

The newsletter designed to connect with you

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N° 23 - November 2020

Vnabse

Feature

Psychiatric disorders,

what we know and what we think we know.



editorial



We're told that the field of psychiatry is in distress.

Alongside the care and management of reactional depression and everyday anxiety, there is also "heavy" psychiatry, the one which is incredibly painful for patients and their family: severe depression, schizophrenia, autism, panic attacks, etc. A host of illnesses that we rarely talk about, sources of stigmatization for patients, and the largest Health budget.

These disorders are relieved by effective treatments: antipsychotics, antidepressants, anxiolytics, etc., which complement psychotherapy. However, in still too many cases, these therapies are insufficient, and a curative treatment has yet to be found. The reason is that these illnesses are brain illnesses and the brain is, by far, the champion of complexity.

And yet, considerable progress has been made: disarticulating countless psychiatric disorders, early diagnosis, epidemiology, biofeedback, genetics, etc. But, unlike neurological illnesses where lesions can be seen under the microscope, this is not the case in psychiatry, as dysfunctions cannot be observed on a cellular scale, and because the environment plays a role in these of course in an even more profound manner.

This research, from social determinants to the most molecular approach, calls for the best researchers to roll out a multidisciplinary approach. And, it's for this reason that the Paris Brain Institute will find the answer.

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

Neuro-Covid-19 Projects campaign: anticipate and be better armed to tackle the virus

Loss of taste and of smell, encephalitis, etc., we quickly became aware that Covid-19 could be responsible for neurological complications. Faced with an affliction which is likely to remain sustainably in our societies, our researchers are taking action. You can help them by making a donation to support their work.

To find out more and make a donation:	

The Paris Brain Institute on france•2

What happens in our brain when we activate the reward circuit? To find out, view the replay of the television program "Les pouvoirs extraordinaires du corps humain" (The extraordinary powers of the human body), broadcast in French on 1st September this year on France 2 TV channel, with Michel Cymes and Adriana Karembeu. A fascinating sequence shot in The Paris Brain Institute's Clinical Investigation Centre!

Watch on: https://www.france.tv/france-2

Cathy Leitus 2021 scholarship

The Cathy Leitus scholarship, created in 2018 in memory of Cathy Leitus, distinguished reporter and administrator of Science Po Alumni, has been financing ambitious research programmes on brain tumours for two years now.

To participate in this act of generosity and donate to the Cathy Leitus 2021 scholarship, then visit: https://icm-institute.org/fr/actualite/ bourse-cathy-leitus/

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A new site for medical technologies and artificial intelligence

iPEPS - The Healthtech Hub, created in 2012 under the impetus of the Paris Brain Institute, is **the first incubator dedicated to nervous system illnesses** and bringing together entrepreneurs, clinicians, patients and industrial experts to accelerate the development of drugs, technologies and digital solutions. Spurred on by its growth and its innovation ambition, **a new 1,500 m² campus equipped with 150 workstations will open next December**, supported by the City of Paris and the Île-de-France region. This building, located halfway between the Pitié-Salpêtrière university hospital centre and the STATION F campus, rue du Chevaleret, embodies the Institute's wish to provide innovators with a mutualized environment where all tools will be pooled together to succeed industrially.

Key figures

for human functional exploration

257 EXAMINATIONS ON AVERAGE PER MONTH

Lionel Naccache

au cœur de la conscience

intérieur

Le Cinéma

Projection privée

Good reads

In his new work, "Projection privée au cœur de la conscience" (published by Odile Jacob), the neurologist and researcher Lionel Naccache explores, with the most recent neuroscience tools, the way in which our mind/brain produces our perception of the world and of ourselves.

According to the author, "we have a sort of interior cinema inside us, which is basically like a cinema given its really surpri-

sing similarities, yet is also different thanks to its incredible exploits". A must-read, to discover right now!



 section of our website.
Altered levels of consciousness: two new key discoveries for diagnosing and treating patients

Find out more in the "News"

- Remyelination in multiple sclerosis
- Huntington's disease: brain defects detectable from embryonic stages

ightharpoonup seen on the web



- Online donor conference from 19/9/2020 on Alzheimer's disease (in French)
- GLUT1 deficiency syndrome, a model for understanding the brain's metabolism



November

Braincast with Lionel Naccache "Our brain is the master of illusion", 4th podcast by *Cerveau & Psycho* in partnership with the Paris Brain Institute (in French)

www.cerveauetpsycho.fr/sr/braincast

Saturday 5 December

Online conference on depression (the video link will be sent to you by email and will also be available on our website) (in French)





news

Translational research on repetitive behaviours



How did you start working in the Paris Brain Institute?

After completing my thesis at the Collège de France followed by post-doctoral research at the Massachusetts Institute of Technology (MIT), I joined the Paris Brain Institute in 2013 and integrated the team of Prof. Luc Mallet, psychiatrist-researcher. The complementarity of our expertise led to the creation of a multidisciplinary team interested in the set-up and regulation of normal and pathological repetitive behaviours, in particular Obsessive Compulsive Disorder (OCD). Our approach enabled us to study the mechanisms of actions involved in deep brain stimulation, which reduce compulsive symptoms in patients suffering from OCD. Concurrently, using experimental models and thanks to the targeted light stimulation of specific neurones (optogenetics), we identified brain pathways involved in regulating compulsive behaviours.

What exactly is translational research?

Making a human being carry out a behavioural task is rather easy, a computer screen, a few instructions and the patient carries out the task in a few hours. It's much more difficult and time-consuming to do it on mouse models of course! To address this methodology issue, handin-hand with the Institute's fablab (prototyping workshop), we designed fully-automated behavioural assessment systems. Our recent work in particular offered us the opportunity to show that the sub-groups of compulsive subjects, humans and mice, were particularly impacted when adapting to new rules. These results show that we need to take the heterogeneity of the subjects studied into account, even if they suffer from the same pathology, and support a more personalized approach to clinical practice.

It was a gamble for us to develop projects in tandem with the patients and in mouse models, as few teams manage to do this even today. "

Does the translational approach change the way a pathology such as Obsessive Compulsive Disorder is considered?

Daily exchanges between team clinicians and researchers enable us to identify new brain pathways which we can study in mice more specifically. In contrast, clinical practice can evolve, for example in the way patients are questioned, based on experimental results observed. Depression, schizophrenia, OCD, etc. all are illnesses which we associate with psychiatry. Why does this word still invoke fear? Why are these personality, behaviour and mood disorders stigmatized by society whenever 1 out of 4 adults has been, is or will be concerned by a psychiatric disorder sometime during their life?

Psychiatric disorders, what we know and what we think we know

report

Better understanding what psychiatric disorders are

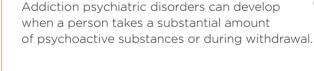
Psychiatric disorders are characterized by a reduction, even a loss of the ability of the mind to function normally and to act in an appropriate manner to life situations. Those suffering from these disorders can no longer adapt to circumstances and can suffer from personality disorders (anxiety, anger, etc.), behavioural disorders (attention deficit disorder, hyperactivity, etc.) or mood disorders (exaggerated, persistent sadness, etc.).

> 10 categories of psychiatric disorder exist*

Organic mental disorders, including symptomatic disorders

Symptomatic mental disorders of brain damage resulting from a neurological illness concerning for example dementia in Alzheimer's and Huntington's diseases. Care and management of these disorders is primordial, as they can lead to a rupture in the patients' therapeutic treatment, like for example with apathy in post-stroke rehabilitation.

Research conducted at the Paris Brain Institute



Mental and behavioural disorders

related to the use of psychoactive

substances (alcohol, drugs, pharmaceuticals)

Schizophrenia, schizotypal disorders and delusional disorders

Schizophrenia is the most negatively perceived illness for the general public whereas it only represents

1% of psychiatric disorders and only 0.2% of schizophrenics pose a potential risk to others.

Mood disorders (emotional disorders)

Depression is the most frequent psychiatric illness and it is estimated to affect around 10% of the French population.

Research conducted at the Paris Brain Institute



Neurotic disorders, disorders related to stress factors and somatoform disorders

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Behavioural syndromes associated with physiological dysfunctions and physical factors.

Eating disorders (anorexia, bulimia, etc.) and severe sleep disorders (fatal familial insomnia, etc.) are psychiatric disorders.

Research conducted at the Paris Brain Institute



Obsessive Compulsive Disorder (OCD) affects around 3% of the population and is generally triggered during childhood, before the age of 25 years old in 65% of cases.

Research conducted at the Paris Brain Institute



Mental retardation is defined as "a halt in mental development or incomplete mental development, characterized by impaired intellectual and adaptive functioning, in particular as regards cognitive, language, motricity and social performance functions".

Psychological development disorders

Personality and behavioural

Paranoia, kleptomania and nar-

cissism are classified here along

disorders in adults

Autism is classified with speech and language development disorders.



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and adolescence Tourette's syndrome is also identified as

disorders generally appear during childhood

Behavioural disorders and emotional

a psychiatric disorder and classified under attention deficit disorders.

Research conducted at the Paris Brain Institute



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Psychiatric disorders are now a major public health challenge. Although their therapeutic care and management has significantly developed thanks to research, societal prejudices persist. These distorted views of reality, fuelled by media coverage of violent, yet "rare" miscellaneous news items (less than 1% of patients are a potential risk for others), give rise, to this day, to discrimination and to considerable delay in diagnosing patients. The psychiatry/insanity association is unfortunately still a widespread belief in society. Yet, the aforementioned psychiatric disorders benefit from adapted care, management and effective treatments today which enable patients to pursue their social, family and professional life.

Targeted, personalized innovative therapies

Psychiatric disorders involve a set of factors which cannot be considered individually: biology (genetics and epigenetics in particular), psychology, the environment, the sociocultural context, life situation, personal history, etc. All these factors must be taken in an integrated manner and all these elements which contribute to the genesis and persistence of these pathologies must be worked on synergistically.

Mechanisms in the brain

Brain imaging techniques (MRI) have enabled identifying the areas of the brain involved in specific psychiatric disorders. The study of experimental models led to identifying specific neurones, whose dysfunction results in mental disorders. In our brain, information is transmitted via chemical molecules called neurotransmitters: serotonin, dopamine and GABA. Imbalance in these neurotransmitters is widely suspected in depression. In Obsessive Compulsive Disorder (OCD), basal ganglia, the root of mechanisms for a great many of our everyday behaviours, are more particularly involved. Losing control of these mechanisms would, for example, lead to a persistent doubt and associated compulsive behaviour.

C are and management for patients suffering from psychiatric disorders is multidisciplinary and must associate psychotherapy, drug treatments, as well as novel therapeutic technologies. The key objective of the Paris Brain Institute clinicians and researchers, working closely with the adult psychiatric unit of the AP-HP Pitié-Salpêtrière Hospital, is to develop the use of existing, effective technologies in more pathologies, as well as to be able to adapt therapies to each patient.

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Today, our objective is to develop tomorrow's treatments to promote a more personalized approach to the therapeutic aspect as well as on overall patient management. Psychiatric innovation comprises technological, clinical, organizational and societal aspects which open up discussion; what real inventions does our psychiatry need?



Prof. Luc MALLET,

professor of psychiatry at the Henri-Mondor University Hospital Centre, researcher in the Neurophysiology of Repetitive Behaviours team at the Paris Brain Institute

A new way of treating psychiatric disorders

These "new generation" therapies are generally associated with psychotherapeutic care and drug treatments specific to each psychiatric disorder.

Virtual reality

The aim of this therapy is to enable the patient to gradually master situations which are anxiety-provoking for them and to become desenitized to them. The patient, wearing a 3D helmet which projects a scene which generally provokes their disorder, can move forward risk-free as they are aware they are only exposed to virtual dangers.

Transcranial Magnetic Stimulation

Transcranial Magnetic Stimulation uses a magnetic field to modify electrical activity in the cerebral cortex. This technology proved its efficacy in severe depressive syndrome cases as well as on schizophrenics with auditory hallucinations. It is currently being assessed for OCD and addictions.

Deep brain stimulation

In cases of severe depression and OCD which resist other therapies, deep brain stimulation is recommended. This stimulation is carried out using electrodes implanted in specific areas of the brain. They deliver permanent electrical stimulations to the neurones of specifically-targeted areas of the brain. The Paris Brain Institute researchers are forerunners in the use of deep brain stimulation in numerous neurological and psychiatric pathologies, such as Parkinson's disease and Tourette's syndrome for example.

E-psychiatry

The development of "connected" systems providing real-time access to clinical information in the patient's natural environment is starting to shake up the ways psychiatric disorders are managed. In cases of suicidal tendencies, for example, variables such as appetite and sleep appear to be highly-informative for the clinician for predicting and preventing a likely suicide attempt.



Share your experience

Many thanks for the questions and experiences which you sent us. In this issue, we wish to share with you the message we received from Sophie, 36, who suffers from depression:

"Make an effort", "Give yourself a good shake", "When there's a will, there's a way", etc. How horrible it is to hear these things on a daily basis.

Guilt-creating, counterproductive advice: whenever you're depressive, you don't decide with a snap of your fingers that you're going to get better.

I know that it's difficult for those around me to understand what I'm going through and what I feel. In the darkest days of depression, the smallest decision, the smallest action becomes a mountain that's impossible to climb.

Today, I've accepted the fact that it's a real illness, I know that the Paris Brain Institute researchers are making progress and that with the support of donors I'll be able to be cured one day." **))**

Sophie D., 36 years old

Let's talk about multiple sclerosis!

Email us your question or experience on the special feature theme in our next issue on the subject of multiple sclerosis, and you may be published in the March 2021 issue of *Synapse*.

contact@icm-institute.org

Two key discoveries in altered levels of consciousness

A research team led by Prof. Lionel Naccache (Sorbonne University/AP-HP) made two significant discoveries related to illnesses associated with long-lasting altered levels of consciousness.

A new clinical sign for investigating levels of consciousness

Researchers have discovered a new clinical sign for identifying, in these non-communicating sufferers, the ones who have the richest level of brain functioning. They observed that the startle reflex response to noise - eyelid blinking following a sudden sound became habit-forming in specific patients. As such, whenever the sounds were repeated, they were able to inhibit this behavioural response. On the contrary, a jolt whenever there was systematic noise was specifically found in patients where detailed clinical examination and brain explorations using

an electroencephalogram (EEG), MRI and PET revealed very poor cognitive and brain activity. In addition to this precious diagnostic value, the presence of this clinical sign, easy to probe for when the patient is in their bed, could be used for predicting an improvement in their level of consciousness over six months.

Improving consciousness by electrically stimulating the cerebral cortex

In a second study, researchers revealed how transcranial direct current stimulation (tDCS) of the frontal lobe of these patients improved their level of consciousness. By comparing patients who showed behavioural improvement after a single session of transcranial direct current stimulation (tDCS) of the frontal lobe, with patients who showed no sign of improvement, researchers showed that the clinical response to tDCS was related to an increase in consciousness-specific EEG markers.

These results are important on the clinical level, as the lead the way for developing new personalized stimulation therapeutic strategies, and on the fundamental research level, as they confirm the importance of the prefrontal cortex and the frontal-parietal network in consciousness physiology.

Huntington's disease: brain defects in the embryo

Brain defects discovered in the brains of human embryos carrying the mutation causing Huntington's disease.

It's the first time that

brain development

defects have been

disease. "

highlighted for this

Huntington's disease is a rare, hereditary genetic disease of the central nervous system. It usually expresses itself between the ages of 30 and 50 through psychiatric, cognitive and motor disorders which gradually worsen. It is due to the mutation of a coding gene for a protein called huntingtin.

"

Sandrine Humbert's teams (Inserm) at the Grenoble Institute of Neuroscience and those of Alexandra Durr (Sorbonne University/ AP-HP) at the Paris Brain Institute are interested in the early stages

of Huntington's disease and in the long period which precedes the appearance of symptoms. They studied the brains of 13-week-old human embryos, donated by parents following medical termination. They observed several differences between the embryos carrying the mutation of the coding gene for huntingtin and others non-carriers.

It's the first time that brain development defects have been highlighted in this disease. Moreover, they are relatively significant and widespread, even though their direct consequences on brain functioning is still unknown. In embryos carrying the mutation, the pathological huntington protein is abnormally located in progenitor cells which are the origin of cortex neurones. This abnormal location is associated with a disturbance in the functioning of these cells, in their division and in their neurone "differentiation".

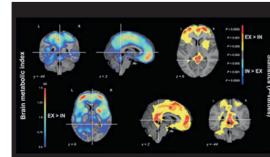
The hypothesis favoured for explaining symptom absence in spite of these defects is that the brain implements compensation mechanisms very

> early on which enable it to function normally. This discovery has, moreover, significant consequences on the way and the stage that treatment which modifies the development of the disease must therefore be considered.



C The presence of this

clinical sign, easy to probe for in the patient, could be used for predicting an improvement in their level of consciousness over six months. 33



The brain metabolism of a vast pre-frontalparietal area is higher in patients who have a startle reflex to exhaustible noise (EX) in relation to patients who have a startle reflex to inexhaustible noise (IN).

technologies and applications



MAGNETOENCEPHALO-GRAPHY AND ELECTROENCEPHA-LOGRAPHY (MEG-EEG)

The increasing complexity of neuroscience research has led to very enriching studies bearing on several recording methods: MEG-EEG experiments, which are used to monitor information flows between different parts of the brain, increasingly include the use of MRI, physiological, neuropsychological and behavioural data. For this purpose, advanced statistical methods need to be developed.

MEG-EEG and bioinformatics platforms are currently developing **the first specialized set of algorithms (R package) for the multimodal statistical analysis of electrophysiological data**, which could be integrated into several studies conducted by Paris Brain Institute teams.



Mon Sherpa, the daily psychological monitoring app

Mon Sherpa app, created in 2019 by the Doctopsy (now Qare) startup, proposes a conversational pathway to wellness.

The aim of Doctopsy founders, Fanny Jacq, psychiatrist, and Benjamin Maquet, entrepreneur, is to address the issues of medical deserts, geographical remoteness and disability limiting access to specialists.

The Mon Sherpa app strives to address national issues by proposing help and support to people suffering from anxiety, stress, depression, sleep disorders, etc. through exercises imagined by a scientific committee comprising 8 mental health experts, psychiatrists and researchers, including Margot Morgiève, PhD in sociology of science and post-doctoral researcher in the team led by Éric Burguière at the Paris Brain Institute. The chatbot is a wonderful example of collaboration between the world of innovation and The Paris Brain Institute's researchers.

> Moreover, the solution's also intended for doctors as a range of specific features have been integrated to help consultants in the field of psychological care and management.

Last February, Doctopsy joined the Qare Group, a telemedicine service connecting practitioners and patients together via video. This merger also focuses on shared ethics. The two companies were co-founded by doctors and both have been supported by a scientific committee since the very beginning. They have designed their solutions hand-in-hand with the medical world and have developed specific accompaniment programmes for health professionals and their patients.

Sport dedicated to research

Every year, a host of sports events are organized in favour of associations and foundations and the Paris Brain Institute is delighted to be able to benefit from this. These meaningful moments bring together ever-growing numbers of people who wish to rally round a cause and we, in turn, wish to thank them deeply.



Here are 3 initiatives which we'd like to talk to you about today.

«Let's blow the SLA final whistle together»

That's the ambitious slogan presented by the French SLA Fondation Recherche (ALS Research Foundation) presided by Jean-Pierre Matheu, former Top 14 rugby referee. This association has already collected almost €120,000 for research by rallying the world of rugby around a host of events (auctions, jerseys, tombola, etc.).

To find out more, visit: http://slafr.fr/



€52,617

raised

An encounter at the Olympia in Paris with World Formula 1 champion, Alain Prost:

On Thursday 6 February last, a highly-original evening took place dedicated to Alain Prost's professional career and personal background, to raise money for the Paris Brain Institute.

This charity event, organized by Team One Group, collected the sum of €10,000.

The Course des héros (Heroes' Run) connected:

This year once again our "heroes" took up the challenge, on Sunday 28 June, to walk or run for the Institute; but, this time round, at home or alone outdoors connected via a smartphone or tablet, due to Covid-19-related measures.

€3,500 was collected thanks to our "heroines", Anne-Claire Lenoir, Juliette Roussille and Floriane Gasnerie!





Sport is a wonderful ambassador of the values which these women and men embrace through their investment where excelling oneself, sharing and generosity rhyme with commitment to research. THANK YOU!

For any queries related to organizing events benefitting the Paris Brain Institute, you may contact Astrid Crabouillet, astrid.crabouillet@icm-institute.org

700

people

attended this evening of interaction with Alain Prost



Philanthropy according to Leticia Poniatowski, family commitment first and foremost

Lucie Moutier How did you hear about the Institute?

Leticia Poniatowski

I heard about the Paris Brain Institute through David de Rothschild who introduced me to Prof. Gérard Saillant. Back then, I was a donor for another association in the medical field but the ambitious project to create a research institute dedicated to the brain appealed to me right away. I think the brain is a fascinating organ that's both fragile and powerful.

What adjectives could you use to describe the Paris Brain Institute?

Audacious, ambitious and indispensable.

Your sister, your husband and your son are also philanthropists of the Paris Brain Institute, as is your mother. How do you explain this family commitment to the Institute's researchers?

Yes indeed, I rallied several members of my family to the cause. There's been so much progress in other fields yet the brain remains a mystery. We believe it's vital to invest to understand how to repair the brain because these illnesses affect increasing numbers of people. This is the Paris Brain Institute's ambition and that's why I talk about it a lot around me, in particular to my family.

Could you tell us about the donation you wished to make on behalf of your mum?

My mother, who lived in Argentina and who supported a medical cause, was really proud that, like her, my sister and I supported the Paris Brain Institute. When she died of a brain tumour, my sister and I decided to make a large donation in her memory. We wished to pursue something that had interested her and the fact that the research is related to the brain made it even more significant.

This year, the Paris Brain Institute is celebrating its 10th anniversary. What do you wish it for the next ten years to come?

LP I hope that the Paris Brain Institute becomes a world benchmark for research on brain-related illnesses, that it can host increasing numbers of researchers from around the world and that this research can be centralized, cross-disciplinary and open to accelerate knowledge sharing.

donor correspondence

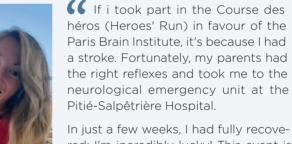
How is it easy to transmit a percentage of your wealth to the Paris Brain Institute using a life insurance policy?

Helen, 64 years old

Naming the Paris Brain Institute as beneficiary (or co-beneficiary) of a life insurance policy is a process that can be done without a will or a notary. You just need to get in touch with your insurance company and to enter our name and exact address in the policy beneficiary clause. This can be done at any time, when you take out a policy or during its validity period.

For any queries, please contact:





In just a few weeks, I had fully recovered: I'm incredibly lucky! This event is engraved forever in my mind and gave me a real taste for life.

Professionally-speaking, and it comes

of no surprise, I've become a specialized educator and I accompany children suffering from motor disability and related disorders, mostly linked to a brain pathology.

This Heroes' Run is important for me because it's an opportunity to raise awareness in those around me to these pathologies and to support the Paris Brain Institute's research and the fight against these nervous system illnesses.

I'm delighted with the keen interest my family, colleagues and sports club friends, who encouraged me in my action, have shown. The amounts raised have exceeded my expectations.

It was definitely a great sports and solidarity-focused adventure! A big thank you to all donors!



How can you go about organizing an online fundraiser for the Paris Brain Institute?

Visit the Paris Brain Institute's space on the alvarum.com website and click "Commencer ma collecte" (start collecting) to create your page. Then, transmit the page link to people you'd like to participate: they can make a secure online donation and even leave a message. A tax receipt will be sent to them by email.

If you have queries, contact the Cercle des Amis Office on +33 (0)1 57 27 40 32 or via cercle@icm-institute.org

Can I donate to the Paris Brain Institute via bank transfer?

Of course! Just request the Paris Brain Institute's bank details from the Cercle des Amis Office on **+33 (O)1 57 27 40 32** or via **cercle@icm-institute.org**

What are the advantages of donating online?

By donating via parisbraininstitute-icm.org,

you help us reduce running costs and you'll receive your tax receipt by email within 24 hours. If you don't, check your spam or contact the Cercle des Amis Office on +33 (0)1 57 27 40 32 or via cercle@icm-institute.org

YOUR PERSONAL CONTACT in Bureau du Cercle des Amis



M^s LUCIE MOUTIER

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



Online donation: another way of GIVING...

> Better resources for researchers to make new discoveries > Better hope for the millions of patients and their families

By making a donation online to the Paris Brain Institute, you are supporting the 700 Paris Brain Institute neuroscience researchers and experts in their relentless fight against neurological and psychiatric illnesses in an easy, fast and secure way. You are supporting a very high-level institute, mobilized to address one of the priority challenges for the health of humanity: to understand and treat the brain. If you are French tax liable, the online donation entitles you to the same tax deductions as the traditional donation.

Residents of other countries, contact us : cercle@icm-institute.org

MAKE A DONATION ON www.parisbraininstitute-icm.org and receive your tax receipt by email within 24h.