

Synapse

The newsletter designed to connect with you

No.26 - August 2021

Special feature

**Epilepsy : when the electricity
in our brain goes wild**

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Partner

KLESIA :
11 years of generosity

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2020 Essentials

P.19

Generosity

An encounter with Guillaume
de Tonquédec



After celebrating its 10th anniversary in 2020, Paris Brain Institute is entering a new phase of growth, despite the climate related to the Covid-19 pandemic. For an entity that has only existed for a decade, the Institute rapidly displayed its scientific and medical excellence, its ability to attract the best researchers and experts from around the globe, and its sound financial health.

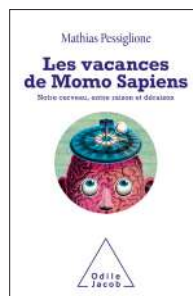
In other words, Paris Brain Institute model, imagined years ago by the Institute's founders, has become a tangible reality and enables major scientific breakthroughs for the benefit of patients.

In spite of the unprecedented health situation we have been going through over the last 18 months, the Institute has been able to meet the challenges presented. By pursuing a high level of scientific publications, by mobilizing for the hospital and by ensuring the safety of its staff, as well as by developing new partnerships and by keeping pace with the financial balance that it had set itself.

In this issue of Synapse, you will discover the work of our experts to better understand epilepsy, a pathology that affects a large number of people, especially children, and to provide treatments for everyone.

In this issue, you will also discover 2020 Essentials, which, in addition to reviewing the highlights of the past year, present an overview of the Foundation's accounts, which are always managed rigorously and seriously. It is a way for Paris Brain Institute to give you an account of the work accomplished through your loyal support, which is more than ever indispensable, and to thank you for what you have enabled us to achieve.

Serge Weinberg
Founding member and Treasurer of Paris Brain Institute



The thin line between rational and irrational

Mathias Pessiglione, Inserm Research Director, specialist in brain mechanisms that motivate behavior in normal and pathological situations, team leader at Paris Brain Institute, discusses in his latest book the paradox of the brain when it comes to making a choice; rational or not... The brain has its reasons, which reason does not know!

Les Vacances de Momo Sapiens, by Mathias Pessiglione, Odile Jacob, 336 pages, 23.93 euros (in French).

Celebrate science with Paris Brain Institute!

As part of the French «Fête de la Science» (National Science Fair), on Saturday October 9, the Institute will invite you on an immersive journey in to the heart of the brain and its mysteries. Come along and meet our researchers, engineers and clinicians who work hand-in-hand to better understand and better treat neurological and psychiatric disorders.



A consortium for neurological disorders

Finding ways to prevent, treat and cure neurodegeneration is one of the most pressing medical issues today. To address this, 4 leading European research institutes from Germany, France, Belgium and the UK have formed CURE ND, a new alliance to tackle neurodegenerative diseases. A real challenge that Paris Brain Institute is committed to taking up!

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10 new "Big Brain Theory Program" projects

Risk-taking and interdisciplinarity are the keys to innovative, original research. This is why Paris Brain Institute launched the "Big Brain Theory Program" in 2015, which awards seed grants to innovative interdisciplinary research through internal calls for projects. To be eligible, researchers must demonstrate innovative capacity to resolve critical issues and/or methodological/technological bottlenecks in fundamental and/or clinical neurosciences. As such, 10 projects - on dystonia, leukodystrophies, multiple sclerosis, Parkinson's and Alzheimer's diseases - out of the 28 projects submitted were selected by the Institute's International Scientific Advisory Board, including 2 in collaboration with the Pasteur Institute.



Summer School 2021

6 au 10 Septembre 2021



A program to imagine tomorrow's solutions

The "Brain to Market" Summer School will take place at Paris Brain Institute from September 6 to 10 this year. This annual international program enables 50 international participants, graduates, scientists, managers, engineers, designers and developers to attend a series of conferences led by experts in entrepreneurship and in nervous system pathology to bring innovative concepts to life. On the agenda this year: adult psychiatry with a focus on anxiety and addiction. Fascinating for sure!

Key figures

1.7 MILLION EUROS

to be invested in 2021 and 2022
to finance 10 cross-disciplinary research
projects under the Big Brain Theory Program.

€250,000 already received thanks to
the commitment of 2 donors.

Our warmest thanks to them!



seen on the web

Find out more in the "News" section of our website.



- A new biomarker in meningiomas identified
- Deep Time: a timeless one-of-a-kind experience which Paris Brain Institute participated in



videos



- Online donor conference from 06.26.2021 on the transmission of neurological disorders (in French)
- Braincast - The voice of neurons, a podcast in partnership with the magazine Cerveau & Psycho, with Dr Stéphane Epelbaum, neurologist and researcher in neuroscience at Paris Brain Institute (in French)



agenda

Tuesday September 21,

World Alzheimer's Day, discover the latest news at www.parisbraininstitute-icm.org

Saturday October 9

Celebrate science with Paris Brain Institute.

September - October

Donors' conference on Alzheimer's disease online on our site. (you'll receive the link by email).

Tuesday November 2

Open Brain Bar in partnership with Pariscience. Information and registration on our site.

From November 12 to 14

Charity Speedrun* organized by the French Restream.

*video-gaming competition

Follow us



Christian Schmidt de La Brélie, CEO of the social welfare group KLESIA, talks to us about the reasons for the Group's unwavering commitment to Paris Brain Institute.



Christian Schmidt de La Brélie,
CEO of the KLESIA Group

It was in December 2008 that the provident institutions of the D & O Group, which became KLESIA in 2012, made their first commitment to Paris Brain Institute even though it hadn't even been built. What made the group decide to embark on this pioneering adventure and what explains your loyal commitment to us?

It was above all an encounter with Professor Gérard Saillant, in 2008, when he told us about his innovative project to combine a research center and a startup incubator on the subject of the brain, how it worked and the diseases that could affect it. And it spoke to us right from the start because this project reflected our values and our DNA as a public-interest insurer. **Understanding the brain, this terra incognita, offers us a source of solutions for tomorrow's health because the challenge is to prevent diseases, not just to treat them.** So, it was only natural for us to support Paris Brain Institute from the word 'go' and to continue to support it today. Research takes time and it's only through this support over the long term that we can ensure it moves forward.

Population aging and related diseases are one of the major public health issues of the 21st century. What answers does your Group provide?

It's an issue that KLESIA takes very seriously. It's also part of **our raison d'être, which is "To ensure a worry-free future and quality of life for all"**. But, to enjoy a worry-free future, you need to prepare it and look after yourself to ensure you stay in good health as long as possible. KLESIA accompanies its clients by offering them simple, innovative, supportive and sustainable personal insurance and prevention solutions, tailored to their needs and to those of their loved ones, throughout their lives. We also act in the interest of society through initiatives on a larger scale, particularly as regards assistance to caregivers, disability and medical research, such as with Paris Brain Institute.

Since then, and thanks to your support, the

Institute has grown and matured. What are you most proud of? What do you aspire to with us?

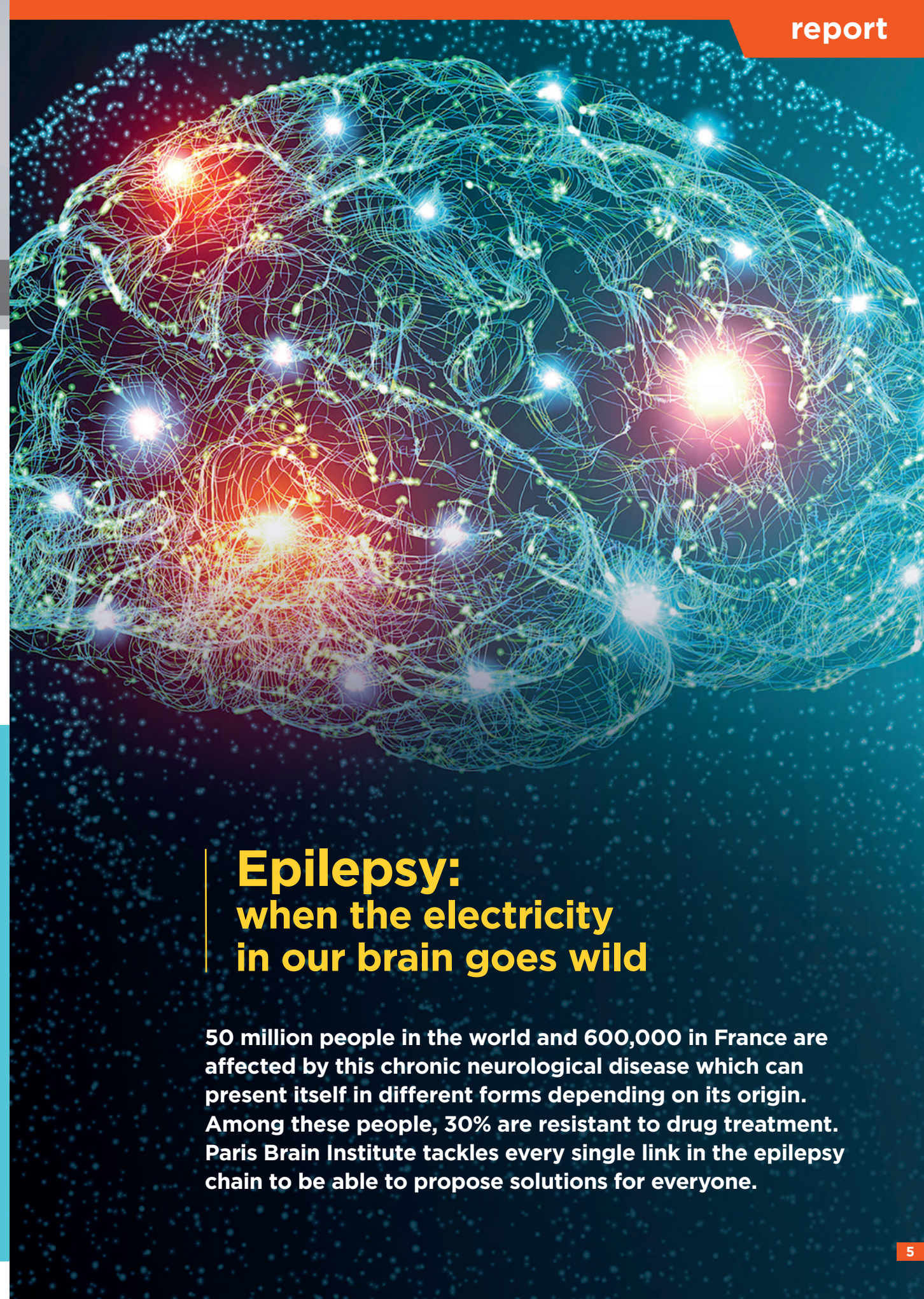
Our support from the word 'go' enabled the Institute to hire two team leaders, who are among the most talented in the world, and to create research platforms from the moment it opened its doors and also to purchase ultra-efficient imaging tools. And **that's something to be really proud of, when you see how far the Institute has come today and the results it has obtained**, particularly as regards of spinal cord injuries and the development of neuroinformatics. We hope our unwavering support will enable the Institute to go even further in its research and address the questions we're still asking today about the brain.

Would your business like to support Paris Brain Institute? We can associate it with the Institute's research mission on nervous system diseases and develop a program with you that meets your expectations.

As a Foundation recognized as being of public utility, donations made to the Institute enable businesses established in France that make less than €2M in donations per year to benefit from a **corporate tax reduction equal to 60% of the amount donated, up to a limit of either €20,000 or 0.5% of revenue. For amounts over €2M, the reduction is 40%.**

Your corporate donations may be eligible for tax deductions in the United States and in 20 countries part of the TGE (Transnational Giving Europe) network including the United Kingdom and Switzerland.

More details
on +33 (0)1 57 27 40 32
or cercle@icm-institute.org



Epilepsy: when the electricity in our brain goes wild

50 million people in the world and 600,000 in France are affected by this chronic neurological disease which can present itself in different forms depending on its origin. Among these people, 30% are resistant to drug treatment. Paris Brain Institute tackles every single link in the epilepsy chain to be able to propose solutions for everyone.

Epilepsy, an electrical dysfunction of the brain

Epileptic seizures, symptom of an epileptic syndrome, indicate cerebral hyperactivity resulting from “hyperexcitation” of the neurons of the cerebral cortex. A distinction is made between generalized epilepsy (1/3 of cases), in which the affected neurons spread the abnormality to the whole brain (the epileptogenic focus), and partial or focal epilepsy, which remains localized in the region where the seizure originated.

There is not just one epilepsy but several epilepsy syndromes of varying degrees of severity that are defined by the age when seizures occur, their cause, their nature, their frequency and the response to drug treatments. Epileptic

seizures can occur for many different reasons: genetic, lesional, metabolic, etc. The mechanisms between the initial disorder and the epileptic seizure are not necessarily the same.

Eptilogenesis is the silent period during which the brain will gradually change to become an epileptic brain. At some point, the phenomenon of ictogenesis occurs, i.e. triggering the crisis itself. Paris Brain Institute’s research focuses on these two phases, so as to act at a very early stage on the phenomena that could be potentially responsible for the onset of an epileptic syndrome, as well as to find ways to act on the seizure triggering process.

A FEW KEY FIGURES



50 million
people affected around the globe



50% of epilepsy occurs for the first time before the age of 10



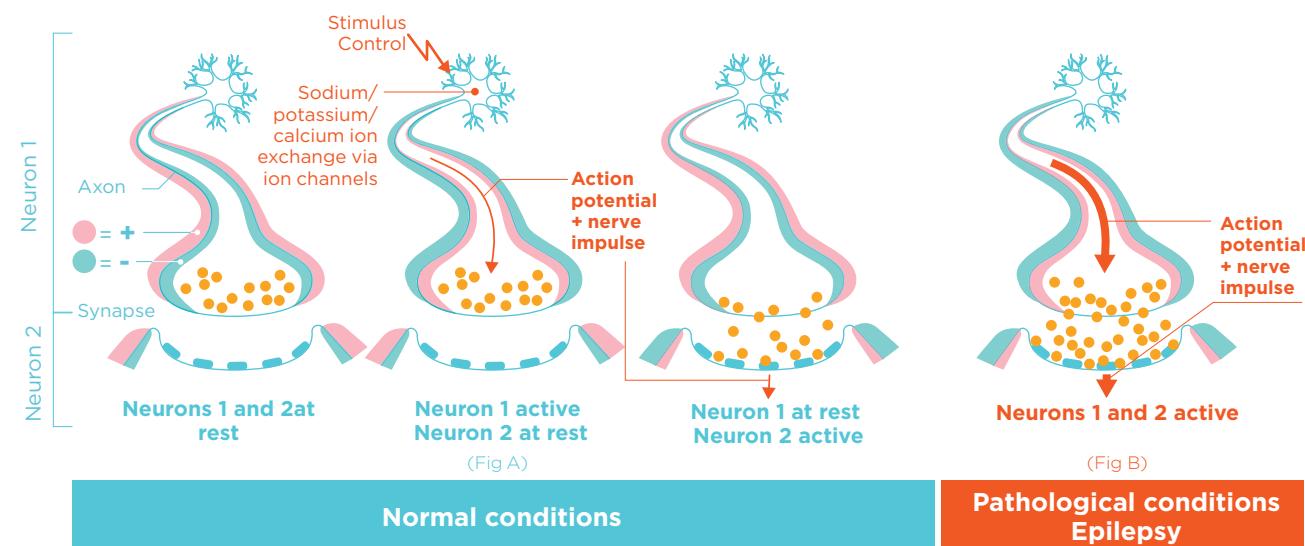
2/3 of patients are responsive to drug treatments



50% number of cases globally for which the cause of the disease is still unknown

Today, drug treatments are effective for 2/3 of patients, 30% of cases, however, remain drug-resistant. **Surgery**, to remove the part of the brain that causes the seizures, can then be considered with effectiveness in a certain number of these patients. To do this, doctors implant **intracerebral electrodes and microelectrodes** to delimit the area to be removed with extreme precision. Like this, they can study neuron behavior during sleep, during a seizure, between seizures... and obtain a new vision of what happens in the brain of epileptic patients. These implants also benefit research, since they provide the opportunity to **study electrical activity inside the brain** against a background of different cognitive functions such as decision-making.

EPILEPTIC SEIZURE



What is an epileptic seizure?

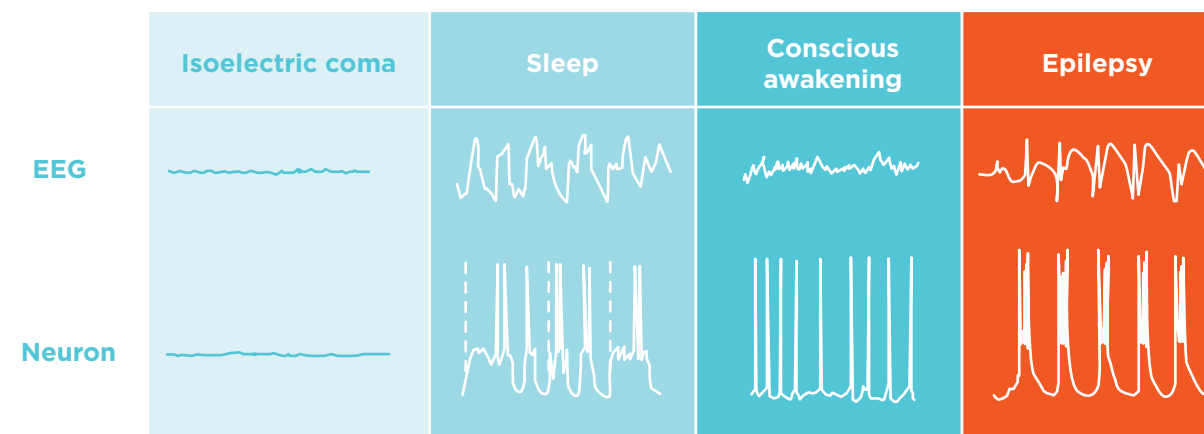
An epileptic seizure is an **abnormally high level of electrical activity in a group of neurons in the cerebral cortex**. The action potential or nerve impulse is an electrical message created by an inversion of positive and negative charges on either side of the neuron’s membrane, resulting from an exchange of ions between the cell and its environment (Fig A).

Under normal conditions, the role of each neuron is to receive, process and transmit the electrical message to other neurons via the synapse thanks to neurotransmitters (orange spheres on the diagram). In the case of an epileptic seizure,

the neurons become hyperexcitable, i.e. a single stimulation does not result in an action potential but in a succession of repetitive action potentials without a rest period (Fig B).

The hyperexcitable neurons form the epileptic focus. A distinction is made between partial or focal seizures, which originate in a very limited area of the brain, and generalized seizures, which are the result of a sequence of action potentials that spread to the whole brain. Hyperexcitability is very often accompanied during seizures by hypersynchrony, with several groups of neurons generating sequences of action potentials simultaneously and at the same rate, amplifying the intensity of the symptoms.

Combined recordings of EEG (electroencephalography) and intraneuronal activity across various states of consciousness (Charpier - Chavez - Navarro team)



Combining clinical aspects and research to better understand epileptic seizures

A translational approach: from the neuron to the clinical expression of the crisis

The team, co-led by Prof. Stéphane Charpier, Prof. Vincent Navarro and Mario Chavez, conducts research :

- on patients to analyze changes in the action potential discharges of neurons, responsible for triggering seizures, and as regards clinical symptoms, as well as research through
- on experimental models of epilepsy, to gain access to the intrinsic and synaptic properties of neurons, which control these abnormal discharges that cause seizures. **The team's aim is to identify the whole chain of command of the seizure, from the neuron to the symptoms, in order to then consider taking action at its different stages,** from the cell physiopathological process to the clinical process expressed by the patient.

Reconstructing the natural history of child epilepsy

For several years now, Prof. Stéphane Charpier (Sorbonne University) and Séverine Mahon (Inserm) have been studying one of the most frequent forms of epilepsy in children, absence epilepsy, where seizures trigger a loss of consciousness in young patients. The electrical



activity of the brain recorded using EEG in these children shows straightaway what appears to be a generalized seizure across all areas of the brain. However, thanks to a more detailed study of neural network activity, followed by that of single neurons in a genetic model of this epilepsy, these researchers were able to discover the region and the neurons that cause these seizures and to show how their electrical and synaptic properties had been gradually altered after birth. Today, researchers are working on the specific mechanisms that cause this neuronal dysfunction. **"We're close to understanding why these neurons are in this state and why they trigger seizures,"** explains Prof. Stéphane Charpier (Sorbonne University).

Drug-resistant epilepsy as a gateway to understanding the pathology

The study of signals recorded in drug-resistant patients before undergoing surgery to treat epilepsy enabled researchers at Paris Brain Institute to highlight that not all neurons in the epileptic focus are recruited during the seizure, which contradicted the existing dogma in epilepsy. This topic is fed by data acquired on an ongoing basis from the hospital's patients. Thanks to the close collaboration between the epilepsy unit of the Pitié-Salpêtrière Hospital and its CENIR-STIM platform, Paris Brain Institute is the only institute in France capable of continuously acquiring all the data from a patient's intracerebral microelectrodes 24/7. **"Today, we're endeavoring to define all the micro-variations in neuron activation during a seizure so as to eventually define common patterns between patients,"** specifies Prof. Vincent Navarro, Head of the Epilepsy Unit at the Pitié-Salpêtrière Hospital (AP-HP,

THE NEURONAUTE

The Neuronaute is a smart garment, developed by BioSerenity, a company formerly incubated at Paris Brain Institute, equipped with integrated biometric sensors for monitoring and diagnosing epilepsy. In the near future, this solution should simplify diagnosis for healthcare professionals and enable long-term recording of patient activity in-hospital or at home.



Sorbonne University).

How genetics has changed our view of epilepsy

In 2013, Stéphanie Baulac (Inserm) and Prof. Eric Leguern's (AP-HP, Sorbonne University) team discovered a major gene, DEPDC5, involved in familial forms of focal epilepsies associated with malformations of the cerebral cortex.

"The development of next-generation sequencing led to discovering new genes, proteins, and signaling pathways in epilepsy. This has led to a paradigm shift in studying the mechanisms of the disease, which now enables us to look for new therapeutic targets." explains Stéphanie Baulac

In this type of epilepsy, the team identified mutations in several genes, known as "mosaics", i.e. only in certain brain cells. They recently provided proof of concept that it is possible to detect these through the DNA circulating in the cerebrospinal fluid (CSF), in which the brain and spinal cord bathe. A key breakthrough for the genetic diagnosis of these pathologies.

The team is pursuing research to better understand the pathological mechanisms that lead to malformation and also trigger epileptic seizures, and how mutations in mTOR pathway genes play a role in the clinical variability observed in patients, with the goal of **identifying new therapeutic avenues.**

Share your experience



Many thanks for the questions and experiences we have received. In this issue, we'd like to share the experience of Renaud, 23 years old, who suffers from epilepsy, with you:

I've had epilepsy since I was 8 and drug treatments have never worked on me. So, for years I had to live with recurrent seizures and it was a real handicap in all aspects of my life. For me, there was only one solution imaginable: surgery. After 5 days in hospital to do a complete neurological assessment (MRI, Pet Scan, etc.), my neurologist announced, "you can have surgery!"

After all these years without a solution, this was like a light at the end of the tunnel for me! The neurosurgical procedure went really well, and I was monitored closely for 6 months. Today, my seizures have eased off greatly and I've even been able to pass my driving license!

Let's talk about clinical trials!

Email us your questions on the special feature theme in our next issue, which will deal with the Institute's clinical trials and technology platforms. You may be lucky enough to be featured in your November 2021 Synapse newsletter.

► contact@icm-institute.org

The birth of neurons, mysteries revealed!

The "Brain Development" team led by Prof. Bassem Hassan at Paris Brain Institute revisits one of the dogmas of the genesis of neurons in the cerebellum, a region of the brain essential for controlling motor functions and specific higher cognitive functions.

To find out more, read the article **"The birth of neurons, a complex mechanism that's still revealing its mysteries!"** on the Institute's website



During human embryonic development, nearly 86 billion neurons are generated (neurogenesis) from so-called pluripotent stem cells, i.e. cells capable of generating all the tissues of the body. The proper functioning of the brain depends on the diversity of its neurons in terms of morphology, functions and ability to make connections.

It is indispensable to better understand these mechanisms in order to study brain diseases, in particular the degeneration of neurons observed in the majority of cases and responsible for the irreversible handicaps that patients suffer from.

Through fundamental research on brain development, we now know that the first outline of the cortex appears around the 6th week of embryo development

and that the first neurons appear around the 4th week. From the 33rd day of embryo development, differentiated development of the spinal cord and the brain is observed. The results of this work show for the 1st time ever that excitatory

“ It is vital to better understand these mechanisms to be able to study brain diseases, in particular neuron degeneration. „

and inhibitory neurons of the cerebellum are derived from the same neuronal progenitors contrary to what was known until now and that the differentiation of the same "mother" progenitor cell is induced by a difference in expression of the "NOTCH" protein.

This protein plays a key role in brain development, particularly

in the balance between cell proliferation and differentiation and in the development of certain tumors.

This protein is of great interest in brain development, as the balance between excitatory and inhibitory neurons

is essential for proper brain function. This work opens up new avenues of research into pathologies associated with poor neuronal excitability.

The Covid-Neuroscience Cohort discloses its results

The Covid-Neurosciences Cohort, launched at an early stage of the Covid-19 pandemic, aimed to study the neurological and psychiatric consequences of SARS-CoV-2 infection and the impact of the infection on patients with neurological disorders over a one-year period.

Given the observation of neurological and psychiatric forms of Covid-19, all the teams of the Neuroscience Medical-University Department of the Pitié-Salpêtrière AP-HP Hospital and Paris Brain Institute rallied together in record time to set up an unprecedented clinical study, the Covid-Neurosciences Cohort. The crucial support of the Fédération Internationale de l'Automobile (International Automobile Federation - FIA), the FIA Foundation and Paris Brain Institute donors, enabled experts to rally together and data to be collected complying with international standards.

Amongst the most frequently observed symptoms, the doctors noted cognitive disorders (confusion, language or memory disorders) in 30% of the patients, psychiatric disorders such as hallucinations, anxiety-depression syndromes in 25% of them and 40% of motor disorders. A few cases were directly related to

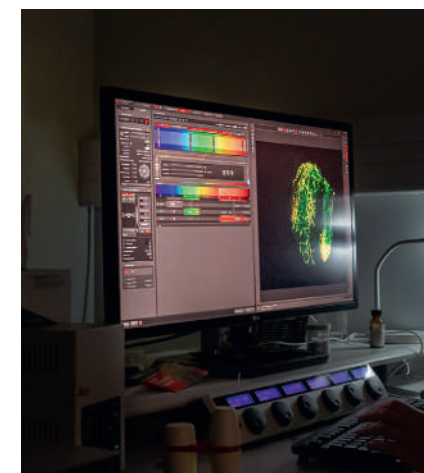
the impact of the virus on the nervous system, such as encephalitis and epileptic seizures, but these cases were rare compared to the total number of patients with neurological symptoms.

"At the end of the day, the source of the neurological disorders seems to be first and foremost in the general complications of severe forms of Covid-19, such as transfer to intensive care, rather than a direct cerebral attack of

the virus." says Prof. Jean-Christophe Corvol (AP-HP, Sorbonne University)

From the perspective of patients with chronic neurological disorders, the forms of Covid-19 appeared to be more severe the more advanced their neurological pathology was. In multiple sclerosis, certain potent immunosuppressive treatments were shown to be associated with a more severe prognosis of Covid-19.

The next step is to monitor these patients in 2021 by studying the long-term consequences on the nervous system and the immune response in these populations. They will be key to increasing our knowledge of the infection and its consequences on the central nervous system, always for the primary benefit of patients.





Paris Brain Institute

a groundbreaking model to accelerate the fight against brain diseases

Paris Brain Institute, created in 2010 with 4 major public partners (CNRS, Inserm, Sorbonne University, AP-HP), and located on the Pitié-Salpêtrière Hospital campus, has achieved its first goal: to create a virtuous, multidisciplinary and translational ecosystem enabling the development of ambitious scientific projects on the brain and its diseases.

With a critical mass and the excellence of 700 researchers, clinicians and entrepreneurs, ten state-of-the-art technology platforms, a clinical investigation center and its artificial intelligence program in neuroscience, Paris Brain Institute now promotes a holistic approach to the brain and its pathologies through prolific translational research.

SCIENTIFIC STRATEGY ON A PAR WITH AMBITIONS

Paris Brain Institute's scientific ambitions are to further our understanding of how the brain works and to prevent and cure the neurological and psychiatric disorders that affect it. To this end, the Institute aims to **play a significant role in preventing and treating nervous system diseases and to drive technological innovation and the development of medical applications.**

This is why the Institute is mobilized to attract the best international researchers in neuroscience, to develop state-of-the-art technology platforms and excellent clinical research, to promote entrepreneurial research and, last but not least, to create a one-of-a-kind, appealing international training center open to society.

PARIS BRAIN INSTITUTE GOVERNANCE

The governance of the Institute, through its Board of Directors, comprising 4 colleges (founders, qualified individuals, ex-officio members and Friends of the Foundation), reflects the deep partnership between the public and private sectors. It ensures that its scientific objectives and resources are aligned. The Management implements measures to ensure the effectiveness of management, and regularly assesses the work and performance of the teams, as such ensuring that excellence is constantly pursued.

In its annual report, Paris Brain Institute reports on its mission and results, in a spirit of complete transparency towards its partners and donors.

Find out more in our comprehensive 2020 Annual Report on our website: institutducerveau-icm.org/en



2020 Highlights

COVID-19 PANDEMIC: PARIS BRAIN INSTITUTE CONTINUES TO MOVE FORWARD

From the start of the pandemic, Paris Brain Institute was in close contact with the medical teams at the Pitié-Salpêtrière AP-HP Hospital and made equipment, consumables and expertise available. All the clinicians working at Paris Brain Institute and the Neuroscience Medical-University Department of the Hospital were on-board. The Institute also set up and carried out voluntary and anonymous salivary Covid-19 PCR tests, offered to the Institute's staff for the safety of all.

PARIS BRAIN INSTITUTE'S CARNOT CERTIFICATION RENEWED FOR 4 YEARS

Carnot certification is a French certification created in 2006 with the aim of developing research partnerships between public laboratories and socio-economic players. The renewal of our Carnot certification for 4 years will enable us to fund Carnot Maturation projects, the Skills Build-up program, Carnot Training and scientific resourcing actions.

PARIS BRAIN INSTITUTE SALUTES PROFESSOR JEAN-YVES DELATTRE'S EXCEPTIONAL COMMITMENT AND THE ARRIVAL OF PROFESSOR CATHERINE LUBETZKI

Professor Jean-Yves Delattre, Director of the Neuroscience Medical-University Department and former Medical Director of Paris Brain Institute retired in November 2020. All of Paris Brain Institute teams wish to thank Professor Jean-Yves Delattre for his exceptional commitment and salute his remarkable career dedicated to patients. Professor Jean-Yves Delattre is replaced in these positions by Professor Catherine Lubetzki.

CURE-ND, A UNITED RESPONSE TO NEURODEGENERATIVE DISEASES

A new alliance, CURE-ND, was launched at the end of 2020. It brings together four European partners, which are very much on the front line as regards neurodegenerative diseases: DRI in Great Britain, VIB in Belgium, DZNE in Germany and our own Institute.

2020 KEY FIGURES



37 startups incubated
8 new technology development programs underway
12 training programs in the Open Brain School
734 members of staff at the Institute



5 fields of research
25 research teams
10 technology platforms
173 clinical trials
15 promising molecules currently being characterized
Over 500 publications in international scientific journals



244,283 donors
€18.3M thanks to public generosity
€16.7M revenue from external competitive grants in 2020
€5.6M in new industrial partnerships

INNOVATIVE AND CREATIVE APPROACHES TO ADDRESS THE CHALLENGES RELATED TO NERVOUS SYSTEM DISEASES

INCUBATION OF INNOVATIVE BUSINESSES

Development work is underway on the Institute's third business incubation site, the "Chevaleret" campus, dedicated to medical technologies and artificial intelligence in healthcare.

The **Medtech Generator & Accelerator project**, coordinated by Paris Brain Institute and financially backed by the BPI (the French Public Investment Bank) aims to develop innovative support programs for startups specializing in healthcare and artificial intelligence in the field of neuroscience, genetic and rare diseases.

Second edition of the endowment fund accelerator program "**Pfizer Innovation France**". Five digital healthcare startups benefited from the support and resources of the incubator, as well as the expertise of a leader in the pharmaceutical industry.

Kick-off of **two new industrial partnerships** with Janssen EMEA, on a pan-European support program, and with Janssen France, AstraZeneca, AG2R La Mondiale and Geopost, on a multi-partner initiative in response to the COVID-19 crisis.

NEW CANDIDATE DRUGS

Three patents have been filed on new medical technology that would curb the build-up of amyloid plaques in Alzheimer's disease, on the potential of new molecules to act on the neuroinflammatory component of neurodegenerative diseases such as Parkinson's disease, and finally on anticipating epileptic seizures using electroencephalography. As regards the "Sleeping Beauties" project, it has

led to pursuing assessment of molecules for therapeutic purposes in glioblastoma, the most common brain cancer in adults.

AN INITIATIVE FOR TRANSMITTING AND SHARING RESEARCH-FOCUSED KNOWLEDGE

The **Open Brain School training center pursued its teaching activities putting digital in the spotlight.**

2020 was marked by the launch of its website where all training programs are listed.

The Institute was able to continue and increase its international cooperation efforts throughout the year. Even though international travel was impossible, and the usual exchanges were suspended (MIT, Stanford, Yale, St John's University in the US), the teams were able to adapt and digitalize many of their initiatives.

Multiple science outreach initiatives to the public despite the current situation:

- **S3ODEON**, hand-in-hand with the Academy of Sciences, the Institut de France and Paris Brain Institute organized a special edition of "S3COVID-19, what does science say?" »
- **An exhibition** to celebrate the Institute's 10th anniversary
- **A podcast:** Braincast, giving neurons a voice, in partnership with Cerveau & Psycho
- **The Course des Héros (Heroes' Run)**

THE ICM BECOMES PARIS BRAIN INSTITUTE!

To support its name change, Paris Brain Institute launched a national outdoor media awareness campaign #yourbrainmakesyouremarkable.

SUPPORTERS NEW AND OLD

The year was marked by the arrival of Fondazione Generali-The Human Safety Net and IRCEM Corporate Foundation as patrons. KLESIA Group (through its Carcept Prévoyance, Ipriac and Klesia Prévoyance institutions), the Bettencourt Schueller Foundation, the Edmond J. Safra Foundation, the Saint-Michel Fund, Boston Scientific, UNIM, the Philippe Foundation, Ever Neuro Pharma, IPSEN, the Abeona Foundation, Rousselet Group, Barrière Group and PHARMADOM ORKYN renewed their agreements to pursue their support for research on nervous system diseases.

Donors and patrons committed alongside researchers to tackle SARS-CoV-2

From the start of the Covid-19 pandemic, Paris Brain Institute called on its donors and patrons immediately to get involved in supporting unprecedented research projects aimed at understanding the neurological effects of the virus. Along with the support of our donors, researchers also received loyal support from the FIA (International Automobile Federation) and the FIA Foundation, the OCIRP Corporate Foundation and Accuracy.

A NEW CAMPAIGN ON BEQUESTS

Through the message of this campaign "At Paris Brain Institute, it's not only researchers who advance research", the Institute wished to honor those who decide to make a bequest to Paris Brain Institute or to name it as the beneficiary of a life insurance policy, vital for pursuing innovative research.

A YEAR MARKED BY SCIENTIFIC BREAKTHROUGHS

In 2020, we witnessed the completion of key groundbreaking projects, led by Paris Brain Institute researchers, which have led to major scientific breakthroughs. Proof that in spite of the difficult climate, Paris Brain Institute teams have continued to work together to bring their projects to fruition.

Amongst these breakthroughs:

- **A new therapeutic avenue to brain tumors** with the meningeal lymphatic network
- Development of the **first complete mapping of cerebral vascularization**
- **Discovery of a mechanism for the emergence of behavioral individuality in the brain of a fly:** a general principle as regards the neurodevelopmental origin of an aspect of personality?
- Identification of the fundamental properties of **brain systems that determine our preferences**
- Breakthroughs in genetics and mechanisms involved in drug resistance in **brain tumors**
- Discovery of a new clinical sign to **explore the state of consciousness**
- Identification of brain abnormalities detectable from the embryonic stage in **Huntington's disease**
- Spatial and temporal characterization of substantia nigra neurodegeneration, **a new biomarker in Parkinson's disease**
- Persevering or exploring: **cerebral basis of the exploiting-exploring dilemma**
- A promising therapeutic avenue for **amyotrophic lateral sclerosis (ALS) aka Charcot's disease**
- New data confirms the benefit of deep brain stimulation for **treating obsessive compulsive disorders**

CALL FOR NEURO-COVID-19 PROJECTS

Paris Brain Institute launched an internal call for projects in collaboration with the Pasteur Institute to fi-

nance new proofs of concept on how infection impacts a healthy or diseased nervous system. This call for projects was launched thanks to the support of its patrons and donors, including the OCIRP Corporate Foundation and Accuracy. 4 projects were selected through this call.

EXCELLENT RESULTS FROM THE ANR GENERIC CALL FOR PROJECTS

Every year, the ANR's (French National Research Agency) generic call for projects finances the research of various players from the scientific community. This year, 16 projects by Paris Brain Institute researchers were among the winners. The Institute records a success rate of 34%, which is twice the national average (16.8%), a sign of the quality and soundness of the projects proposed.

CUTTING-EDGE TECHNOLOGY PLATFORMS

In 2020, the Institute committed to increasing cross-disciplinarity between platforms and creating a more extensive service offering to address research teams' needs. In spite of the health situation, the Institute's platforms were able to maintain a high level of service that ensured scientific projects were completed and moved forward.

- Acquisition of a new custom-made multiphoton microscope thanks to the support of the Edmond J. Safra Foundation
- Development of the Institute's FabLab into a research and development platform
- Extension of the iGenSeq platform's Novaseq sequencer capabilities

2020 Financial situation

INCOME STATEMENT BY NATURE AND FUNCTION (ISNF) AND EXPENDITURE STATEMENT - ALLOCATION OF RESOURCES (ES)

New accounting regulations relating to the annual accounts of non-profit legal entities under private law require the presentation of an income statement by nature and function (ISNF) to reflect the economic model of the entity and an annual expenditure statement (ES) for financial resources received from the public using the data from the previous income statement.

The purpose of the ISNF and the ES is to give an instant overview of the use that any foundation or association makes of financial resources collected from the public to finance its social outreach programs. The ISNF and ES presented herein as such reflect Paris Brain Institute's economic model and social outreach programs.

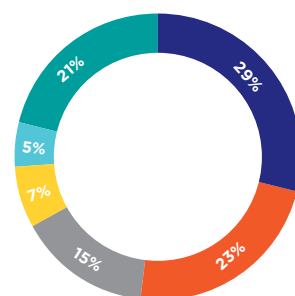
Pursuant to accounting regulations, allocation mechanisms underlying the development of these ISNF and ES statements reflect management and allocation rules defined by Paris Brain Institute and are therefore based on distribution keys established internally (analytical breakdowns). Allocations are appraised at full cost per destination.

2020 REVENUE BY ORIGIN

Research project funding is typically diverse in terms of sources of funding, with a long-term perspective in order to produce knowledge and key neuroscience breakthroughs.

2020 revenue totaled €63.2M, including €50.1M in revenue for the year and €13.1M in carry-over of resources allocated and not used in previous years. Revenue for the financial year mainly represents fundraising revenue (€18.3M, i.e. 37%), which includes donations (€11.6M, i.e. 63%), patronage (€5.3M, i.e. 29%), bequests and donations (€1.4M, i.e. 8%).

- Revenue from fundraising
- Public and private grants
- Revenue from platform activities and industrial partnerships
- Funding for the "UHI program"
- Other revenue (rental revenue, re-invoicing of expenses, investment revenue, etc.)
- Carry-over of resources from previous years



It also includes:

- Revenue from technology platform activities (€6.2M) and research collaborations with industrial partners (€3.4M);
- Public and private grants (€14.3M);
- Funding for the University Hospital Institute (IHU) program (€4.7M);
- Miscellaneous revenue (rental revenue, re-invoicing of expenses, investment revenue) (€3.1M).

N.B.: The overall amount from bequests, donations and life insurance policies accepted in 2020 totaled €1.9M (versus €1.7M in 2019, i.e. + 11%). The legal application of the new accounting regulations as of January 1, 2020 means that bequests accepted in the course of processing and not collected are now recorded on the balance sheet. The impact of these funds carried forward to FY 2020 is €0.5M.

2020 EXPENSES BY FUNCTION

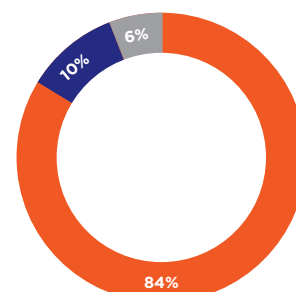
Overall 2020 expenses totaled €62.2M: €45.7M used in 2020 and €16.5M to be used subsequently from the allocated resources. Of the 2020 allocations, €38.2M was allocated to **social outreach programs**, representing **84%** of total ISNF allocations.

Paris Brain Institute's social outreach programs include:

- Research programs;
- Technology platforms;
- Scientific activities and the development of international partnerships;
- Incubation of innovative businesses.

Allocation breakdown 2020

- Social outreach programs
- Fundraising and communication expenses
- Operating costs



Funding for research projects is mainly allocated to nervous system diseases and spinal cord injuries. The technology platforms (neuroimaging, vectorology, genotyping sequencing, cell culture, histology and bioinformatics) support these projects. **Fundraising and communication expenses** correspond to the expenses incurred to fundraise from individuals (donations and bequests) and private businesses and foundations (corresponding to patronage and sponsorship actions), as well as communication campaigns. This represents a total of €4.3M, i.e. **10%** of the overall total of ISNF allocations.

Operating costs comprise the costs of the support teams (general administration, finance, human resources, legal, information technology and logistics), which account for **6%** of the overall total of ISNF allocations, i.e. €2.7M.

ALLOCATION OF RESOURCES RECEIVED FROM THE GENERAL PUBLIC

The resources received from donors and sponsors used in 2020 totaled €18.3M. In a nutshell, for every €100 of resources received from the general public, €73.8 was used to finance social outreach programmes and investments, €23.6 was used to cover the costs of fundraising and communication, and €2.6 was used to cover the operating costs of Paris Brain Institute.

2020 BALANCE SHEET

| Assets (€M) | 2019 | 2020 |
|-------------------------------------|------------|------------|
| Net fixed assets | 65 | 65 |
| Current and available assets | 67 | 86 |
| Total | 132 | 149 |
| Liabilities (€M) | 2019 | 2020 |
| Associative funds | 51 | 55 |
| Profit and loss for the fiscal year | 2 | 1 |
| Dedicated funds | 15 | 20 |
| Debts | 41 | 41 |
| Deferred revenue | 23 | 32 |
| Total | 132 | 149 |

The total sum of investments made by Paris Brain Institute since its creation totals €49M, mainly dedicated to the technology platforms that support research. Investments for FY 2020 total €3M and include:

- Investments in scientific materials and equipment (€1.5M including 4 microscopes for a total of €0.75M),
- Investments to update the IT network (€1M),
- Continued construction at the rue du Chevaleret site (change in assets in progress).

Net fixed assets totaled €63M. At December 31, 2020, cash and cash equivalents totaled €40.1M, of which €14M was dedicated to earmarked funding. Paris Brain Institute's associative funds totaled €55M. They included shareholders' equity of €33M, complemented by investment grants of €22M. Non-expendable endowment totaled €1.2M. At the end of the fiscal year, dedicated funds (funds still to be committed to multi-year programs) totaled €20M.

Monetary reserve policy

When it was created in 2006, Paris Brain Institute Foundation received an endowment of €11.7M, of

which €1.2M was a non-expendable endowment. Through careful budget management, Paris Brain Institute Foundation has been able to balance its expenses and revenues for the past 5 years, as such avoiding having to draw on its reserves. Furthermore, the investment policy of the members of the Board of Directors is extremely conservative. Paris Brain Institute's cash flow is invested in marketable securities (capitalization contract taken out with leading banking institutions, capital-guaranteed and 100% in euro funds).

VOLUNTARY CONTRIBUTIONS IN KIND

Volunteering:

Paris Brain Institute benefited from volunteer hours during the fiscal year, in particular for communication campaigns. The volume is estimated at 0.6 FTEs, i.e. on the basis of French hourly minimum wage, totaling an amount of €17K.

Patronage in kind:

In 2020, Paris Brain Institute Foundation benefited from patronage in kind within the frame of its communication initiatives and from an appeal to the public's generosity, namely:

- Media space: FIA-Fédération Internationale Automobile, Groupe Barrière, JC Decaux, Klesia, Richard Mille, Next Radio TV, Media VB, NRJ Global, M6, Lagardère Publicité, Radio France, France TV, Amaury Media, Canal +, BeinSports, Les Echos/Le Parisien, Figaro Magazine, S4M Network, Le Bon Coin, Adikteev Network, Emoteev Network, Equipe.fr Network, Teads Network, Cerise Network, Madvertise Network, Tabmo Network, DailyMotion Network, Webedia Network, TF1 Network, SublimeSkins Network, Capify Network, Criteo Network, Ogury Network.
- products and services provided free of charge: ANACOFI, IDEC, Orrick Rambaud Martel, Publicis Groupe, ZenithOptimedia.

As Paris Brain Institute is particularly committed to pursuing its level of excellence, it has rolled out internal and external control procedures to ensure it is managed rigorously and efficiently: member of the "Comité de la Charte du don en Confiance" (Donating with Trust Charter Committee) and calls on the services of an independent statutory auditor.

"Don en confiance" (Donating with Trust)

On November 3, 2010, Paris Brain Institute received the approval of the "Comité de la Charte du don en Confiance" (Donating with Trust Charter Committee), which was renewed in October 2019. For over 20 years, this Committee has been responsible for the professional regulation of the appeal to the public's generosity. Its initiative is based on 3 commitments: accredited bodies must comply with the rules of ethics, they must observe a collective policy towards donors, and they must accept ongoing monitoring of the commitments made.





An encounter with Guillaume de Tonquédec, actor engaged in the fight against brain diseases

Profoundly moved by the dedication of Paris Brain Institute's researchers, and fascinated by the tangible progress they are making there, the famous actor reveals the reasons for his commitment to them. Interview, far from the limelight...

Why did you get involved with Paris Brain Institute?

G. de T. Unfortunately, I've got the "winning trio" of Alzheimer's-Parkinson's-Multiple Sclerosis in my family. Some people around me have also suffered from a stroke or depression. So, three years ago, when I discovered Paris Brain Institute, I suddenly found the commitment I was looking for, one that had real meaning for me and concerned people close to me.

How did you hear about Paris Brain Institute?

G. de T. It all started with an invitation my father received to attend a conference on multiple sclerosis. My brother and I were really interested to find out more about this disease. We were struck by this extraordinary place, right at the heart of the famous Pitié-Salpêtrière Hospital in Paris, the birthplace of French neurology since the end of the 19th century.

Can you tell us about the "Découvreurs d'Espoir" (Discoverers of Hope) campaign, of which you are the patron?

G. de T. It's an appeal for donations campaign. There's not enough public money out there to fund medical research. Paris Brain Institute really needs private donors to make great discoveries, in particular discoveries concerning neurodegenerative diseases often linked to old age.

The "Découvreurs d'Espoir" (Discoverers of Hope) are actually researchers.

G. de T. Exactly, but also donors! One of Paris Brain Institute's incredible ideas is to bring the best French and international researchers together in the same place. This enables them to combine knowledge, continue their own training and accelerate research with state-of-the-art equipment.

It goes without saying, these researchers work on brain diseases. However, their research work also leads to parallel discoveries that can be used in other diseases such as cancer. It's just amazing!

Although it can be frightening sometimes because of its dysfunctions, the brain still fascinates us...

G. de T. Even though researchers learn more about our brain every day, it seems crazy that it's still so mysterious when you think we've managed to walk on the moon! The brain continues to offer us a tremendous field for investigation. Setting diseases aside, it's incredibly exciting to discover little by little how it works and, as such, how our body works. We're constantly discovering things about ourselves and that's fascinating! And, this is why I believe the brain will continue to be a subject of research for hundreds of years to come.



LE CONCERT
D'ASTRÉE
Emmanuelle Haïm

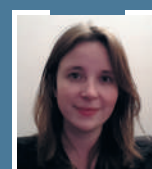
Le Concert d'Astrée is celebrating its 20th anniversary and is organizing two concerts for the benefit of Paris Brain Institute

A treasure of baroque repertoire dedicated to our researchers. Le Concert d'Astrée, an instrumental and vocal ensemble, led by Emmanuelle Haïm, is celebrating its 20th anniversary and is committed to our cause. In November 2021, two exceptional gala evenings will take place, one at the Berlin Staatsoper and the other at the Théâtre des Champs-Élysées in Paris and the proceeds will be donated to Paris Brain Institute.

Le Concert d'Astrée is joined for this occasion by eminent guests such as Sabine Devieille, Sandrine Piau, Laurent Naouri, Tim Mead and Patricia Petibon. Simon Rattle will conduct the first part of the gala in Berlin, and a host of highly-renowned soloists will lend their voices to the celebration. A must-be-there event this fall for lovers of 17th- and 18th-century music, played on instruments of the period.

Paris Brain Institute would like to extend its warmest thanks to Emmanuelle Haïm, Founder of Le Concert d'Astrée, Patricia Faulon-Ruault, its Executive Director, François Bouvard, President of Le Concert d'Astrée Foundation, and the entire team on-board, in particular the 90 high-profile artists who have all decided to donate their fees to support our researchers.

"As we celebrate our 20th anniversary, it seemed only fitting for us to offer all the know-how and energy of Le Concert d'Astrée network to the service of a great cause. Paris Brain Institute was the obvious choice. The fight led by the researchers against nervous system diseases deserves our wholehearted support." Patricia Faulon-Ruault, Executive Director of Le Concert d'Astrée



YOUR DEDICATED CONTACT at the Circle of Friends Office

Ms MARIELLE
LETHROSNE

+ 33 (0)1 57 27 45 72
cercle@icm-institute.org

F.A.Q.?

I'm an American Express cardholder. Can I use it to make a donation?

Yes, it has been possible for several weeks now. To make life easier for our generous philanthropists around the world, Paris Brain Institute welcomes Amex as a new means of payment. Check the donation form on our website right now.

Is Paris Brain Institute eligible to receive donations of securities?

Absolutely. Donating securities consists in the transmission of ownership of shares, bonds, SICAV (open-ended investment fund) or FCP (mutual fund trust) shares to a public-interest body.

It is particularly suitable for donors who wish to make a donation without drawing on their cash flow. It is also a way of giving that can be advantageous from a tax point of view as it does not generate capital gains tax for the donor.

Do not hesitate to talk to your tax or wealth management advisor or to contact us: **Circle of Friends Office**
+33 (0)1 57 27 40 32 or
cercle@icm-institute.org

At Paris Brain Institute,
it's not only researchers who advance research.

Like Patricia and Robert, make a legacy
and help our 700 researchers reach
new heights of discovery.



ALZHEIMER'S - PARKINSON'S - BRAIN TUMORS - DEPRESSION - STROKE

 Paris Brain
Institute

To find out more about bequests, donations and life insurance policies,
contact Carole Clément on +33 (0)1 57 27 41 41 or visite.legs.institutducerveau.fr

Institut du Cerveau - Hôpital Pitié-Salpêtrière - 47 boulevard de l'Hôpital 75013 Paris, France

DONATION FORM

Please make your check payable to the Institut du Cerveau and send it along
with this form to the Institut du Cerveau - Hôpital Pitié-Salpêtrière - CS 21414
75646 Paris Cedex 13 - France

 Paris Brain
Institute

☒ **Yes, I'd like to help Paris Brain Institute researchers go even further in their
research into brain and spinal cord diseases.**

I'd like to donate: _____ €
(amount at my discretion)

☐ Ms ☐ Mr ☐ Mr and Mrs

Last name: _____ First name: _____

Address: _____

Post code:City: _____

Email: _____ @ _____

☐ I'd like to receive free information on bequests and donations.



Paris Brain Institute
Foundation complies with
the rules of ethics of the
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