

Synapse

The journal designed to connect with you

N° 22 - August 2020

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Generosity

Make a bequest to the Paris Brain Institute



In recent months, everyone at the Paris Brain Institute has taken an active part in the fight against the COVID-19 pandemic. The clinician-researchers were strongly committed to the COVID-19 patients hospitalised at Pitié-Salpêtrière, while continuing to closely monitor their neurology patients, whose daily lives were even more disrupted than usual. Our researchers also decided to contribute to our understanding of the neurological and psychiatric aspects of the disease, notably through the Cohort COVID-19 Neurosciences study, and to screening for COVID-19 by developing diagnostic tests.

But the experts at the Paris Brain Institute have also remained highly focussed on their core mission: to search for, find and cure diseases of the nervous system. Despite all the recent difficulties, researchers have continued to advance our knowledge of the diseases that affect the most profound part of our being: our thoughts, movements and freedom.

In this issue of *Synapse*, you will find the work of doctors and researchers on diagnosing Alzheimer's disease, a terrible illness that strips its victims of the very essence of their being, their memory and recollections. We must be able to better understand this disease sooner rather than later. This issue also includes the 2019 Essentials, a review of the highlights from the past year and a presentation of the foundation's accounts, which are always managed with great care and professionalism. The Paris Brain Institute would like to share the work we have been able to do with your support, which is more essential than ever, and to thank you for what you have enabled us to accomplish.

Jean-Pierre Martel
Founding member of the Paris Brain Institute

COVID-19: the FIA Foundation and the FIA take action



The FIA has renewed its support for the Paris Brain Institute and the FIA Foundation, a historical sponsor, has provided €400,000 for the Cohort COVID-19 Neurosciences study launched in partnership with the AP-HP-Sorbonne University Neurosciences Department at Pitié-Salpêtrière Hospital to assess the neurological and psychiatric impacts of the disease on patients with the aim of improving their treatment, monitoring and recovery.

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



An animated film to better understand donations

Curious about writing your own will? What are the pitfalls to avoid and who should you entrust it to after writing it? Our "Jacques and the universal donation" video has the answer to all your questions!

Watch it now on our website:
<https://icm-institute.org/fr/legs-donations-et-assurances-vie/>



Help us with our research on creativity!

Creativity is our ability to produce ideas, services, works... that is appropriate to the context. It allows us to adapt to new situations and find effective solutions in dealing with them. Our researchers have developed an anonymous survey to better understand the effects of the current COVID-19 crisis on creativity.



SYNAPSE, the Paris Brain Institute's newsletter addressed to its donors. N° 22 - 2020. Editorial board: Jean-Louis Da Costa, Axelle de Chaillé, Astrid Crabouillet, Nicolas Brard, Isabelle Rebeix, Claire Pennelle, Lauriane Gallier, Carole Clément and Aurélie Grosse. Design: Adfinitas. Printer: Imprimerie Jean Bernard. Print run: 115,000 copies. © Institut du Cerveau.



The Institute's researchers are here to help with deconfinement.



Covid-Out is a tool to help people experiencing psychological stress. It allows you to evaluate your mood daily and provides videos, practical advice and training programmes.



ADIÓS CORONA



Adios Corona is a site created by a team of scientists, including Claire Wyart of the Paris Brain Institute. This site, designed by Headquarters, reviews publications on COVID-19 and provides expert advice on how to protect yourself, understand and act to stop the spread of the SARS-CoV-2 coronavirus responsible for COVID-19.

To find out more, check out the website:
<https://www.adioscorona.org>



@oliver_wyart

Between 20 March and 30 April,

The figures

55 M³ OF HAND SANITISER, which is about 275,482 200 ml bottles, were produced at the Institute to fight the COVID-19 epidemic.

482 BOXES OF GLOVES and sets of masks, gowns, hair nets, shoe covers, examination table sheets, etc.

4 PALLETS OF EQUIPMENT were donated to the Pitié-Salpêtrière hospital.

An award for excellence!

Prof. Jean-Christophe Corvol, a neurologist (Sorbonne University/AP-HP) and co-team leader at the Paris Brain Institute, is one of the 4 international winners of a scholarship offered through the partnership of the Edmond J. Safra Foundation and the Michael J. Fox Foundation for Parkinson's research. Each year, this programme rewards talented specialists who provide high-quality care and study movement disorders, especially Parkinson's disease.



seen on the web

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



- Myelin deficiency triggers cognitive impairment in schizophrenia
- Activation of the innate immune system in the central nervous system: a marker for impairment in multiple sclerosis?

video



- ▶ Watch all of the donor conferences
- ▶ Dystonia and rare abnormal movements: a team of trailblazers
- ▶ Tourette's Syndrome

agenda

Erratum

The Brain Forum
Originally scheduled for 7 November this year, this event has been postponed to 2021 due to the health measures required as a result of the COVID-19 epidemic.

Saturday 19 September

Online conference on Alzheimer's disease
(the video will be available on our website).

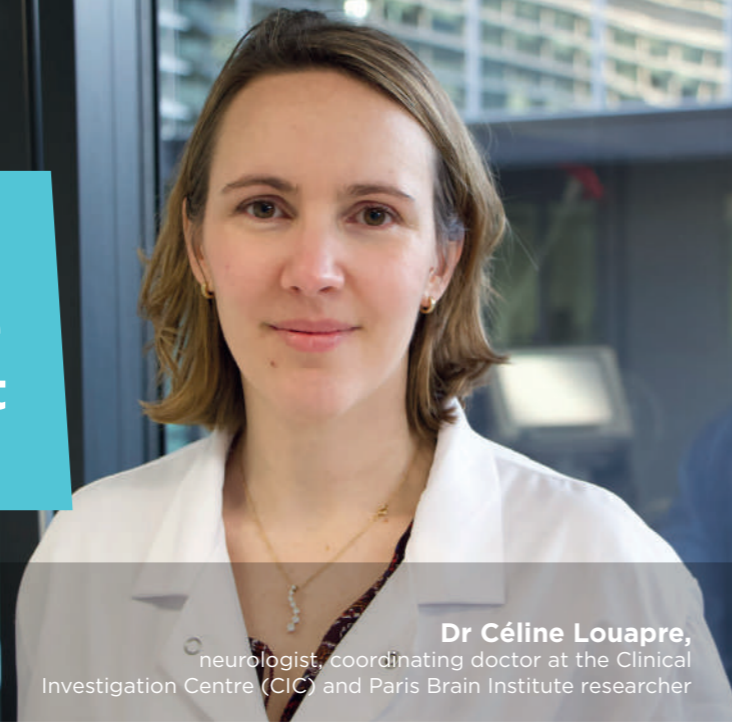
Thursday 24 September

Les Echos Golf Tournament in Chantilly
<http://www.tropheedegolfleechos.fr/>
Invitation on request by emailing cercle@icm-institute.org

Follow us



Clinical research at the Paris Brain Institute during confinement



Céline Louapre, neurologist (Sorbonne University/AP-HP) and coordinating doctor of the Clinical Investigation Centre (CIC), tells us about her department's activities during the two months of confinement.

“During confinement, the CIC continued to see patients involved in therapeutic trials to ensure their ongoing monitoring. We had to implement specific measures adapted to the different profiles of the patients involved in the ongoing clinical studies: telephone consultations and delivery of medication for the study to patients' homes.

Approximately 30-40% of the staff was mobilised to keep this essential activity running. Our team was also contacted by the health care services as a result of the COVID-19 pandemic. Louise Richard-Gilis, a health manager at the CIC, was seconded to neuro-resuscitation, as was one of our nurse's assistants in neurology. Much of our activity during this time involved helping hospital departments to enrol patients in COVID-19 trials.

A loss of taste or smell in some patients was observed. Other neurological manifestations also began to appear. However, we still do not know much about the impact of this coronavirus on our nervous system. To **address this critical**

Dr Céline Louapre, neurologist, coordinating doctor at the Clinical Investigation Centre (CIC) and Paris Brain Institute researcher

issue, we created two national cohort studies: "Cohort COVID-19 Neurosciences" to evaluate the impact of the coronavirus on the nervous system, including in patients already undergoing treatment for neurological or psychiatric diseases, and "CoviSEP", which is specifically dedicated to patients with multiple sclerosis.

These studies are being carried out with the support of the NSPARK and FCRIN4MS clinical research networks, hosted at the Paris Brain Institute, the Institute's iCRIN program, the University Medical Department (DMU) of Neurosciences, the Sorbonne University and the AP-HP.

These studies have furthered our knowledge about the relationship between the coronavirus and the nervous system, and the findings will soon be available.

“Approximately 30-40% of the staff was mobilised to keep this essential activity running. ”

The success of our activities during containment was made possible thanks to the dedication of all of the CIC's staff, technicians, engineers, CRAs and administrators, who sometimes even had to change roles. We came together during

this difficult period and we are now in good shape to get back to our normal pace of activity quickly. ”

Alzheimer's disease under the microscope: From diagnosis to prognosis

With 225,000 new cases each year, Alzheimer's disease is a major public health issue. The challenge today is to act earlier using reliable biological markers for diagnosis and prognosis.



PREVENTION IS BETTER THAN CURE!

Alzheimer's disease affects 900,000 people in France today, with serious consequences for their loved ones. In almost 50% of cases, dependent patients are cared for exclusively by their families. However, according to INSEE, the increase in life expectancy and the decrease in the number of family care givers, due to the baby boom, will lead to an increase of 35% in public spending and the recruitment of 80,000 people by 2030.

Alzheimer's disease is often known for the memory loss it causes in patients. It is a progressive disease that usually begins with isolated, progressive memory loss that the patient is unaware of.

Gradually, problems with language (aphasia), writing (dysorthographia), movement (apraxia), and loss of the ability to recognize objects and faces (agnosia) progressively set in. These symptoms may also be associated with mood (anxiety, depression, irritability), behaviour and sleep disorders.

The disease is characterised by two brain disorders:

- **amyloid plaques** (or senile plaques) are made up of deposits of β -amyloid peptides. In a healthy brain, the β -amyloid protein is broken down into soluble fragments (peptides). With Alzheimer's disease, these peptides become less soluble and accumulate in the brain in an abnormal way;
- **an accumulation of Tau protein** in the neurons, which leads to neurofibrillary degeneration and neuron death. Under normal conditions, this protein is involved in the stability of the neuron structure.

An Alzheimer's disease diagnosis is based on 3 criteria:

- **a clinical examination** to test the patient's memory, language and behaviour;
- **an MRI scan** to visualise any lesions in the brain;
- **an analysis of specific proteins**, Tau protein and β -amyloid peptide in the cerebrospinal fluid (CSF).



How to distinguish age-related memory deficits from those due to Alzheimer's disease.

Age is the main risk factor for Alzheimer's disease. But ageing does not necessarily lead to this disease. Nearly 52% of people between the ages of 70 and 85 report cognitive impairment, whereas Alzheimer's disease affects only 2 to 8% of people in this age group. Alzheimer's disease can start before you are old, and you can start to age without it appearing.

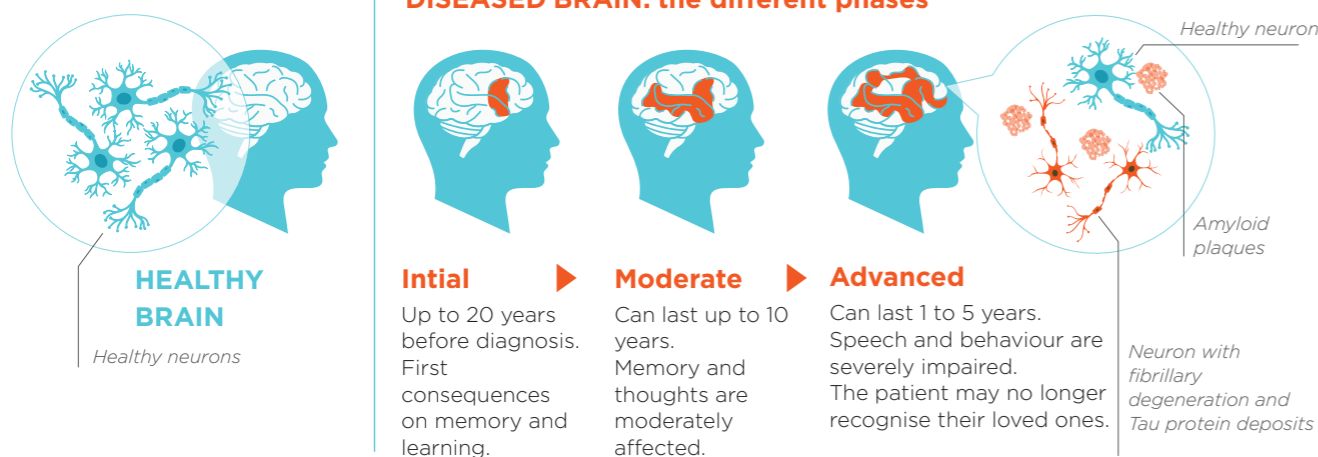
Age-related memory loss

- Memory of forgetting
- Overestimation of their impact
- The person is concerned
- Request for diagnosis

Alzheimer's disease

- Forgets about forgetting
- Ignorance of the severity of the memory impairment
- Family and friends are concerned

ALZHEIMER'S DISEASE PROGRESSION



The first case described by Dr Alois Alzheimer

In 1906, German psychiatrist and neurologist Aloisius Alzheimer described the case of a patient, Mrs Auguste Deter.

Dr Alzheimer had been treating this woman since 1901. Her symptoms included loss of memory, loss of reference points in time and space, and changes in behaviour. When she died in 1906, the doctor was able to study her brain and discovered an atrophy of the cortex and the characteristic lesions of the disease: amyloid plaques and neurofibrillary degeneration.

In the years that followed, several similar cases were described by other psychiatrists and neurologists. The term "Alzheimer's disease" was finally given to the condition by another eminent psychiatrist of the time, Emil Kraepelin, who included it in his textbook on psychiatry published in 1910.

You can find the work of Dr Alzheimer, published in 1908, in French, on page 156 of *L'Encéphale*, the journal of psychiatry and neurology, available on the website of the Bibliothèque nationale de France.





EARLY DETECTION FOR BETTER TREATMENT!

“*By the time symptoms appear, it is often too late to take effective action to stop the disease from progressing. Research into Alzheimer's disease and its early stages is crucial, in order to be able to respond as early as possible and develop new treatments.*”

Dr Stéphane Epelbaum, neurologist (AP-HP) and researcher at the Paris Brain Institute.

Whether for Alzheimer's disease or other conditions, **the medicine of the future will be "predictive, personalised, preventive and participatory"** (the "4 Ps"). The aim is to identify specific predictive markers of the disease, to study homogeneous sub-groups of patients in order to include them in suitable clinical trials, to treat at-risk individuals before the onset of symptoms and to seek the agreement of these potential patients to participate in studies.

The concept of the "4 Ps" is one of the major challenges of research conducted at the Paris Brain Institute, particularly in the field of Alzheimer's disease.

Four teams at the Institute are working on projects to address this issue and are attempting to identify early markers of the disease in cohorts of presymptomatic and/or at-risk patients, such as the INSIGHT cohort (Prof. Dubois, IM2A).

The MINIAD or "mini-brain" project (with the support of MSDAVENIR)

Most of the approaches that have been developed for treating neurodegenerative diseases focus on slowing the disease's progression and/or treating the associated symptoms. Philippe Ravassard's team at the Paris Brain Institute is working on **creating human cell models that would allow for the development of reparative therapies.**

Induced pluripotent stem cell (iPSC) technology makes it possible to use patients' skin (or blood) cells of patients to create neuron lines that have all the characteristics of the neurons present in the brains of Alzheimer's patients.

The "mini-brains", created from 3D cultures of patients' iPSC cells, are "miniaturized brains" that replicate the characteristics and specificities of the associated disease.

They are a powerful tool for identifying new therapeutic targets, testing their efficacy and establishing molecular signatures specific to Alzheimer's disease.

"Mini-brains" derived from the cells of patients with different forms and stages of the disease (degenerative lesions from Tau proteins, β -amyloid plaques, etc.), are already available. The study is ongoing and is expected to enter an early phase of treatment evaluation in 2020.

Early diagnosis of Alzheimer's disease using electroencephalography (EEG)

A project conducted by 3 research teams at the Institute and 2 hospital departments at the Pitié-Salpêtrière Hospital, involving two pre-clinical cohorts, MEMENTO and INSIGHT-preAD, has revealed early changes in cerebral electrical activity in subjects at the presymptomatic stage of Alzheimer's disease through electroencephalography (EEG).

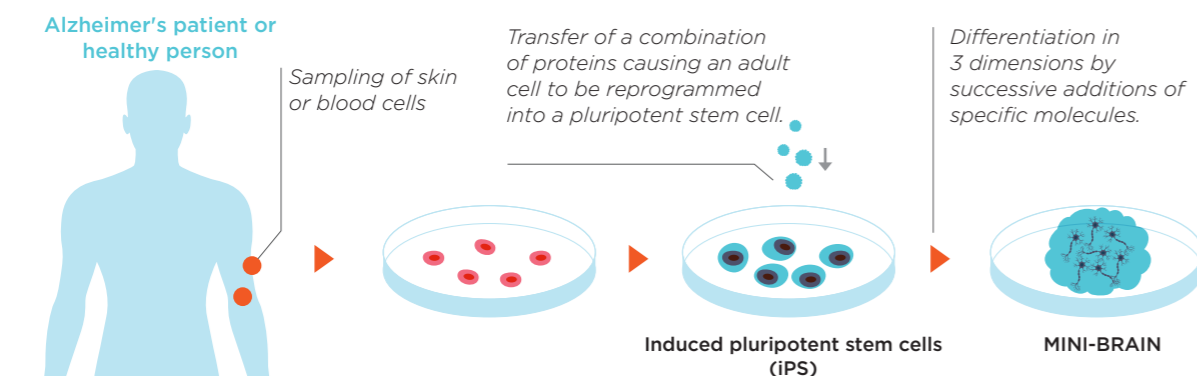
These changes in brain activity in patients who are at risk of developing Alzheimer's disease but have no symptoms open up new possibilities for treating patients before irreversible impairments can develop.

This study is the first in the world to demonstrate electroencephalographic changes in the pre-clinical phase of Alzheimer's disease.

“*Electroencephalography, a non-invasive and inexpensive examination, appears to be a very promising technique for identifying subjects in the presymptomatic phase of Alzheimer's disease, thus allowing them to be treated early.*”

Dr Sinead Gaubert, neurologist and researcher at the Paris Brain Institute.

3D MINI-BRAINS derived from patient cells



Observation of a **MINI-BRAIN** under dynamic microscopy. The teams at the Paris Brain Institute.

Share your experience



Many thanks for the various questions and accounts that we have received. In this issue, we decided to address the following question:

"Is Alzheimer's disease a real disease or simply an indication of the brain's ageing?"

This is a valid question because, while the answer may appear simple, it is actually more complex than one might think.

In the vast majority of cases, Alzheimer's disease begins with memory loss. Older people can also be affected by similar difficulties, but there is a clear difference: in the normal ageing process, it is a case of minor forgetfulness. The memories have been stored in the brain but have trouble being "recalled": this is what happens when you are thinking of a name and can't remember it until later.

In Alzheimer's disease, memory problems are not just more severe; but they grow worse over time and become permanent. Memories are no longer stored in the brain, and neurons disappear, slowly and inexorably. As the brain normally ages, there is no (or very little) loss of neurons. Some nerve connections may disappear, but the clinical impact is minimal because there are reserves of neurons that are able to compensate for their deficiency.

Prof. Yves Agid, Professor of Neurology and founding member of the Paris Brain Institute

Let's talk about psychiatric disorders!

Email us your question or experience on the special feature theme for our next issue on the subject of psychiatric disorders, and you may be published in the November issue of *Synapse*.

► contact@icm-institute.org

Inflammation and disability with multiple sclerosis

Is the activation of resident immune cells in our central nervous system, called microglial cells, predictive of the course of disability in multiple sclerosis?

While there is currently no cure for multiple sclerosis, **significant progress has been made in managing the disease in recent years.** In order to offer each patient the most effective solutions for their condition, having a better understanding of how the disease develops and how the disability progresses is of the utmost importance.

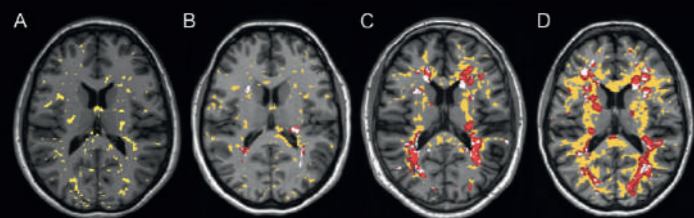
Bruno Stankoff's team (AP-HP/Sorbonne University) at the **Paris Brain Institute has been working with the French Atomic and Renewable Energy Commission (CEA) for several years** to develop innovative

imaging methods **combining positron emission tomography (PET) and magnetic resonance imaging (MRI) for an in-depth study of the mechanisms of central nervous system damage in multiple sclerosis patients.**

Researchers have developed a new method to map the activation of microglia in the brain's white matter, which contains the majority of neuron axons. They were able to successfully recreate individual profiles and distinguish white matter lesions in patients with persistent microglial activation

that were considered perfectly stable and non-active using standard MRI scans. They then compared the maps from 37 multiple sclerosis patients with the progression of their disability. The researchers have shown that activation of the microglia around and inside the lesions is associated with a more severe progression of disability in patients.

The discovery of this new biomarker represents an important prospect for better treatment of patients with multiple sclerosis and the evaluation of new therapies to prevent the progression of the disability.



■ Inactive voxel in T2 lesion ■ DPA+ voxel in NAWM ■ DPA+ voxel in T2 lesion ■ DPA+ voxel in peri-lesion

Individual maps of microglial cell activation in a healthy subject (A), and in 3 patients with MS. The yellow and red areas show significant activation of innate immune cells in the normal-appearing white matter.

Brain systems that determine our preferences

What are the brain processes that allow us to make decisions and determine our preferences? How is the value of a choice calculated by the brain?

A study carried out by Mathias Pessiglione's team (Inserm) at the Paris Brain Institute has revealed the main characteristics of the neuronal signal involved in value judgements.

Using electrodes implanted in the brains of 36 epileptic patients who were awaiting surgery, **researchers recorded the electrical activity of neurons as the patients considered various choices.**

Patients were asked how much they liked the options presented to them on a screen, such as eating a chocolate cake or viewing a painting by Picasso. This task was followed by a task where they were asked to choose between two of options, which verified that the value judgements reported by the patients were predictive of their preferences.

This study identified four essential properties of the neural signal observed in the region of the orbito-frontal cortex (cerebral area located in the prefrontal cortex, just behind the ocular orbits). It is baseline-dependent, generic, automatic, and depends on confidence in one's own decision-making skills.

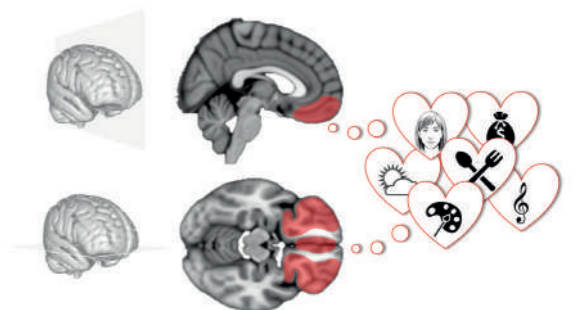


Taken together, these properties explain misattribution in value judgements.

For example, a person dining at a restaurant faces a number of environmental influences, such as what they are eating, the background music, the decor and the chatter of other diners. Interferences between the values associated with

these different factors may, for example, lead the person to believe that she likes the person across the table, when in fact she likes the food she is eating.

“Taken together, these properties explain misattribution in value judgements.”



These results provide a better understanding of brain dysfunction in diseases such as mood disorders, where decision-making is sometimes impacted.

The challenge of the 21st century: understanding how the brain works and curing nervous system diseases

Our brains are the greatest mystery of all. Understanding the brain is an epic quest that many scientists and doctors pursue every day. The Paris Brain Institute benefits from its powerful ecosystem based on a private-public partnership. Founded in 2010 by four major public partners (CNRS, Inserm, Sorbonne University, AP-HP), the model and approach adopted make it unique, as the Institute brings together patients and medical, scientific and entrepreneurial expertise under the same roof.

A 360° ECOSYSTEM

To meet the challenges of the 21st century, the Institute supports innovative and creative initiatives, led by teams that include both leading researchers and renowned clinicians. One of the Institute's greatest strengths in facing the challenges involved in understanding nervous system diseases is its ability to foster cross-disciplinary and multi-disciplinary research. Thanks to the University Hospital Institute (IHU) programme that was renewed in 2019 and will run until 2024, combined with a Clinical Investigation Centre (CIC) within the Paris Brain Institute, extensive translational research can be carried out. Cutting-edge technological platforms and a concentration of multi-disciplinary expertise in a single location mean that the Institute is now able to acquire an optimal understanding of the nervous system. The Institute's international influence gives its researchers the opportunity to contribute to many international research consortia, which are sources of fruitful collaborations. Finally, the presence of a start-up incubator within the Paris Brain Institute's ecosystem (iPEPS - The Healthtech Hub) provides an opportunity to nurture an entrepreneurial spirit on the one hand, and to encourage the application of discoveries for the benefit of patients on the other.

Given its unique position at the crossroads of various fields, the Paris Brain Institute promotes a comprehensive approach to disease, breaking down the barriers between pharmacy, technology and the human sciences in order to develop integrated health care services that start with prevention and include disability management, using technology as a tool "at the service of the patient".

A SCIENTIFIC STRATEGY TO MEET THE CHALLENGES OF BRAIN RESEARCH

The scientific ambitions of the Paris Brain Institute are:

- to understand how the brain works;
- to prevent and cure neurological and psychiatric diseases.

The Institute's objectives are clear and strongly confirmed:

- to make major contributions to the prevention and treatment of diseases of the nervous system;
- to take part in technological innovation and its application to medicine.

To do so, the Institute must:

- attract the best international researchers, particularly in translational neuroscience;
- develop state-of-the-art technological platforms;
- encourage entrepreneurial research;
- create a unique, attractive, international and public-oriented training centre.

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 evaluates the work and performance of the teams, thus ensuring that a high level of excellence is maintained. In its annual report, the Paris Brain Institute reports on its mission and results, in a spirit of complete transparency towards its partners and donors.

2019 Highlights

As of 1 January 2019, the Paris Brain Institute began a new term for its Joint Research Unit (UMR). The Paris Brain Institute's initial strategic decisions were based on specific research topics, with a high-value ecosystem to address the challenges of neuroscience and nervous system diseases. The Institute has succeeded in bringing together fundamental neuroscience research capabilities and high-level clinical research expertise under one roof. The extension of the UMR confirms the Paris Brain Institute's ambitious scientific and medical strategy of adopting an increasingly multi-disciplinary approach, which gives our Institute its unique identity.

The Paris Brain Institute also secured the renewal of its IHU programme, to the tune of 17 million euros. This renewal demonstrates the scientific, medical and economic success of the "IHU model" introduced in 2010 following a call for projects from the French Ministry of Higher Education and Research and the French Ministry of Health, as part of the future investment programme to boost France's attractiveness in the field of medical research. The government has thus reiterated its support for biomedical research, a major component of the country's competitiveness, and for the Paris Brain Institute.

The Pitié-Salpêtrière nervous system diseases centre has recently become the University Medical Department (DMU) of Neurosciences, as part of a reorganisation of the hospital services within the AP-HP - Sorbonne University group. The Neuro-

sciences DMU has the distinct advantage of being highly coherent in terms of focus, and is a core component of the country's one and only neuroscience IHU, the Paris Brain Institute.

Finally, the Institute has invested in a new building to further accelerate the development of medical technologies. A major change of scale is therefore in the works, with three separate sites for the iPEPS incubator coming soon. "The Healthtech Hub" will be spread across three sites: the historic incubator, in the heart of the Paris Brain Institute building, which will primarily serve young companies developing drugs and research acceleration tools; a space dedicated to digital health, located at Station F; and, by the end of 2020, a new building halfway between the Brain Institute and Station F, which is made possible through the support of the City of Paris and the Île-de-France region.



2019 Milestones

SCIENTIFIC BREAKTHROUGHS

In 2019, Paris Brain Institute researchers were responsible for more than 500 major scientific publications and earned 96 national and international funding awards and more than ten prestigious prizes.

Major scientific breakthroughs include:

- cerebral anoxia and resuscitation seen in real time from inside the neurons;
- the first complete mapping of cerebral functional lateralisation;
- the identification of early brain changes in Alzheimer's disease at the pre-clinical stage using electroencephalography;
- the identification of genetic mutations present in brain malformations associated with epilepsy;
- the discovery of a new potential therapeutic target for certain types of spinocerebral ataxia;
- the demonstration of the benefits of coffee in treating dyskinesia;
- the detrimental effect of overly intense physical training on cognitive brain ability;
- greater creativity discovered in patients with narcolepsy.

AMBITIOUS RESEARCH PROJECTS CURRENTLY UNDERWAY

The scientific ventures of the Paris Brain Institute's researchers regularly receive national and international recognition, notably through competitive funding.

European Research Council (ERC) :

- **"SYNAPTOENERGY"**: identification of the energetic deficits of neurons responsible for pathologies such as epilepsy, by Jaime De Juan Sanz;
- **"BCINET"**: understanding and decoding connections between neurons to help restore patients' motor skills after stroke, by Fabrizio De Vico Falani (Inria);
- **"CORTIGRAD"**: identifying and mapping neural networks within the cerebral cortex, by Daniel Margulies (CNRS).

Call for university hospital projects (RHU):

- **COSY**, which aims to develop new therapies to treat a rare disease: disharmonic overgrowth syndrome, with Stéphanie Baulac (Inserm);
- **BETPSY**, which works on developing diagnostic tools for encephalitis and paraneoplastic neurologic syndromes caused by autoimmune disorders, to improve patient management, with Agustí Alentorn (AP-HP).

Health Data Hub :

- **The NS-PARK cohort**, which encompasses 24 expert centres in the field of Parkinson's disease, coordinated by Jean-Christophe Corvol (AP-HP/Sorbonne University).

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

- NeuroTrials, the early clinical development unit, has signed its first contracts with manufacturers to develop medical devices for evaluating gait, pain management using virtual reality, and an innovative drug to treat optic neuritis.
- The "sleeping beauties" project led to the identification of several families of molecules that were evaluated in cellular models of diseases such as Parkinson's and multiple sclerosis.
- Development of the first highly innovative tiny therapeutic molecules with the best medicinal chemists in France.
- New Living Lab prototypes for stroke recovery.

COLLABORATIONS AND PARTNERSHIPS FOR RESEARCH AND HEALTH

- Several industrial clinical trials testing innovative therapies for rare neurodegenerative diseases, such as antisense oligonucleotides for Huntington's disease and amyotrophic lateral sclerosis, or anti-Tau antibodies for progressive supranuclear palsy.
- Launch of the Pfizer Healthcare Hub accelerator program for 4 start-ups in the field of digital healthcare.
- A European network of excellence focusing on neurodegenerative diseases with DRI (Dementia Research Institute, UK), VIB Leuven (Belgium) and DZNE (Germany).
- An exchange program with three major American universities: MIT, Stanford and St. John's, and a clinician exchange program with Yale University (New Haven, USA).
- A ramp-up of our incubated start-up, WeFight, and its virtual companion Vik, were able to raise €1.8 million in investments, and Neurallys stepped up the development of its smart implant thanks to a new investment of €750,000.
- The arrival of six new companies, including HealthyMind, which has developed a virtual reality solution to help with pain management, and Cairn Biosciences, to develop new anti-addiction drugs.
- Bioserenity, formerly incubated at the Paris Brain Institute, has joined the Next 40, which brings together the 40 most promising start-ups, and is the only company in the health sector.

AN APPROACH TO TEACHING THE KNOWLEDGE GAINED THROUGH RESEARCH

- Creation of the Open Brain School training centre.
- Launch of the first Master Class dedicated to creativity for non-experts.
- 1st edition of the Brain Bee programme at the Paris Brain Institute, created for high school students interested in neuroscience and its pathologies.
- Participation in and organisation of a number of communication events on advances in research for the public: Open Brain Bar, Semaine du cerveau, S3 Odeon, Pariscience Festival, etc.

SUPPORTERS NEW AND OLD

- Bequests, donations and life insurance, an increasingly important resource for advancing brain research.
- The support of the Janssen Horizon Endowment Fund, the AXA Research Fund, and AXA Bank Asset Management and its donors, through the Thellie platform, for a research project on gene therapy for neurodegenerative diseases and a programme on rare refractory epilepsy in childhood, respectively.
- The Institute can count on strong support from watchmaker Richard Mille, the Hospices de Beaune and the International Contemporary Art Fair (FIAC).
- The Paris Brain Institute and Euryale AM were awarded the 2019 Grand Prize for Philanthropy, as well as the BFM RMC Association Award at the BFM AWARDS.



© Martin Carbo-Tano

2019 Financial situation

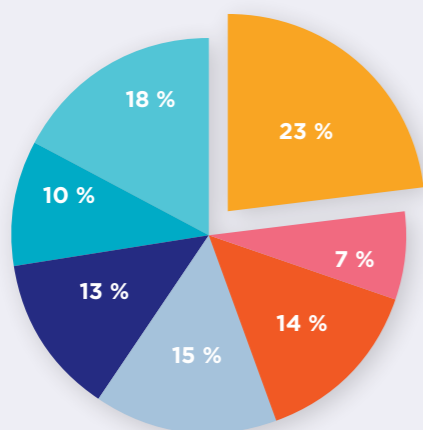
2019 RESOURCES

Research project funding is typically diverse in terms of sources of funding, with a long-term perspective in order to produce knowledge and major advances in the neurosciences.

The total resources for 2019 amounted to €58.3 million, comprising €48.1 million of income for the year and €10.2 million of carry-over of resources allocated but not used in previous years. Income for the financial year mainly corresponds to revenues from fundraising (€17.3 million), either from the general public (€13.4 million) or from companies and private foundations (€3.9 million).

It also includes:

- revenues from technology platform activities (€5.3 million) and research collaborations with industrial partners (€3.5 million);
- public and private grants (€8.4 million);
- funding for the IHU programme (€7.6 million);
- miscellaneous income (rental income, re invoicing of expenses, investment income) (€6 million).



Resources

- Funds raised from the general public
- Funds raised from companies and private foundations
- Public and private grants
- Revenues from technology platform activities and industrial partnerships
- Funding for the IHU programme
- Other income (rental income, re invoicing of expenses, investment income, etc.)
- Carry-over of resources from previous years

2019 SPENDING

The overall figure for 2019 spending is €58.3 million: €43.4 million spent in 2019 and €12.6 million to be spent later on earmarked resources. Of the 2019 expenditures, the total devoted to social outreach amounts to €36.8 million, representing 85% of the total expenditures for the fiscal year. The Paris Brain Institute's social outreach programmes include:

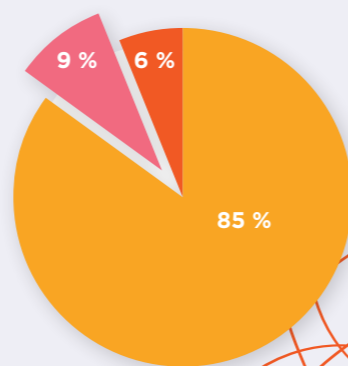
- research programmes;
- technology platforms;
- scientific activities and the development of international partnerships;
- incubation of innovative companies.

Funding for research projects is allocated mainly to diseases of the nervous system and spinal cord injuries. The technology platforms (neuro-imaging, 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 companies and foundations (corresponding to patronage and sponsorship actions), as well as communication campaigns. They account for 9% of expenditures.

Operating costs comprise the costs of the support teams (general administration, finance, human resources, legal, information technology and logistics), which account for 6% of total expenditures for the fiscal year. The spending to come from the earmarked resources (€12.6 million) correspond to donations from companies or foundations and funding for multi-year projects from private or public funds (ANR, etc.) received during the year that will be used later for specific multi-year research programmes.

Jobs

- Social outreach
- Fundraising and communication costs
- Operating costs



ALLOCATION OF RESOURCES RECEIVED FROM THE GENERAL PUBLIC

The resources received from the general public that were spent in 2019 amounted to €13.4 million. In a nutshell, for every €100 of resources received from the general public, €72 was used to finance social outreach programmes and investments, €22 was used to cover the costs of fundraising and communication, and €6 was used to cover the operating costs of the Paris Brain Institute.

2019 REVIEW

ASSETS (€M)	2018	2019
NET FIXED ASSETS	56	65
CURRENT AND AVAILABLE ASSETS	65	67
TOTAL ASSETS	121	132

LIABILITIES €M	2018	2019
ASSOCIATIVE FUNDS	57	51
PROFIT AND LOSS FOR THE FISCAL YEAR	- 0,2	1,7
DEDICATED FUNDS	13	15
DEBTS	34	41
DEFERRED REVENUE	18	24
TOTAL LIABILITIES	121	132

COMMENTS

The total sum of investments made by the Paris Brain Institute since its creation amounts to €46 million, mainly allocated to the technological platforms that support research. Investments for the financial year amounted to €15.7 million. They include:

- scientific investments: acquisition of a state-of-the-art sequencer (€800 K) and scientific materials and equipment (€1,238 K);
- the acquisition of scientific computer storage capacity and computing clusters (€1,042 K).

Net fixed assets amounted to €65.2 million. At 31 December 2019, cash and cash equivalents totalled €42.5 million. The Paris Brain Institute's associative funds amount to €56.1 million. They include shareholders' equity of €47.9 million, in addition to investment grants of €4.6 million. The non-expendable endowment of the Paris Brain Institute is €1.2 million. At the end of the fiscal year, there were €15 million in dedicated funds (funds remaining to be allocated to multi-annual programmes).

Reserve policy:

When it was created in 2006, the ICM Foundation-Paris Brain Institute received an endowment of €11.7 million, of which €1.2 million was a non-expendable endowment. Through careful budget management, the ICM Foundation-Paris Brain Institute has been able to balance its expenses and revenues for the past four years, thus avoiding having to draw on its reserves. Furthermore, the investment policy of the members of the Board of Directors is extremely conservative. The Paris Brain Institute's liquid assets are invested in marketable securities (capitalisation contract taken with leading banking institutions, guaranteed in capital and 100% in euro funds).

VOLUNTARY CONTRIBUTIONS IN KIND

Volunteer work:

The ICM Foundation-Paris Brain Institute benefited from volunteer hours during the year, particularly for communication campaigns. The volume is estimated at 1.2 FTEs, i.e., on the basis of an hourly minimum wage, an amount of €32,000.

Patronage in kind:

The ICM Foundation-Paris Brain Institute has benefited from sponsorship in kind as part of its communication activities and fundraising appeal to the public, namely:

- media space at: Air France, ReedExpo/Fiac, ZenithOptimedia, Richard Mille, TF1, Klesia;
- products or services provided free of charge: Fédération internationale automobile, Publicis Group, Orrick Rambaud Martel, Idec, Anacofi.

Particularly committed to maintaining its level of excellence, the Paris Brain Institute has put in place internal and external control procedures to guarantee the professionalism and efficiency of its management: it is a member of the Comité de la Charte du don en Confiance (Committee for the protection of donors) and uses an independent auditor.

PROTECTION OF DONORS

On 3 November 2010, the Paris Brain Institute received the approval of the Comité de la Charte du don en Confiance (Committee for the protection of donors), which was renewed in October 2019. For more than twenty years, this committee has played the role of professional regulation of fundraising appeals to the general public. Its work is based on 3 commitments: accredited bodies must abide by rules of ethics, they must comply with a shared policy towards donors, and they must accept ongoing monitoring of the pledges made.



Making a bequest to the Paris Brain Institute means becoming part of the major scientific breakthroughs of the future

2 questions for Carole Clément, Responsible for testator relationships at the Paris Brain Institute

The Paris Brain Institute is a foundation recognised as a public utility and is entitled to receive bequests, donations and life insurances. Carole Clément is available to assist you in your consideration of the issue.

How would you describe your involvement with those who wish to make a bequest to the Institute?

It's important that I listen to them so that I can support them as best I can without ever trying to influence them. If they wish, I can arrange a meeting with our notary.

I also update them regularly about what's going on at the Institute and our researchers' progress. A special relationship develops over time.

What are some of the reasons people call you?

Most of the time, people want to tell me about their plans for their wills. Others want to know what makes us different from other non-profits or foundations.

> Read the full interview on our website <https://legs.icm-institute.org/>.



MS CAROLE CLÉMENT

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Meet Philippe and Anny



Philippe and Anny, aged 67 and 71, are a couple with no children. They have chosen to make a bequest to the Paris Brain Institute and share their project with us.

Why did you choose the Paris Brain Institute?

It is a well-established, strong, serious institution, working in an essential and innovative field. The fact that it is located within the Pitié-Salpêtrière Hospital was also a positive factor, because we were very well cared for there. We also appreciated the great responsiveness of its donations department in response to our enquiries, compared with other foundations.

How did this service help you in your project?

The first time we met, we were given a very warm and empathetic welcome. Carole Clément was a great listener and answered our questions in detail. We were also provided with extensive documentation. We feel that the contact we had with this department was absolutely essential.

What does this kind of support mean to you?

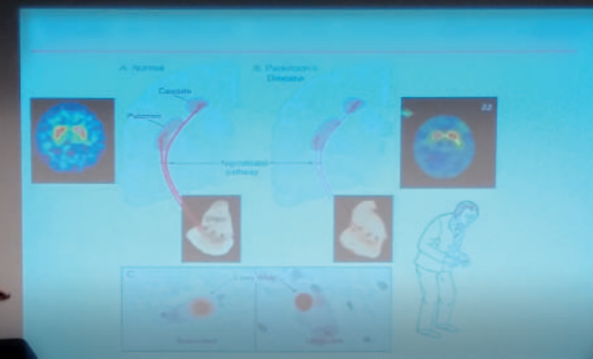
It is essential to support the development of research to fight diseases and develop new treatments. Making a bequest means helping to build a better future for generations to come.

“ Why does the Institute's name no longer include the "spinal cord"? ”

Daniel T.

We found that the acronym "ICM" was difficult to understand and remember, which is an obstacle to the development of the Institute's reputation. This reputation is crucial in raising awareness about brain research issues and the exceptional work done by our researchers on a daily basis. That's why the ICM became the Paris Brain Institute, quite simply. We are not giving up on the spinal cord, of course, which is the essential conduit for the enormous amount of information that circulates in our bodies every second, and which has considerable importance for public health. We are simply moving towards simplicity, in an effort to be make the issues at stake in neuroscience research more accessible to the general public.

ONLINE DONOR CONFERENCE



Due to the current health situation, we are unfortunately unable to welcome you to the Institute to attend the conferences we usually host for our donors.

As we know, these conferences are an essential way for us to update you on the progress of the research being carried out at the Institute and are also an opportunity to talk to our researchers.

We have decided to hold a **conference on Alzheimer's disease** that will be filmed and made available to you online starting Saturday, 19 September at 9 a.m. (on the home page of our website).

Please send us any questions you may have about research being done on Alzheimer's disease at the Institute by email to: **cercle@icm-institute.org**. We will share them with the conference speakers so that they can be answered as far as possible during the conference.

F.A.Q.?

I live in Europe and would like to make a donation to the Paris Brain Institute while enjoying the tax benefits of my home country.

Is this possible?

Yes, of course. The Paris Brain Institute is authorised to receive donations through TGE (Transnational Giving Europe). This network allows you to bypass tax barriers and make transnational donations to and from 21 partner countries, including Belgium, Luxembourg, Switzerland, Portugal and the United Kingdom. It allows you to take advantage of the tax benefits and exemptions provided by the legislation of your country of residence. Contact the Cercle des Amis office at **+33 (0)1 57 27 40 32** or via **cercle@icm-institute.org**.

I would like to organise a fundraising event in honour of a loved one.

How do I go about it?

Please contact Sylvie Carré, who can assist you in this process and answer all your questions. She can be reached either by telephone at **+33 (0)1 57 27 45 11** or by email at **sylvie.carre@icm-institute.org**. You can also visit our webpage on this subject: **https://icm-institute.org/fr/don-memoriame**

YOUR PERSONAL CONTACT in Bureau du Cercle des Amis

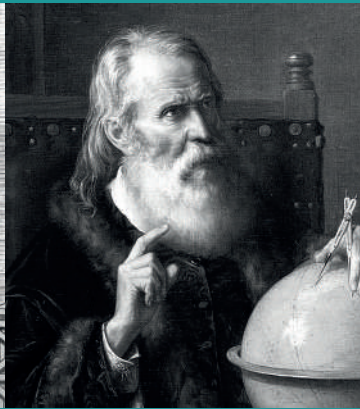


Ms LUCIE MOUTIER

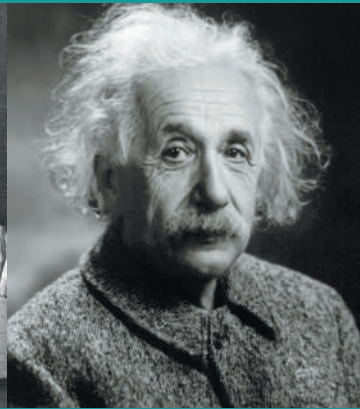
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> Archimedes



> Galileo



> Albert Einstein



> Researchers at the Paris Brain Institute

Alzheimer's disease, Parkinson's disease, multiple sclerosis, brain tumours, stroke...

Today, you can take action against neurological diseases by saving a place in your will for the Paris Brain Institute. By bequeathing all or part of your wealth, you will help the Paris Brain Institute's 700 researchers, doctors and scientists accelerate the pace of discovery. To change the course of history and find effective treatments that will lead to better and healthier lives for all.

As a foundation recognised as being of public utility, the Paris Brain Institute is authorised to receive bequests, donations and life insurance, completely exempt from inheritance tax.



For any questions:

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Find out more about:

www.institutducerveau-icm.org

SUPPORT FORM

Please make your cheque payable to the Institut du Cerveau and send it with this form to the Institut du Cerveau - Hôpital Pitié-Salpêtrière - 47, boulevard de l'Hôpital CS 21414 - 75646 Paris Cedex 13 - France



Yes, I would like to help the Paris Brain Institute researchers go forward in their research into brain and spinal cord diseases.

I am sending a donation of: €
(voluntary amount)

M^s Mr Mr and M^s

Name: First name:

Address:

Post code: Town:

E-mail:@.....

I would like to receive free information on bequests and donations.



The Paris Brain Institute Foundation adheres to the rules of ethics of the Comité de la Charte du don en Confiance (Committee for the protection of donors).

The information collected in this newsletter is recorded in a computer file managed by the Paris Brain Institute for the purposes of transmitting your fiscal receipt, reporting on the use of your donation, inviting you to conferences or events, appealing to your generosity and sometimes for study purposes to get to know you better, elicit your opinion and improve our practices. This data, intended for the Paris Brain Institute, may be passed on to third parties mandated to carry out the printing and mailing of your receipts, our donation appeal campaigns or studies. You have a right to access, rectification, deletion, limitation, opposition or portability of your personal data by contacting the Bureau du Cercle des Amis de l'Institut du Cerveau Hôpital Pitié-Salpêtrière - 47, boulevard de l'Hôpital, CS 21414 - 75646 Paris Cedex 13 - France. You also have the possibility of filing a complaint with a public authority. The Paris Brain Institute attaches the utmost importance to the protection of your personal data and respecting your wishes. The Paris Brain Institute does not transmit or exchange the contact information of major donors.