N° 25 – FIRST TRIMESTER 2014

THE ICM **NEWSLETTER**

Brain & Spine Institute - Paris

Why the brain for the focus of our latest newsletter? For 4 main reasons:

Philosophical. The brain is the organ that perceives, thinks and acts. It is, thus, the brain that enables us to attribute meaning to our existence. Indeed, suppressing its functioning would signify true death.

Sociological. As is the maestro of the organism, the brain controls both the organism and itself. The brain is, therefore, responsible for our behaviours and, consequently, our interactions with the individuals who compose our society.

Scientific. We are now beginning to understand the functioning of the brain. We live in an exciting period in the unveiling of the genesis of our intellectual faculties and emotions as well as the motor behaviours through which they are expressed.

Medical. We are also beginning to understand brain disorders from neurological diseases (Alzheimer, Parkinson, amyotrophic lateral sclerosis, multiple sclerosis, epilepsy, spinal cord trauma, etc.) to psychiatric disorders (depression, panic attacks, schizophrenia, autism, obsessive compulsive disorders, etc.).

This is the foundation on which the ICM exists. The ICM regroups the scientific and medical elite, at the heart of the Pitié-Salpêtrière Hospital in Paris, which is known for high-quality patient care, and the Pierre and Marie Curie University, renowned for its leading scientific training programs, with support from the CNRS and INSERM, two distinguished research institutions.

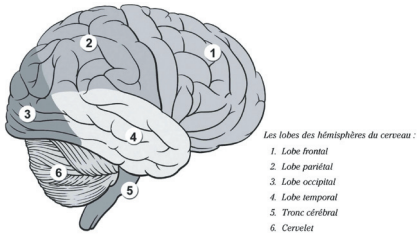
The installation of new start-ups in its incubator, the presence of more than 500 researchers in its laboratories and the clinical application of their research at the Centre for Clinical Investigation are the means developed by the ICM to promote the rapid discovery of new therapeutics.

Please don't hesitate to contact us with any questions...

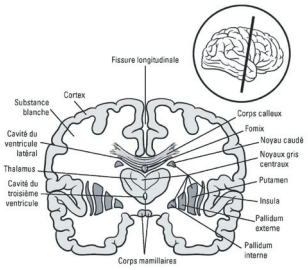
Pr. Yves Agid
Professor of Neurology and Neuroscience, Founding Member

UNDERSTANDING THE **BRAIN** AND ITS **FUNCTIONING**

THE BRAIN SEEN FROM THE OUTSIDE



VIEW OF A SECTION OF THE INSIDE OF THE BRAIN



The brain is the centre of the nervous system, capable of integrating information, controlling motricity and assuring cognitive function. The title of this issue is undoubtedly a bit ambitious, but it is the overarching objective of the Brain and Spine Institute, aimed at eradicating all diseases of the nervous system.

WHAT YOU NEED TO KNOW

- It's the best protected organ
- It weighs **1.3kg**
- It bathes in **cerebrospinal fluid** (CSF)
- Three layers of meninges cover the brain
- The brain:

2 hemispheres, right and left, connected by the **corpus callosum** (a network of fibres),

The cerebellum, a kind of small ancestral brain situated at the base, responsible for balance

- In each hemisphere:

A frontal lobe: where reasoning, linguistic functions and coordination of voluntary muscles take place

A parietal lobe: where consciousness of the body is controlled

An occipital lobe: responsible for the integration of messages

A temporal lobe: the centre of audition, memory and emotions

- It's composed of:

100 billion nerve cells, **"neurons",** which constitute a precise network of cable-like connections

Myelin: a protective sheath covering the axon of neurons that facilitates the propagation of the electrical impulse. It is formed of **glial cells**, 10 to 50 times more numerous than neurons

A **cortex** or **grey matter:** the outermost part of the brain, consisting of neuronal cell bodies

White matter: the innermost part of the brain, where nerve fibres in their myelin sheaths are located

4 cerebral ventricles: cavities in which the CSF circulates

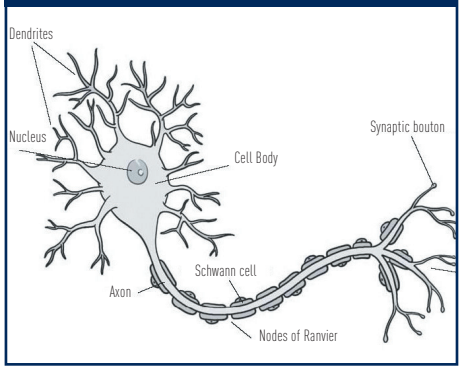
In the centre, the **central gray matter,** or basal ganglia is found. This is implicated in the control of behaviour and learning

- Principal nutrient: **glucose**
- A highly vascularised and oxygenated organ

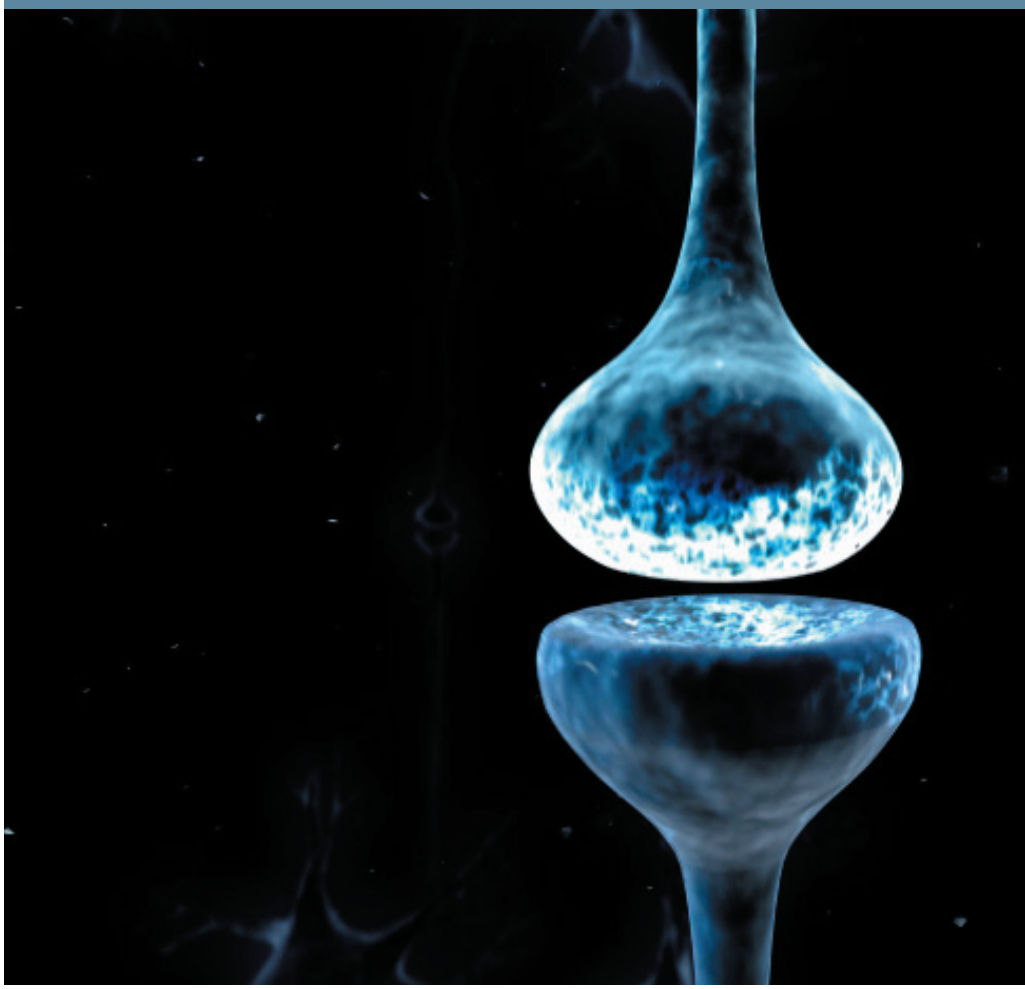
THE BRAIN: AN EXPERT COMMUNICATOR

Neurons communicate with eachother through electrical signals called **nerve impulses** (or action potentials). Each neuron is composed of a cell body and projections called dendrites and axons. These projections make connections among other neurons through their terminals, which look like small vesicles. These terminals form **synapses.**

THE NEURON



THE SYNAPTIC CONNECTION



A nerve impulse is propagated down the axon until it reaches the synaptic terminal. The greater its frequency, the more chemical substances it produces: **neurotransmitters** (or **neuromediators**).

The latter, contained in vesicles, are released in the extracellular medium at the level of the synapse and, in turn, activate or inhibit a second neuron at its dendrite or cell body. The nerve impulse continues down the second neuron, and so forth. There are several types of neurotransmitters. They can be excitatory, like glutamate, or inhibitory, like GABA. Dopamine, serotonin, histamine and acetylcholine are among the best known. The neurons responsible for the production of dopamine (situated in a region deep in the brain called the *"substantia nigra"*) are essential for the control of movement.

Parkinson disease is related to a massive destruction of dopaminergic neurons, which results in tremor and muscular rigidity associated with gait disorders. In addition to neuronal damage, histopathological stigmata appear in the lower parts of the brain. These propagate to the cerebral cortex at more advanced stages of the disease.

Current treatments use a precursor of dopamine or derivatives of the neurotransmitter called agonists, which attempt to restore the normal concentrations of dopamine, but also **deep brain stimulation.**

Dr. Etienne Hirsch's team has demonstrated the crucial role of neuro-inflammation, responsible for neuronal death, by studying the interactions between dopaminergic neurons and cells of the immune system. These discoveries open up new therapeutic avenues, because they enable us, thanks to a better understanding, to identify molecules to effectively treat Parkinson disease effectively.

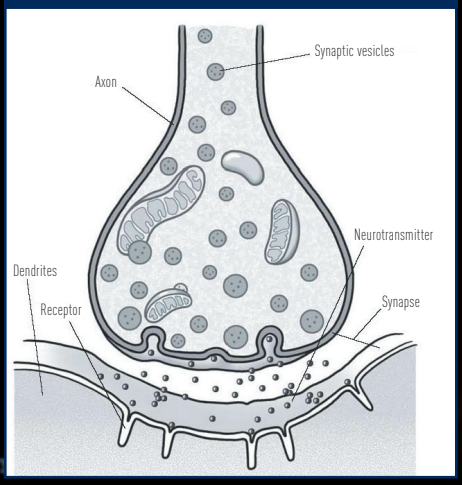
Prof Alexis Brice's team is adressing the problem of the pathogenic mechanism by studying families with the disease. The study of their genetic heritage has already led to the identification of major genes involved in the pathology and has enabled us to understand its underlying mechanisms.

Prof Marie Vidailhet's team has followed groups of subjects, both healthy and ill, over several years in order to indentify precursors of the disease with the view of promoting very early diagnosis.

As we've previously seen, nerve impulses are responsible for neuronal transmission, however, when the activity is too great, they result in abnormal, paroxysmal (very brief) electrical discharges by neurons in the cerebral cortex. These are called **epileptic seizures.**

The causes are numerous, such as a lesion caused by a brain tumour, the consequences of a stroke or brain trauma, or genetic abnormality. The epileptic focus can be

A SYNAPSE



brain regions. Since neurons are no longer protected, nerve impulses are disturbed. At the ICM, **Pr. Bertrand Fontaine**'s team is working across several fields of research: genetics, immunology and neurobiology. As part of an international network studying MS, this team is trying to determine how the immune process might favour endogenous re-myelination. Their work has opened up new therapeutic possibilities.

With innovative cellular tools, **Pr. Catherine Lubetzki**'s team, in collaboration with a group led by Anne Baron, has succeeded in identifying new molecules naturally present in the organism that can stimulate the synthesis of the myelin sheath. In parallel, Pr. Lubetzki's team has developed new markers for brain imaging that enable the visualization of lesions through positron emission tomography.

Another approach at the ICM, coordinated by Anne Baron and **Brahim Naït-Oumesnar,** consists of evaluating the potential to produce myelin from **stem cells** to later be transplanted into patients.

Last but not least, Brahim Naït-Oumesnar has identified a new synthetic molecule derived from vitamin E that can reduce the appearance of inflammatory lesions and restore myelin production.

THE MOTOR BRAIN

The motor brain controls gestures and movements. **Brodmann's** motor area, which is located frontally, commands every muscle in the body. The neurons found at this level are called **pyramidal cells.** Their particularity is that they have very long axons, grouped together in bundles, that project to the lowest part of the brain, **the bulb.** The pyramidal tract then crosses and descends along the lateral parts of the spinal cord, activating the motoneurons that stimulate the muscles. The cerebellum coordinates movements and the basal ganglia make them more precise.

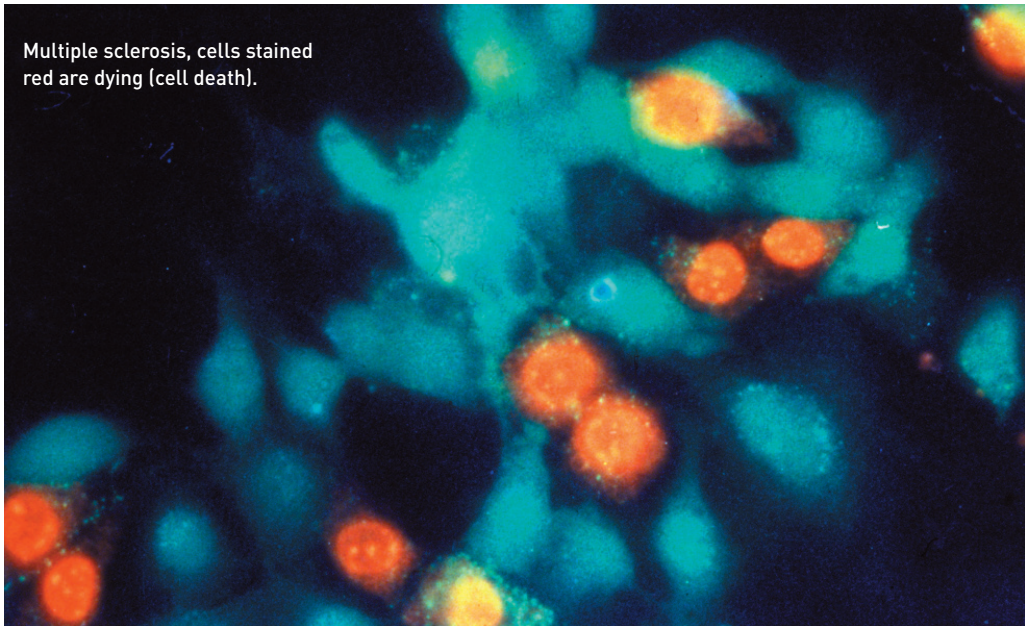
Dystonias, which are characterized by sustained muscle contractions and abnormal postures, are movement disorders. Other types of movement disorders are Gilles de la Tourette syndrome and Parkinson disease.

Marie Vidailhet 's team is exploring the relationships between anomalies in neuronal circuits and deep brain structures, such as the basal ganglia, the cerebellum and the brain stem, and abnormal functions (motricity and behaviour). Their aim is to identify the brain networks responsible for abnormal movements in patients, in particular those with dystonia.

situated at the occipital, frontal or temporal lobes. The seizure, which has a tendency to spread, "inflames" a larger part of the cortical surface. The patient, who was alert up until this point, loses consciousness and may experience convulsions.

Their implantation at the Pitié-Salpêtrière Hospital has allowed the research teams of **Pr. Eric Leguern** and **Stephanie Baulac, Pr. Stéphane Charpier,** and **Richard Miles** to work, collaborating with hospital departments in close contact with epileptic patients. Research axes in the fields of genetics and electrophysiology are multiple and complementary.

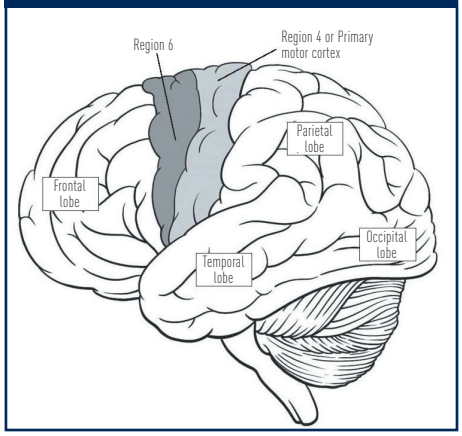
Multiple sclerosis (MS), an inflammatory and autoimmune disease, is characterized by the destruction of myelin in multiple



Multiple sclerosis, cells stained red are dying (cell death).

INTEGRATED FUNCTIONING OF THE

REPRESENTATION OF THE MOTOR BRAIN



Amyotrophic lateral sclerosis (ALS) is a severe neurodegenerative disease characterized by progressive muscular paralysis due to the degeneration of motoneurons in the primary motor cortex, brain stem and spinal cord.

This neuromuscular disease, for which there is no effective treatment, is the object of very active research at the ICM. **Edor Kabashi**'s team is using zebra fish as a vertebrate model to characterize the genes implicated in ALS and other neurodegenerative diseases. By combining technological advances with the zebra fish model, they are developing fish that will enable us to understand the disease mechanisms and screen for candidate drugs.

Stéphanie Millecamps, a researcher in a team led by Séverine Boillée, is looking for new genetic anomalies implicated in ALS by studying the genes of affected persons.

In collaboration with clinical departments, Séverine Boillée and her team are also studying the fate of motoneurons in the spinal cord, looking for ways to slow the disease. They have confirmed the implication of a specific type of glial cell, called microglia, in the development of ALS. With their mouse models, they have shown the influence of these cells on the speed with which the disease spreads.

Other neurodegenerative diseases that affect motoneurons, like hereditary spastic paraplegias, are the object of research at the ICM led by **Alexandra Dürr** and **Giovanni Stevanin,** as part of Alexis Brice's team.

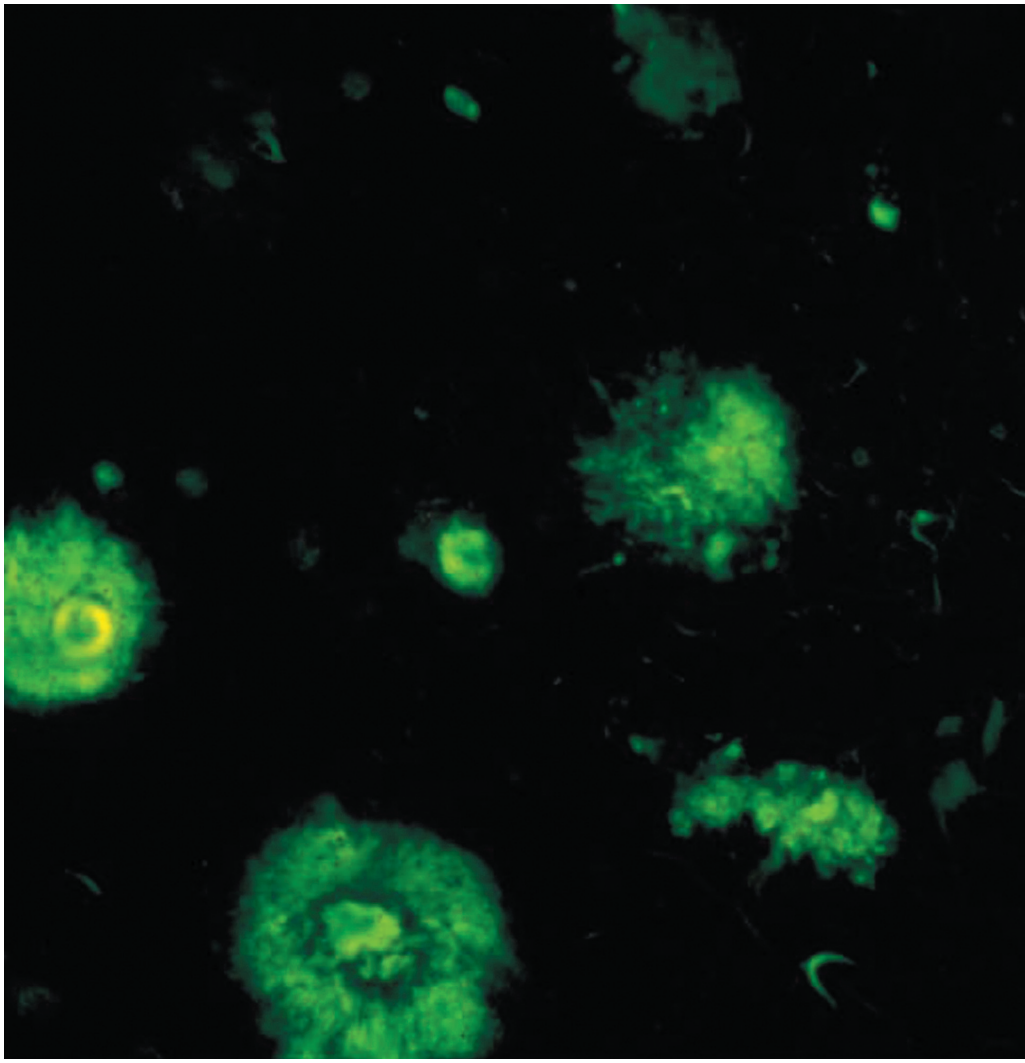
Memory

The structural and functional supports of memory in the brain are beginning to be understood. There are 2 types of memory: short-term memory and long-term memory. Memories are first stocked in the brain regions implicated in the initial experience and are consolidated during sleep. They are then retrieved by neurons in the frontal lobe.

Memories are constructed in the circuit of the **hippocampus** and grey matter structures deep with in the brain, **the circuit of Papez** (thalamus, amygdala, mammillary bodies and fornix). The latter is implicated in the expression of emotions. It should be recalled that the hippocamus is one of the only regions where new neurons are created from stem cells. This **neurogenesis** increases with physical activity and learning.

The highly complex structural and functional organisation of the brain can undergo deregulations that cause neurodegenerative disorders, such as **Alzheimer disease,** that are accompanied by dementia. In this case, patients only retain old memories. This can be explained by the fact that these memories have been conserved and consolidated by the hippocampus. Once damaged, this structure is no longer able to construct new memories or consolidate those that are relatively recent (less than 5 years).

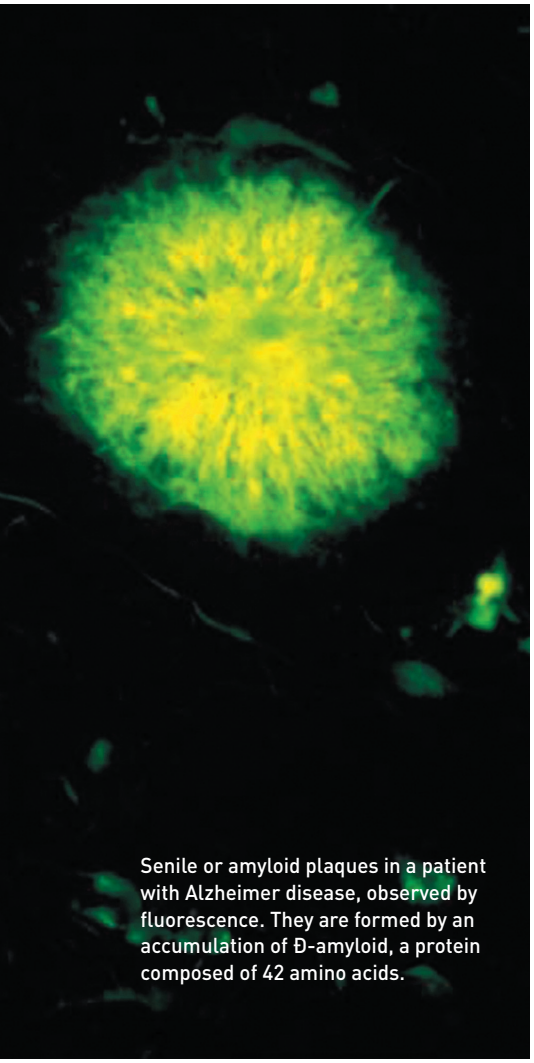
At the ICM, **Marie-Claude Potier**'s team is attempting to understand the physiological mechanisms of this degeneration. These researchers are interested in the production and secretion of amyloid peptides that form senile plaques.



BRAIN, COGNITIVE TASKS

Thanks to the combination of clinical observations in patients with brain lesions and the exceptional technical platform provided by the ICM, **Pr. Bruno Dubois**' team has increased its knowledge of brain functioning. They have shown that Alzheimer disease can be diagnosed 3 years before the first clinical signs appear, due to the presence of specific memory disorders (of the hippocampal type) and the modification of certain proteins in the cerebrospinal fluid.

There are similarities between Alzheimer disease and prion disease. A team of researchers led by **Stéphane Haïk** has shown in brains of patients affected by prion disease, that the prion protein accumulates in the form of amyloid.



Senile or amyloid plaques in a patient with Alzheimer disease, observed by fluorescence. They are formed by an accumulation of Đ-amyloid, a protein composed of 42 amino acids.

Language and reading

Only humans have cortical regions adapted to spoken language and reading. Language results from a collection of tasks carried out in different regions of the brain: the **Wernicke area** (understanding words) and **Broca area** (producing words) connected by a fibre tract. Language disorders are termed **"aphasia."** **Pr. Laurent Cohen** is studying the brain processes that underlie reading, in particular the recognition of letters and words.

The social brain: the emotional brain versus the rational brain

The emotional brain coexists with the rational brain (frontal cortex). It produces our thoughts, our actions, our desires and our motivations. Situated at the centre of the brain, the small structures implicated are primarily the **hypothalamus,** the **nucleus accumbens** (centre of pleasure, part of the basal ganglia) and the **amygdala** (centre of emotions such as fear, stress). The rational brain constantly adapts our behaviour. The brain regions solicited are located in the prefrontal cortex. The latter integrates sensory and emotional information, organizes actions over time and plans human behaviour as a function of our environment.

Loss of social control is linked to neuronal dysfunction in the prefrontal cortex (presence of a tumour, frontal dementia). The ICM is very active in the field of **cognitive neurosciences. Nathalie George,** researcher, and **Pr. Philippe Fossati,** clinician and researcher, are trying to understand how the concerned brain regions are coordinated for dynamic and flexible cognitive functioning. In particular, they are studying the treatment of emotional and social information during depression.

Mathias Pessiglione, Jean Daunizeau and **Sébastien Bouret** are studying the biological and psychological bases of motivation.

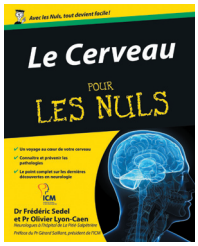
Finally, **Luc Mallet**'s team is trying to identify the role of the basal ganglia in neuropsychiatric disorders, in particular obsessive compulsive disorders (OCD). They have recently developed new treatments using deep brain stimulation.

Sleep and consciousness

Sleep is a complex function involving numerous brain structures. The transition from a waking to a sleeping state is triggered by a system called "flip-flop," situated at the centre of the brain in the anterior hypothalamus. Chemically, a substance called **"adenosine",** present in the extracellular medium of the brain, seems to be responsible for the sensation of falling asleep. Clinicians and researchers are studying certain sleep pathologies, such as Kleine Levin restless leg syndrome, a rare neurological disorder of unknown origin that is characterized by episodes of hypersomnia associated with cognitivo-behavioural disorders. Very recently, **Pr. Marie Vidaihet** showed that certain sleep disorders are early markers of Parkinson disease.

Primary consciousness designates different levels of vigilance, ranging from a deep coma to complete wakefulness. The circuit implicated originates in the brain stem and passes through the thalamus. It then activates somatosensory neurons in the cortex. Neuromediators, such as acetylcholine, noradrenaline, dopamine, serotonin, as well as hormones provide the chemical support for primary consciousness.

Prs. Laurent Cohen and **Lionel Naccache,** clinicians and researchers, recently participated in the development of a system that quantifies the distribution of information in the brains of patients who are unable to communicate. Their initial results have shown that this parameter increases systematically in function with the patien's state of consciousness of the patient. With these tools, it is now possible to predict whether a patient will awake from a coma. Understanding of higher level consciousness has greatly progressed over these past few years, thanks to approaches combining electrophysiology and functional neuroimaging, advanced technologies that are present at the ICM.



We thank the editor of *"Le Cerveau pour les Nuls"* by Dr. Frédéric Sedel and Pr. Olivier Lyon-Caen (Editions First) for the schemas presented in this article.

NEWS

SPORTING AND CULTURAL EVENTS TO BENEFIT THE ICM

Music Passion Parkinson

The concert organized by the association Music Passion Parkinson of Caissargues was a success; all of the funds collected were allocated to the ICM.

Who said that card games and generosity didn't go together? The Parisian bridge club **BC13,** presided by Mr. Hitier Hubert, at the initiative of Ms Tran Anne, supported medical research by dedicating their regular tournament, November 26, 2013, to the Institute.

On January 22, 2014, at the initiative of the **Chambre Syndicale Internationale de l'Automobile et du Motocycle (CSIAM),** and in partnership with AMC promotion, organizer of the Salon de la Moto, salon professionals joined together to support the ICM.

Liz McComb at the Olympia in support of the ICM

Monday, January 27, Liz McComb's concert at the Olympia, the incredibly energetic gospel diva, provided the occasion for the first gala of the year of the Brain and Spine Institute.

SPECIAL VISITORS TO THE ICM

On Tuesday, December 17, 2013, Mr. Claude Bartolone, President of the Assemblée Nationale, met with researchers of the Brain and Spine Institute – ICM.

On Thursday, January 16, 2014, **Ms. Geneviève Fioraso, Ministre de l'Enseignement Supérieur et de la Recherche,** met with different members of the research community in the presence of Pr. Gérard Saillant, President of the ICM, M. Frédéric Salat-Baroux, President of the IHU-A-ICM, M. Jean Glavany and Pr. Yves Agid, Founding members of the ICM, Pr. Alexis Brice, Director General of the ICM and Pr. Bertrand Fontaine, Director of the IHU-A-ICM. The research axes of the ICM, a Carnot Institute, were presented during her visit.

ICM PARTNER OF PIERVAL SANTE

The 1st « SCPI à fonds de partage » has been launched, in partnership with Euyrale AM. The SCPI, accredited by the AMF, will invest in real estate and health, particularly in neurodegenerative diseases. Donations to support research at the ICM can be made as part of a subscription.

PRESTIGIOUS PRIZES FOR THE ICM

- **Dr. Luc Mallet** received the **Marcel Dassault 2014 "Researcher of the year"** prize for his research on OCD.
- The **Fondation Marie-Ange Bouvet La Bruyère – ICM prize** was attributed to Mohamed El Behi for his work on multiple sclerosis.
- The **Young Woman Scientist 2013** prize was received by **Claire Wyart,** doctor in biophysics and neuroscience and researcher at the ICM in the field of motor control.
- Fabien Vinkier, researcher at the ICM, won the **Louis Forest** prize of the chancellery for his thesis "Physiology and physiopathology of visual word recognition."
- The ICM, in partnership with its publicity agency, Publicis, received the **3rd prize in the "display" category** for its campaign, "Lost in the Métro."

AT THE HEART OF THE ICM

The ICM not only hosts scientific events, but is also a space where different worlds, literary and philosophical for example, meet to discuss subjects of interest for the neurosciences. The Institute had the privilege of welcoming, for its prestigious extra-scientific lectures, major personalities who presented their reflections on diverse fascinating subjects. These have included over the past months, **Jean-Pierre Changeux,** neurobiologist, Professor at the Collège de France and member of the Académie des Sciences, **Luc Ferry,** renowned writer and ex-Ministre de la Jeunesse, de L'Education Nationale et de la Recherche, **André Comte-Sponville,** philosopher and member of the Comité Consultatif National d'Ethique (CNE) and finally **Jean Claude Ameisen,** President of the CCNE.

André Comte-Sponville and Luc Ferry at the ICM

Société des Neurosciences

IN EUROPE AND IN MORE THAN 30 CITIES IN FRANCE

Brain Awareness Week

March 10 to 17, 2014

At the Brain and Spine Institute 47 Bd de l'Hôpital Paris 13

Monday March 10 — **Lecture**

Inaugural lecture. Brain: the underside

Christophe Mulle (President of the Society for Neuroscience)
Roland Salesse (Coordinator of Brain Awareness Week in France)
Alexis Brice (Director General of the ICM)
6:30 PM Reservation recommended* **Auditorium of the Brain and Spine Institute.**

The localization in the brain of mental processes fascinates and sometimes gives rise to interpretations.

Wednesday March 12 and Saturday March 15 — **Workshops and Visits**

An afternoon at the Brain and Spine Institute

2:00 PM Reservation recommended* **Workshops on the research carried out in the Institute, laboratory visits and photography exhibit.**

Wednesday March 12 — **Lecture**

Hysteria: the source of Charcot's vision

Catherine Bouchara (psychiatrist), Lionel Naccache (neurologist, researcher at the ICM)
6:00 PM Reservation recommended* **Auditorium de the ICM Lecture followed by a discussion.**

Wednesday March 12 — **Movie-debate**

In Praise of Movement

Alexandra Dürr (ICM neurogeneticist), Iris Trinkler (ICM researcher), David Gil (director), Philippe Chehere (choreographer), Françoise Pétry (Chief Editor of Cerveau et Psycho)
8 :00 PM Cinéma Le Grand Action - 5 rue des Ecoles Paris 5e

Documentary on the benefits of dance for patients with Huntington's disease.

*Reserve on semaineducerveau.fr

Find more details at: semaineducerveau.fr/paris

ICM Institut du Cerveau et de la Moelle épinière

MY RECURRENT DONATION

Please fill out and return this form with your contribution and your bank identification (RIB) to the following address: Institut du Cerveau et de la Moelle épinière, Hôpital de la Salpêtrière - 47/83 bd de l'Hôpital 75013 PARIS

☒ **YES, in 2014, I will provide long term support for the researchers of the ICM with a contribution of:**

❑ 10 € ❑ 20 € ❑ 30 € ❑ 40 €

❑ Other amount: .....€

❑ Every month ❑ Quarterly

Starting on 05/...../2014*

*The date can be one month later, depending on when the first withdrawal is authorized.

IMPORTANT:
Don't forget to include your RIB (BIC-IBAN)

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By signing this form, you authorize the ICM to instruct your bank to debit your account, and your bank to debit your account according the instructions of the ICM. You can be reimbursed by your bank according to the conditions that you have established together. A request for reimbursement must be presented within 8 weeks of the date of an authorized withdrawal, and without delay or at the latest within 13 months of a non-authorized withdrawal. Your rights concerning the present authorization are explained in a document you can procure from your bank.

REDUCE YOUR ISF WHILE SUPPORTING RESEARCH

By supporting the innovative research projects of the ICM, you can reduce your "Impôt de Solidarité sur la Fortune."

What amount can be deducted?

75% of the amount of your donation to the ICM can be deducted from your ISF, up to 50000€ (corresponding to a donation of 66667 euros). This limit is reduced to 45000€ if you also invest in PME.

How do I calculate and reduce the amount of my ISF?

The calculation in 2014 is the same as in 2013. Your assets above 1.3 million euros net are taxable, according a progressive scale that is the same as in 2013.

If you wish to reduce your ISF to 0 by making a donation, apply the following formula:

Amount of your ISF/0.75 = Amount of your donation.

What are the final dates for a donation and the ISF declaration?

The ISF calendar for 2014 has not been established as we publish this newsletter. We therefore invite you to follow the information related to ISF donations**, which will be published on our internet site: www.icm-institute.org.**

You can also contact directly our Donor Relations Contact, **who is at your entire disposal to answer your questions, assisted by fiscal advisors:**

Ms Carole CLEMENT- 01 57 27 44 87 - carole.clement@icm-institute.org

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ICM Brain & Spine Institute

ONE-TIME DONATION FORM

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☒ YES, I support the research programs of the ICM

on brain diseases and traumatisms of the spinal cord

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..... €

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❑ **By credit card** ❑ CB ❑ CB BLEUE VISA ❑ MasterCard

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Your contribution to the ICM is deductible from your income tax up to **66% (within the limit of 20% of your taxable revenue) or 75% of your ISF** (within the limit of 50 000 euros).

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

Information concerning you is needed for us to obtain your donation and prepare your fiscal receipt. In conformity with the law "Informatique et Libertés" you can access, rectify and delete information simply by writing to the ICM, 47, boulevard de l'hôpital -75013 Paris. You can refuse the use of your address by third parties by checking the box ❑.

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