AIHBB, as well as the Neuroaging interdisciplinary thematic platform (PTI), targeting brain ageing. These platforms are research and innovation instruments, created to address multidisciplinary challenges having high scientific, economic and social impact. These platforms comprise research groups from different CSIC centres and are open to the participation of companies, government, other institutions and social agents.

The optical fibre developed by Nanobright, smaller in breadth than a human hair, can harbour so-called plasmonic structures on its surface - metallic nanostructures that help amplify the spectroscopic effects of light as it interacts with the brain’s microenvironment. “Just as a ship uses sonar to comb the seabed and establish the profile of underwater mountains, we use light, modulated by a holographic manipulation strategy, to sweep the brain tissue and observe the alterations associated with the presence of cancer cells or trauma,” says Menéndez de la Prida.

In the instance of cancer, the new technology can discriminate between types of metastases by defining biomarkers clearly associated with a more accurate diagnosis. The same strategies are applicable in the case of primary brain tumours to help define the boundaries of tissue alterations. Furthermore, it offers novel therapeutic options because it facilitates diagnosis and allows for less invasive resection of the affected tissue, as the micrometre-scale resolution of the probes provides a much more detailed image than current imaging techniques, such as magnetic resonance imaging (MRI).

Magnetic resonance imaging (MRI) uses magnetic fields to produce detailed images of the inside of the body to see if tumours are present and to measure their size, or to delimit the extent of lesions associated with trauma. The image it provides allows experts to localise the regions to be operated on and helps them plan surgery. However, it is not very precise in terms of the microscopic confines of the lesion, which is of great clinical importance, especially when these are located close to certain functional areas, such as, for example, the area that controls speech. In these cases, individually tailored surgery affords new options.

The same probes, modified to increase their spatial range, can also be applied to studying resected brain tissue for comparison with a diagnosis made in the pathology laboratory. This type of analysis, which is carried out after biopsies, confirms the diagnosis, and identifies - for example - cancer cells, their type and clinical classification. This other characteristic of the project extends the probes’ range of applications. Application of the technology developed by Nanobright is still in the experimental phase, but researchers are already working on its potential extension to the clinical phase. These trials would have to be carried out in the operating theatre, during an operation or, later, during the analysis of biopsies. “If it were intraoperative, it would be done under anaesthesia and by inserting the probe into the region being analysed by the surgeon. An incision would have to be made. In the case of biopsies, it would be done in the analytical laboratory by a pathologist. But we haven’t reached that stage yet,” says the CSIC’s IC researcher.

These probes have potential application in the fields of study encompassed by the AHUB and Neuroaging platforms. De la Prida and her team have discovered that by combining artificial intelligence techniques with data collection from these sensors, they could glean much more information and make more progress in personalised diagnosis. In addition, this technique could help to characterise tissues altered in processes such as ageing or Alzheimer’s, in order to determine the composition of lipids, which show easily identifiable characteristics. “The possible extension of the technique to the early diagnosis of Alzheimer’s is an unexpected result, which demonstrates the value of basic research as a producer of value and catalyser of inventions that enable us to advance in our fight against these threatening challenges,” concludes Liset Menéndez de la Prida.
Q. To what extent does the congress venue, in this case Granada, influence attendance?
A. Granada has several attractive characteristics. It is a relatively small city, but it is a university city, where, for example, the offer of accommodation in halls of residence and inexpensive hotels makes participation possible for students, who are looking for affordable places. And, also, given its small size, it is a city that you can get around without a car, or even public transport. Moreover, Granada boasts an immense cultural history, it has the attraction of the Alhambra, and has been a melting pot of cultures, in as much as Jews, Arabs and Christians coexisted here, peacefully. This means that Granada has roots for many of the cultures we want to attract to the congress: Asians, Arabs, Muslims, Jews, Christians. This is one of the attractions we promoted in order to win the candidacy. Of course, to all this we must add the goodwill enjoyed by Spain and the SENC in the organisation of this type of event, as demonstrated by the organisation of the Congress of the European Federation of Neuroscience Societies, FENS, in 2012, which achieved record participation.

Q. How did you select the speakers?
A. As we stated when we presented our candidacy, the local committee did not want to select science, we wanted science to be selected in a multinational and objective way, without local ties. That is why we selected a Programme Committee coordinated by the Spanish researcher Paola Bovolenta, president of SENC (Spanish Society of Neuroscience), the North American Gordon Fishell, renowned in developmental biology, and MuMing Poo, from China, who spent most of his scientific career in the United States, but has been recruited by the Chinese government to set up a neurosci...
ence programme in his country. They then selected the rest of the committee according to geographical distribution and gender parity. In short, people who are beyond board in their ability to select top-notch topics and speakers.

Q. You have been highly aware of gender balance in terms of numbers, are you planning to run any activities to highlight the difficulties women face in their scientific careers when it comes to balancing motherhood and childcare?
A. Yes. In this respect, we have a Woman in Science committee, which is designing activities that will address the problems faced by women researchers in their career progression in the field of neuroscience, and we will also have first-rate women speakers who will talk about their experience in neuroscience and in science in general. This is important because the congress aims not only to be informative on the state of the art, but also to be educational for young people.

Q. Are you planning to organise activities open to the public in Granada, the host city?
A. Yes. Another important aspect for the local organising committee is that Grenada is made aware of the neuroscience congress and that 4,000 or 4,500 neuroscientists will be spending five days there to discuss issues related to the brain and its diseases. We want them to appreciate the need to study the brain in order to understand what we are like and the diseases affecting the brain. To achieve this, we are planning an exhibition of Cajal’s drawings, in La Madraza, which will start before the congress and will last for several months, from June until the end of September. La Madraza palace, also known as Casa de la Ciencia, was the first public University of Al-Andalus and currently belongs to the University of Granada.

We have received 142 applications from 56 countries; half of them are from Europe, followed by the USA and Latin America, and finally from Asia and Africa.”
Young CSIC scientists are researching depression, rare-disease related brain dysfunctions, neurodevelopment and neurodegeneration, ultrasound for therapeutic use, recording brain activity with graphene neuronal sensors and studying optical illusions.

By María González

Understanding how different areas of the brain work, at the most microscopic level, and how the relationships between brain areas are altered in pathological states is an exciting challenge," says Candela González-Arias, a PhD student at the IC (Cajal Institute, CSIC). She is one of the young researchers training at the CSIC, trying to answer the questions posed by the organ that centralises the nervous system’s activity, the most complex in the organism, the result of hundreds of millions of years of evolution. In order to find answers, these scientists approach research from multiple disciplines - neurosciences, optics, materials science... - to advance in our knowledge of its structure, the search for new therapeutic targets, the understanding of neurodegenerative diseases and the functioning of vision, among others.

Candela González-Arias’ research aims to understand the role played by astrocytes, a type of glia cell (cells found in the nervous system), in depression. More than 300 million people suffer from depression worldwide and by 2030 it will be leading cause of disability among young people and adults, according to the World Health Organisation (WHO). "For years, neurobiology has focused on the study of neurons and their dysfunction, but the causes of this pathology are still unknown," explains the scientist.

Astrocytes represent one of the most abundant populations of glial cells in the mammalian brain and are vital for the nervous system to function properly, hence the importance of understanding what physiological alterations occur in depression. So far, she says, “we have seen how selective manipulation of these cells can reverse some of the main symptoms of the disease, which reveals their potential as therapeutic targets. According to the researcher, the consolidation of the results obtained would represent a significant step forward not only in the knowledge of the pathophysiology of depression, but also in terms of new treatment strategies.

Marina Guillén, a PhD student at the IBM (Alberto Sols Institute for Biomedical Research, CSIC-UAM), is working towards the same goal, namely to gain a better understanding of the brain and the phenomena occurring therein. However, she focuses on a rare genetic disease diagnosed in only 320 people worldwide. She studies the alterations existing in the brains of patients suffering from Allan-Herndon-Dudley syndrome. “People with this disease lack a protein that enables thyroid hormones, which are necessary for proper brain development, to enter the cells. This causes significant neurological dysfunctions, such as severe intellectual disability, paraplegia or inability to coordinate movements in people with the disease,” explains Guillén. “In order to improve these patients’ quality of life, we work with a murine model that carries one of the mutations and we use techniques like immunohistochemistry, transmission electron microscopy and nuclear magnetic resonance to analyse the brain structure.

Treatments for neuropathologies

“Despite the amount of research being carried out worldwide, the number of people affected by neuropathology continues to grow and, so far, there are not that many effective treatments,” says Daniel Muñoz, from the IQFR (Institute of Physical Chemistry Rocasolano, CSIC). His research project aims to understand, at the atomic and molecular level, how the NC51 protein is capable of interacting with and regulating other target proteins involved in multiple diseases, both in neurodevelopment and in behavioural disorders and neurodegeneration.

“Understanding the basis of NC51 specificity would facilitate the development of new regulatory molecules with biotechnological and therapeutic potential. It is a very attractive pharmacological target,” says Muñoz. “Current therapeutic strategies for the treatment of neurodevelopmental and neurodegenerative diseases are designed to act on
Despite the amount of research being carried out worldwide, the number of people affected by neuropathology continues to grow, and so far, there are not that many effective treatments”

Daniel Muñoz (IQFR)
Cajal: an explorer in the forests of the human soul

The histological drawings by the Nobel Prize in Medicine, kept at the IC (Cajal Institute), are of both scientific and artistic value, showing the basic elements forming the structure and function of the central nervous system.
Cajal was a pioneer, an explorer in what is perhaps the most complex forest on earth: namely the brain. This highly complex biological structure is made up of around one hundred billion neurons, in which each neuron is connected to 10,000 other neurons, transmitting signals to each other through 1,000 trillion synapses, or electrochemical connections. These vertiginous figures give an idea of the dizzying web of connections in which the human soul resides.

However, when Santiago Ramón y Cajal (1852-1934) took on this challenge at the end of the 19th century, little was known about the structure and functioning of the central nervous system. Histological techniques did not afford much precision, but Cajal made up for this with his irrefutable talent for drawing. Thus, like a navigator in a terra incognita, Cajal took up the microscope and began to portray the marvellous electrochemical forest that he discovered on his path through brain tissue samples.

The testimony of this journey is recorded in around 35,000 histological drawings, which combine scientific relevance with pure artistic value. This treasure trove of science and art is known as the Cajal Legacy and part of it is housed at the IC (Cajal Institute, CSIC) where it is being digitised to conserve it and facilitate handling. A small sample of the Cajal Legacy, which includes other objects such as microscopes and a diary, is on temporary display at the MNCN (National Museum of Natural Sciences), as part of the events organised for the Año Cajal, a tribute which actually spans a three-year period from June 2022 to May 2025.

“The twelve histological drawings on display at the MNCN are a small but valuable selection of the nearly 2,000 drawings in the Cajal Legacy. They have been selected to show how a single drawing can provide a great deal of neuroanatomical information to anyone knowledgeable on the subject,” says researcher Juan Andrés de Carlos, director of the Cajal Institute’s legacy. Cajal revolutionised knowledge about how neurons, or nerve cells, which are the building blocks of the central nervous system, i.e., the brain and spinal cord, communicate. His disruptive theory proposed that neurons are in contact without touching each other; somehow, he reasoned, neurons must be able to communicate without their ends fusing.

Time proved him right. In 1952, just 18 years after Cajal’s death, the electron microscope confirmed that neurons communicate through tiny clefts or gaps called synapses. These consist of electrochemical transmissions by which one neuron talks to another, from the axon of one (a truncal extension) to the dendrite (its arborescent root) of the other. Cajal’s visionary intuition, which science would prove decades later, earned him the Nobel Prize in Physiology or Medicine in 1906, shared with the Italian histologist Camillo Golgi.

“So, one of the drawings shows us how the cerebral cortex is made up, with two basic types of neurons, some that project their axons outside this structure and others with short axons that contribute to forming different intra-cortical circuits,” says De Carlos. “It also shows us how axons coming from deep nuclei can encroach on the cerebral cortex, making contacts and helping to form different circuits,” he adds.

Other drawings show diagrams that explain the functioning of specific systems, such as the respiratory mechanism or the course of nerve currents in the connections of the cerebellum. “Diseases are also addressed: one drawing describes the formation of degenerative plaques in a case of senile dementia, or the morphological variations in the Golgi apparatus of different neurons, as a consequence of degenerative diseases,” he concludes. These are images reflecting Cajal’s talent in observing the neuronal branches of the brain and which today bear witness to his genius, the giant of neuroscience, who delved deep into the forest of the human soul.
A good drawing, like a good microscope preparation, is a fragment of reality. Such scientific documents maintain their value indefinitely and the study thereof will always be useful, whatever interpretation they may inspire.” Santiago Ramón y Cajal, 1899
You have almost certainly heard that our brain is the most powerful computer in the world. But what do you think of when you are asked what it is made of? Chances are that the first word that springs to mind is neurons. Not bad, but for this unique machine to work to its full potential, it needs other equally important cells to function. Among them are astrocytes, named after the stars. Let’s start at the beginning.

The brain works because neurons transmit information through electrical currents. The connection points between one neuron and another are known as synapses. At these synapses, substances called neurotransmitters are released, which enable the electrical impulse to keep going from one neuron to another. At this connection point, the astrocyte plays a fundamental role in the inter-neuronal dialogue, modulating and regulating the communication between them.

What are the advantages of a three-way conversation? This system, which is more complex than a two-way conversation, allows for a greater variety of messages and adds a mediating element to ensure that the information is transmitted correctly, i.e., the astrocyte. The point is that we do not have just one astrocyte per synapse. In mice, a single astrocyte is able to modulate, mediate and participate in more than 100,000 synapses simultaneously. It is as if a single astrocyte were present and talking in 100,000 WhatsApp groups simultaneously. In humans, a single astrocyte is involved in two million synapses. In other words, our astrocytes have 20 times the capacity to process information... And we have millions of them. What if the explanation (or at least part of it) for our intelligence lies in the great refinement that astrocytes bestow on our brains?

Astrocytes: stars speaking in our brains

These star-shaped cells play a crucial role in the inter-neuronal dialogue, modulating and regulating communication with each other. Researcher Irene Serra Hueto investigates them at the Cajal Institute.
For us to answer this question, we need to find out more. Specifically, my research at the Cajal Institute, CSIC, targets astrocyte-neuron circuits; specifically, those established in the nucleus accumbens, the area of the brain that is triggered when we like something. This area receives information from other brain regions related to memory (hippocampus), emotions (amygdala) and decision-making (prefrontal cortex), and it is really important because it is affected in addiction disorders, among others.

We know that astrocytes play a fundamental role in regulating this nucleus and, more recently, that the brain has different types of astrocytes, just as it has different types of neurons. However, we do not yet fully understand why astrocytes differ from each other nor how they differ. Do we have specialised astrocytes in the nucleus accumbens regulating memory-based information about what we like? Are there others associated with emotions? Are they involved in decision-making circuits?

**Astrocytes on a large scale**

In the latest work published by researchers at the IC-based laboratory working on synaptic plasticity and astrocyte-neuron interactions, directed by Marta Navarrete, we explore these questions in depth. We present a new tool that has enabled us to study the activity of astrocytes on a large scale and with temporal precision, for the very first time. With this calcium sensor, CaMPARIG-FAP, we have been able to observe the whole nucleus accumbens and detect which astrocytes respond to specific stimuli.

Microscope lenses are limited in size, and this makes it impossible to observe all the astrocytes in a brain region at the same time. The special feature of CaMPARIG-FAP is that it detects, by fluorescence, the calcium emitted by astrocytes when they are activated. It is like taking a photo: by emitting a flash of violet light, inactive astrocytes show up in green and active astrocytes in red. This is how we can analyse how large regions of the brain respond to a given stimulus.

Using this tool, we discovered that astrocytes in the nucleus accumbens form functional networks that respond differently depending on the source of the stimuli - memory, emotions or decisions. These results indicate that astrocytes are able to tell where information comes from and also that they integrate the different signals in a parallel processing to that of neurons. This suggests that astrocytes are much more specialised in brain circuits than we thought.

Understanding in depth how they interact with neurons and how they regulate the information coming from different brain areas would bring us much closer to finding effective solutions to treat addiction. And this is just in the nucleus accumbens, so understanding how astrocytes interact in other brain regions would shed light on our brain’s potential, which still conceals as many mysteries as those hidden in the universe.
Neurocientífico Javier DeFelipe destaca que la especificidad de cada especie del cerebro hace que sea difícil para nosotros entender el cerebro humano a través de la experimentación con animales, una reflexión que desarrolla en su nuevo libro, *De Laetoli a la Luna. El insólito viaje del cerebro humano* (From Laetoli to the Moon. The human brain’s extraordinary journey).

**Unic平性 of the human brain**

What is the neural substrate that makes people human? If all species’ brains were organised so that the same design of several microcircuits was repeated in each of the brain’s divisions, without significant inter-species variations, and if the only difference was the number of such circuits and their connections, we would now know much more about the human brain. However, the principles of structural design (spatial distribution, number and types of neurons, local synaptic circuits, etc.) vary greatly in different parts of the nervous system, as well as between species.

In other words, the problem is that there are structural, functional and cognitive features that are unique to humans, just as each species has a brain that is typical of that particular species. Therefore, the question remains: What kind of information obtained from studying another species can be reliably extrapolated to the human brain? And then: What is the best strategy to obtain the missing data, taking into account the obvious ethical limitations when experimental methods are required that cannot be used in humans? In this respect, we should remember that the mouse - the experimental animal most commonly used to study the brain in research labs today - and the genus Homo evolved from a common ancestor some 6 million years ago, so it stands to reason that this huge evolutionary distance affects the structural and functional organisation of the brain.

Indeed, during brain evolution, many cortical areas have developed differently in primates compared to rodents, including unique patterns of gene and molecular expression, and neural circuits have emerged that do not exist in rodents, or else they are highly modified. According to these criteria, there are extensive regions of the human cortex that are absent in rodents, such as the dorsolateral prefrontal cortex, the frontal polar cortex and the temporal pole. These regions are involved in several higher cognitive functions and are mainly affected in some psychiatric, neurological and neurodegenerative diseases, such as schizophrenia, epilepsy or Alzheimer’s disease.

Using larger mammals as experimental animals, such as the macaque or cat, is believed to provide more relevant information on the human brain than would be possible by using small mammals, such as rats and mice. What is more, some scientists suggest that research with non-human primates is essential, as the structural and functional organisation of the rodent brain is far more distant than that of these primates. However, all species’ brains differ and we will never understand how the human brain works by studying, for example, the brain of the macaque or chimpanzee, the primates most closely related to humans; the evolutionary lines between them and us separated just six million years ago!

True to say, the study of the non-human primate brain has provided us with valuable insights into the functional organisation of certain brain regions where generalisations can be made. Comparative studies are valuable if we want to examine some attributes that humans share with other species, such as orientation preference maps or ocular dominance columns of the visual cortex, which are highly developed in macaques and humans but absent in other species, like mice and rats. Macaques, for example, can be considered more similar to humans than rodents in terms of the visual cortex. However, from a micro-anatomical and neurochemical perspective, the macaque brain reveals many important differences compared to our own, probably reflecting obvious cognitive and behavioural differences between the two, so results obtained using experimental animals as models of human disease or to study the normal brain organisation should be taken with caution when extrapolating data to humans.

In short, the human brain shares many features with those in other non-human mammals, but ours also possesses several specialisations that are unique to humans and are likely to be crucial for human functions. Thus, the similarities between different species could be seen as the basic building blocks of brain organisation. Conversely, differences may indicate evolutionary adaptations of neural circuits to the particular functions of each brain region in each species. We do not yet know what all these variations might signify when we try to correlate them with human qualities or those of other species, but undoubtedly these observations represent an essential step forward in the exciting study of the neural substrate that makes humans human.

"All species’ brains differ and we will never understand how the human brain works by studying, for example, the brain of the macaque or chimpanzee, the primates most closely related to humans!"
The brain and afflictions of the soul

Juan Lerma and José Luis Rozas. Espasa

The brain is the most complex biological structure in existence (“the very organ that thinks”), with nearly 100 billion neurons, each with thousands of connections; two simple facts that illustrate its extreme complexity. In this essay, neuroscientist Juan Lerma and biologist José Luis Rozas take the brain apart to explain its fundamental components: neurons (the basic unit), memory and learning, emotions, consciousness. They also describe its dysfunctions (“the diseases of the soul”), such as schizophrenia, autism, depression, anxiety, epilepsy and Alzheimer’s disease. “Putting aside the concept of the transcendent soul, which is based on faith alone,” write Lerma and Rozas, “there is what we call our essence or soul. And what is this essence? It is the set of properties of our mind, which stem from the functioning of our mind, a functioning that is rooted in the laws of chemistry, physics and biology. Our soul is, therefore, a biological, material soul, which is defined in terms of all the processes it performs”. Lerma and Rozas take us on a journey to the foundations of the biological substratum of the soul, showing us what science has found out, without forgetting to warn us about the long road ahead.

How do neurons communicate?

Juan Lerma, CSIC-Catara. 

The brain is a perfect machine, chiseled and refined over millions of years of biological evolution,” writes Juan Lerma, CSIC neuroscientist, in this essay. From time to time, he cautions, this machine breaks down and solutions must be sought. Lerma studies the molecular basis of neuronal communication and in this book he explains the characteristics of this prodigious system. “Calculations estimate that the one hundred billion [neurons] making up the human brain form around 100 trillion synaptic connections. So, it’s not surprising that even small disturbances in the communication between neurons can cause one or more systems to malfunction, eventually leading to brain function failure,” he says. Lerma takes us through the chemistry of brain communication, through synapses, neurotransmitters and brain plasticity, and reveals how altered synaptic communication causes diseases such as schizophrenia, epilepsy and Parkinson’s disease. An entertaining and rigorous journey into the biological substratum of the human soul.

Brain and exercise

José Luis Trejo and Coral Sanfelu. CSIC-Catara.

Physical exercise undoubtedly has benefits for the whole body, for health and, of course, for the brain. However, in the last decade, numerous neuroscientific advances have received relatively little attention. Researchers José Luis Trejo and Coral Sanfelu explain in an entertaining and informative way some of these achievements, pointing out which type of exercise is good for what, that the intensity of exercise is a crucial factor in obtaining specific results, which brain areas benefit from moderate vigorous exercise, as well as the latest findings on the effects of exercise on depression, anxiety, cognition, ageing and neurodegeneration. Although we are far from being able to devise a personalized exercise plan, which is useful for all people and produces benefits for the different physiological systems of the body without increasing stress, there is no doubt that a sedentary lifestyle is the enemy of a healthy brain.

Alzheimer’s

Ana Martinez, CSIC-Catara.

In 2021, some 55 million people worldwide were suffering from dementia. Among these, Alzheimer’s disease is one of the most common. “It is a neurodegenerative process of the central nervous system characterised by progressive neuronal death in certain areas of the brain,” says Ana Martinez, a CSIC researcher and expert in the search for innovative therapies against neurodegenerative diseases. Alzheimer’s, a major health problem in developed countries, lacks reliable diagnostic and treatment methods. Martinez discusses several theories about its origin, as for example the aggravated presence of the tau protein in the brain could be involved in the destruction of neurons, and the link found with the herpes virus responsible for lip sores. Martinez also lists possible prevention and treatment methods and, above all, sets the goals neuroscience must achieve in order to understand and cure it.

Tasting with our brain

Francisco Javier Cudeiro Mazaira. CSIC-Catara.

What happens when we enjoy food? Neurophysiologist Francisco Javier Cudeiro Mazaira explains the complex brain processes behind sensory perception in the context of cooking. “I will try to explain that everything we are boils down to our brain activity,” says Cudeiro. “To say that we ‘smell with our nose’ would be as inaccurate as saying that we ‘hear with our ears’. Perception is a creative action and, to understand it, we have to delve inside the nervous system to see how the information from the senses is analysed, how the different information pathways mix and interact and how, finally, the perception of the world around us emerges from our neuronal activity, millisecond by millisecond,” he explains.

¿QUÉ SABEMOS DE?

Francisco Javier Cudeiro Mazaira. CSIC-Catara.
The science of healthy ageing
Carlos Dotti and Pablo Gonz. Shackleton Books

As life expectancy goes up, a new challenge arises: to achieve healthy ageing. To do this, it is essential to observe the mechanisms of brain ageing. This is addressed in the essay by CSIC researcher Carlos Dotti, together with Pablo Gonz. Dotti delves into the biological mechanisms that constitute and produce the signs and symptoms of brain ageing, and explains the strategies for preventing or delaying the loss of intellectual capacities. He also discusses other aspects related to brain ageing, such as stroke, peripheral neuropathies, Parkinson's disease and Alzheimer's disease.

Parkinson's
Carmen Gil and Ana Martínez. CSIC-Catarata

Parkinson's affects movement and triggers changes in memory, learning and the expression of emotions. This happens because the disease affects the central nervous system directly. Parkinson's is the second most common degenerative disorder, second only to Alzheimer's disease, and, like Alzheimer's, the risk of suffering from it increases with age. Carmen Gil and Ana Martínez, CSIC researchers, review the history of the disease, possible prevention, the search for diagnostic markers, as well as discussing the treatments available to halt the advance of this currently incurable condition. “High level research is targeting Parkinson's disease and promises definitive advances in the coming years. Regenerative medicine undoubtedly plays a key role in understanding the disease and in developing a new generation of therapies and technologies in the near future,” say the researchers.

Dementia
José Ramón Alonso and Juan Andrés de Carlos. Next Door

Dementia is the loss of intellectual capacity, which prevents those affected from leading a normal social and professional life. In developed countries, dementia affects 1.3% of the population, especially people over the age of 65, with the proportion doubling every five years and increasing at a disturbing rate. In this essay, CSIC neuroscientist Jesús Avila addresses the study of dementia, which, along with cancer and cardiovascular diseases, is one of the major health concerns and the one necessitating the greatest expenditure, as it requires constant care. Some types of dementia, such as neurosyphilis, can be controlled; others, such as schizophrenia, can be treated, and hopefully better lifestyle habits can reduce the incidence of dementia. However, for the prevention of senile dementia, such as Alzheimer's, there are still no solutions.

Sense of smell
Laura López-Mascarque and José Ramón Alonso. CSIC-Catarata

Smell is the most mysterious of the five senses; it is also the first, the most direct, the one that can most evoke memories and the one that most lingers in our memory. Smell is controlled by neurons exposed to the outside world with a system of protein receptors representing a substantial part of the human genome. This often-ignored sense, capable of attracting a moth from huge distances, is what lets us enjoy a good wine and, thanks to its early evolutionary development, created our brain. CSIC scientist Laura López-Mascarque and José Ramón Alonso discuss the importance of smell, which is actually a fine chemical sensor able to analyse products on the go, and which may be a new diagnostic tool for some diseases. It is a complex system that keeps us informed and in permanent contact with our environment or, as Helen Keller said, “smell is a potent wizard that transports you across thousands of miles and all the years you have lived.”

Multiple sclerosis
Leyre Mestre and Carmen Guaza. CSIC-Catarata

Multiple sclerosis is a chronic, inflammatory and neurodegenerative disease of the central nervous system, with an important autoimmune component (the cells of the immune system itself attack the body's own cells). This is caused by the destruction of the myelin surrounding the axons (a part of the neurons), thus compromising the transmission of nerve information. MS affects 2.5 million people worldwide and is the leading cause of non-traumatic disability in young adults between the ages of 20 and 40. CSIC neuroscientists Leyre Mestre and Carmen Guaza address the origin and evolution of this disease, known as ‘the disease of a thousand faces’, and review its mechanisms and novel therapeutic approaches, as well as its relationship with the immune system and the intestinal microbiota.
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