The Institute of Brain Sciences in Toulouse is a multidisciplinary research centre with interests in a wide range of subjects, such as neurons and cognition and genes and disease.

The fundamental unit of the nervous system, the neuron, is now better known thanks to advances in cellular and molecular biology and in genetics. To decrypt neuronal codes underlying higher cognitive functions such as perception, attention, movement, learning, memory, language and even thought, is the main goal of research in neuroscience. This goal can only be reached thanks to a multidisciplinary approach.

Seeing how the brain functions, identifying neuronal networks underlying cognitive function and monitoring their activity over time is the goal of the Institute of Brain Sciences in Toulouse (ISCT).

The ISCT aims at promoting the interactions between the different actors in neuroscience research in Toulouse by associating basic and targeted research, focusing on elucidating the mechanisms behind cognitive function and dysfunction in nervous system diseases. The ISCT has a MRI 3T machine dedicated to this research.

One site
Opened in October 2011, the refurbished “Pavillon Baudot” houses approximately 220 people (researchers, clinicians, engineers and students) and over 2000m² of offices organized around a modern technical plateau. Piloted by INSERM, CNRS, Université Paul Sabatier, Université du Mirail and the CHU Toulouse, this project is supported by local communities and the government through two successive state-region plans.

A wide range of skills
Researchers from different fields, such as integrative neurophysiology, cognitive neuroscience, clinical neurology, neuropsychology, pharmacology, linguistics, neuroimaging, neuroanatomy and developmental biology of the brain...
work together. Various brain functions, such as vision, hearing, smell, motor skills, language, learning and memory are studied through complementary methods that require both clinical, pharmacological and experimental approach in animals (from bees to primates), healthy people and patients. The teams thus bring together expertise in a wide variety of areas related to life sciences, sciences, engineering and social sciences.

**Large neuroimaging equipment**

These teams have access to equipment in functional neuroimaging, combining MRI, PET, evoked potentials and transcranial magnetic stimulation for studies on human and primates. It is now possible to justify, in terms of neuronal circuitry hypotheses, the relationships between the brain and cognition. One of the major objectives of the ISCT is to be able to describe the neuronal computations localised in structures of the brain identified and known to be involved in various cognitive functions.

**Models and complementary approaches**

Knowledge of brain function in humans is incomplete and certain descriptions of the relationship between structure/function (brain connectivity and characterization of neuronal activities underlying these functions) remain inaccessible. These require detailed invasive methods of investigation possible only in animals. With in the ISCT, clinical pathophysiology and neuropsychological studies that analyse functional disturbances associated with lesions of the brain in humans are being conducted in animals using invasive methods that establish links between neuronal activity and integrative functions.

**Elucidating mechanisms behind cognitive functions**

One of the main goals of the researchers of the Institute is to characterize sophisticated brain function. The integrative approach using different models and techniques allows us to investigate these functions in a coherent way. This is the case for memory, for example, that is being studied at the fundamental level through animal and human models, applied to patients suffering from neurodegenerative diseases. Some examples are illustrated in this dossier.

**Neurological deficits and brain diseases**

This integrative approach is thus a privileged field of research for characterizing neurological deficits and their mechanisms, in the field of brain reorganization, functional recovery, as well as in managing handicap following various acute and chronic brain injuries. Aging and Alzheimer’s disease, and neurodegenerative or neurovascular diseases, are also being studied by characterization of motor or cognitive disturbances in animal models such as mice with amyloid plaques or focal lesions, to diagnosis of MRI cortical thicknesses and therapeutic evaluations using fluorinated molecular imaging techniques in patients.

**The six ISCT laboratories**

The ISCT brings together six laboratories or teams: The Research Center Brain and Cognition (CerCo, UPS/CNRS), Centre for Research on Animal Cognition (CRCA, UPS/CNRS), the Brain Imaging Laboratory and Neurological Disability (ICHN, Inserm/UPS), the Laboratory of perceptual and motor adaptation and learning (Lapma, UPS), the interdisciplinary research unit Octogone (University of Toulouse-Le Mirail) and the Clinical Neurosciences pole in Purpan.
Memories

The human memory is compartmentalised. Identifying and characterizing the different systems involved in memory has been one the great advances in the field of cognitive neuroscience in the last few decades.

The systems making up human memory are relatively independent of one another and can be separately affected by different pathologies, and particularly by neurodegenerative diseases. For example, Alzheimer’s disease affects explicit or “declarative” memory (memory of facts and events), but leaves implicit or “procedural” memory intact. This memory, which is the unconscious memory of skills and how to do things, is, however, affected by Parkinson’s and Huntington’s diseases. Declarative memory depends upon an ensemble of structures situated in the internal part of the temporal lobes, of which the most well known is the hippocampus. Research at Toulouse focuses on these particular internal structures.

Memory dysfunction

Scientists at CerCo and the Laboratoire imagerie cérébrale et handicaps neurologiques are studying how declarative memory is intrinsically organized. Their work has allowed to evaluate the memory of patients suffering from focal cerebral lesions, following, for example, brain haemorrhage, and the memory of patients suffering from lesions that are more spread out, such as is the case in Alzheimer’s disease. One of the main goals of this research is to show the neuronal correlations that exist between recall memory and recognition memory that would be supported by different regions of the internal part of the temporal lobe (the hippocampus and sub-hippocampus regions respectively). Preliminary work on Alzheimer’s disease that combines different imaging techniques (MRI and PET scans), the researchers have shown that structural, metabolic and molecular lesions are linked to the onset of problems in declarative memory recall. Another study that involved the use of cerebral electrodes on drug-resistant epileptic patients (during routine treatment to treat their disease) showed that temporal and spatial cerebral activity was reduced during memory tasks. This work was performed in collaboration with doctors at the Toulouse CHU.

Normalizing memory

A team from the Octogone Interdisciplinary Research Unit at the University of Toulouse le Mirail is studying patients with epilepsy of the median temporal lobe and patients that have undergone a temporal lobotomy in an attempt to control drug-resistant epilepsy. This work looks at the patients’ memory of personal events and their memory of public ones. The results show that patients with this type of epilepsy have trouble remembering public events but recall personal ones. Surgery of the temporal lobe does not appear to have a significant effect on either personal or public memory recall.

Post-traumatic stress

The Crca team is studying memory in rodents, and in particular the role of the hippocampus in the CA3 region when it comes to consolidating and reconsolidating memory. This latter process is very important because the reactivation of a memory trace that had been previously consolidated makes it unstable again. In order to re-stabilize this reactivated memory trace and to re-stock it once again in the long-term memory, it must undergo a process called “reconsolidation”. It is thus possible to act upon this memory reconsolidation and modulate it or delete it by blocking certain processes involved in memory reactivation. Indeed, we have succeeded in blocking the reconsolidation of an unpleasant memory in rodents thanks to the beta-blocker propranol. In collaboration with the psychiatric department at the Toulouse CHU, similar results were obtained in patients suffering from post-traumatic stress disorder.

Contacts

emmanuel.barbeau@cerco.ups-tlse.fr; voltzenlogel@univ-tlse2.fr; roullet@cict.fr; jeremie.pariente@inserm.fr
The brain revealed by multimodal neuroimaging

To explore the human brain, markers are employed to help accentuate specific functions during imaging. Such biomarkers are being developed and tested at the Institut des sciences du cerveau in Toulouse (ISCT).

It would be impossible to understand how the brain functions without all the different neuroimaging instruments available today. These instruments have led to a significant number of advances in the field.

**Atrophy**

The majority of current structural neuroimaging work focuses on the extent and localization of brain atrophy as a marker of physiological and pathophysiological change. But, other markers of microstructural change can be obtained from MRI. Indeed, MRI can also measure iron deposits and the microstructure and orientation of this iron. ISCT teams have shown that MRI is able to distinguish between the brains of Parkinson’s disease patients and the brains of healthy subjects in a study involving 30 PD patients and 22 control subjects. A simple MRI exam can, by simultaneously measuring different brain parameters, diagnose Parkinson’s disease with more than 95% reliability, thus revealing its «brain signature».

**Laboratory of excellence**

At the ISCT, new tracers in the field of neuroscience, particularly concerning diseases related to cognitive impairment, cerebral ischemia and neuroinflammation, are being developed. The syntheses are performed using a platform that permits fluoridation and radiopharmaceuticals quality control. The ISCT has access to a PET scan coupled to a CT scan. Combining these two techniques allows researchers to explore numerous physiological and pathophysiological processes in vivo after injection of radiopharmaceuticals. These advances were awarded the LABEX IRON (Innovative Radiopharmaceuticals in Oncology and Neurology) earlier this year. Many translational and clinical projects are also currently looking at the possibility of using PET and MRI techniques. For example, a PET tracer for amyloid and a measure of cortical thickness in MRI are currently being used in various protocols to better understand the pathophysiology of Alzheimer’s disease.

**Temporal precision**

Finally, electroencephalography (EEG) is a technique that records the brain’s electrical activity through dozens of electrodes placed on the scalp. Although it is less suited than MRI to precisely isolate the brain areas involved in each cognitive mechanism, it has the advantage of very high time resolution. Using EEG, one can observe the dynamics of brain activations over times scales of milliseconds, or follow fast oscillating rhythms of several tens of cycles per second, commonly observed in sensory processing tasks. As shown by recent work by the CREMe CerCo team, we can detect certain brain activity patterns that may indicate a state of alertness or «attention wandering». Visual perception, in turn, comes and goes periodically, following a specific EEG rhythm. Far from being mutually exclusive, these neuroimaging techniques therefore appear to be quite complementary.

**Contacts**

patrice.peran@inserm.fr, payoux.p@chu-toulouse.fr and ruffin.vanrullen@cerco.ups-tlse.fr

**Black substance, loss of microstructural orientation**

**Multi-parametric MRI signature of Parkinson’s disease**

Patrice Péran, senior Inserm scientist (Inserm/UPS), Pierre Payoux, university and hospital professor at the Laboratoire imagerie cérébrale et handicaps neurologiques (ICHN, joint Inserm/UPS lab) and Ruffin VanRullen, senior CNRS scientist at the Centre de recherche cerveau et cognition (joint UPS/CNRS lab)
Unravelling the secrets of vision

Human beings are exceptionally good at perceiving their surroundings - a remarkable achievement given the complexity of this environment! Vision plays a major role and in primates and about a third of the cortex is devoted to this sense.

The ISCT research laboratories study all aspects of normal or pathological vision and focus on pre-attentive and attentional vision, vision in creatures all the way from honeybees to monkeys, vision in children and adults and vision in biological and artificial systems. The CerCo plays a special role since all four of its research teams are interested in vision: vision of space, objects, and action, working at multiple scales from single neurons up to the whole individual.

Episodic vision

Significant results have been obtained in recent years that have had a major impact on some standard dogmas. For example, while most people think of visual perception as a continuous phenomenon, our laboratory recently showed that cortical excitability in the visual system fluctuates periodically with oscillations following the «alpha» rhythm (of around 10Hz). Thus, our visual perception is not continuous but is instead an episodic process, sampling the world rather like a video camera.

Other studies have shown that the brain favours visual processing in a region of space that is of crucial importance: the «straight ahead» region. When you want to analyze an object in detail, your eyes will move so that the image of the object is processed by the «fovea», the region of the retina most densely packed with receptors.

But consider the situation where we move our eyes to an object of interest - for example, a shop while walking down the street. The image of the part of space that is «straight ahead» would now be processed by the peripheral retina and should be much less efficient. But it turns out that the brain uses a trick that favours the processing of this crucial region of space. Specifically, when an eye movement brings the receptive field of a visual neuron into the «straight ahead» region, a study in the lab found an increase in the neuronal response.

Ocular saccades

We make sequential saccadic eye movements to explore our world. Recently the use of a saccadic choice test based on fast eye movements has drastically constrained the temporal limits of visual processes.

We had already demonstrated the impressive speed of visual processing, for example in the case when humans and monkeys have to categorize objects such as animals, faces or vehicles in natural scenes. The fastest manual responses can be seen at latencies of around 250-70 milliseconds. But our eyes can move towards a target-object at much shorter latencies: 120 ms when the target is an animal, and only 100 ms when the target is a face! Considering the complexity of underlying processes needed to solve such a recognition task, this remarkable speed is a major challenge for current models of object recognition.

Vision improved by hearing

Finally, our perception of the surrounding world is not only visual - it is multisensory in essence. Other senses, such as hearing, for example, can be improved when combined with visual formation. We recently demonstrated the important role of learning in such multisensory behaviour. When only one ear is used, it is difficult to locate a sound in space, but performance improves after only a few trials during which the sound is associated with visual information. Such mechanisms open the door to rehabilitation strategies based on multimodal interactions in people with profound hearing loss and in patients fitted with a cochlear implant.

The miniature brain of the honeybee

The honeybee is a well-established animal model for studies on vision. Bees perceive and learn colours and shapes if these stimuli are paired with a drop of sugar solution. Recently, it has been shown that bees can also learn to categorize visual stimuli. Moreover, calcium-imaging recordings in visual areas of the bee brain have uncovered complex retinotopic processing mechanisms. These experiments, conducted at the CRCA (UMR 5169), show how the miniature brain of bees processes visual information.
Cerebral plasticity

The brain possesses astounding abilities to adapt. Well understood, these could be used to help patients recover following cerebral lesions and to improve hearing.

The Therapeutic innovations in cerebrovascular diseases team in the “Cerebral imagery and neurologic handicap” laboratory is looking into strategies for clinically treating stroke. Their main result is that spontaneous cerebral plasticity and more precisely ipsilesional activity must be encouraged. Non-invasive stimulation focused on the cerebral cortex can help when it comes to motor recovery. Prozac, an antidepressant, modulates cerebral plasticity and helps patients recover their independence. Other strategies rely on cerebral bioprosthesis (cellular therapy combined with biomaterials) that are currently being tested on animals.

Improving motor coordination

Bimanual coordination is particularly altered in elderly people and daily life activities such as buttoning up a cardigan or tapping on a keyboard become difficult. The Programme de recherche interdisciplinaire et sciences du sport et du movement humain team is focusing on improving motor coordination. Recent results from the team show that when participants have to produce bimanual movements that coordinate with sounds, images or sounds plus images, the stimuli seems to benefit the elderly more than younger people when it comes to synchronizing their movements. This finding suggests a form of plasticity in the cerebral regions that are responsible for auditory-motor function in the elderly.

Deafness and cortical plasticity

The plastic properties of the brain play an important role in rehabilitating serious deafness using a cochlear implant. A Cerco team, working with the ORL department at the CHU Purpan is looking at the parts of the brain deprived of auditory signals and how the spoken word is recuperated following a neuro-implant. During long periods of deafness, the regions dedicated to the treatment of sound are “taken over” by those involved in vision. This reflects a vicarious mechanism developed by patients that begin to rely more on sight for understanding language — that is, by lip reading. Following a cochlear implant, this reorganization regresses with time and the patients recover their hearing abilities. This result is encouraging for patients with hearing implants and is based on cortical plasticity combined with relevant retraining strategies.

Troubles with memory

Memory formation relies on cerebral function modifications that affect cerebral plasticity. The Mémoire, plasticité et vieillissement team at Crca tracks these cerebral modifications in healthy mice and in Alzheimer’s disease models. Their work shows that memorizing information requires the synthesis of new proteins in the hippocampus, which is the seat of memory. More surprising still, other proteins must be degraded for the memory to subsist. Studies by the team indicate that new neurons form in the adult brain that participate in coding memory. This process is disturbed in mice models and in Alzheimer’s disease and could contribute to the memory dysfunction characteristic of this disease.

Contacts

pascal.barone@cerco.ups-tlse.fr
Claire.Rampon@cict.fr
jessica.tallet@univ-tlse3.fr
isabelle.loubinoux@inserm.fr

Language and the brain

Language is one of the most complex brain functions. It plays a major role in human relations and in the relationship between humans and their environment. Understanding how the brain treats language is a challenge for researchers and requires multidisciplinary methods.

The effect of training on the ability of dyslexic patients to better recognize the written versus the spoken word was evaluated by monitoring their behaviour and by using the methods outlined in this article. We were able to show that different training techniques can have different effects depending on the task and the type of dyslexia the patient has. Here, we see a modulation in cerebral activity following visual exposure to written letters after phonological training.

Based mainly on MRI and PET techniques, we have been able to explore the neural networks of language in several populations. In healthy subjects, we have been able to identify different pathways for semantic and phonological processing. Moreover, the role of each hemisphere – more bilateral for language comprehension and more lateralised in the left hemisphere for production – has been explored.

Recovery from aphasia

When it comes to language disorders, a number of studies have investigated the mechanisms that allow a stroke-damaged brain to recover efficient language function following aphasia. We believe that this cerebral plasticity relies on areas immediately adjacent to those destroyed by the stroke, within the left hemisphere, which is the dominant hemisphere for language function. Recovery appears to be better when perilesional areas can be used for language rather than when language function simply has to rely on more distant areas, particularly in the right hemisphere. Moreover, exploring cerebral areas involved in recovery following rehabilitation suggest that the perilesional areas of the left hemisphere are better suited when it comes to supporting recovery of language function than areas in the right hemisphere, although they are symmetrical to the destroyed areas. Investigating the dynamics of neuro-functional systems following a handicap will allow us to improve recovery techniques, especially during the early stages of the disease.

Brain mapping

A combination of techniques using transient inactivation of cortical activity during surgery under "awake" conditions and functional MRI has allowed scientists to investigate one of the areas involved in writing: the superior premotor cortex. This area, dubbed the "agraphia area" in the last century, has been formally identified as the writing centre. The same technique has been used to explore the areas involved in the processing of different languages in multilingual subjects. The preliminary findings suggest that the processing of a later learned language generally activates larger zones within the language areas than the processing of languages acquired early in life. Moreover, the prefrontal dorsolateral cortex, for instance, seems to play a key role in selecting and controlling the relevant language.

With an increasing number of multi-linguals in the world, research on how the brain processes each of the different languages is becoming more important. The progress of interdisciplinary research conducted by linguists and neuroscientists allows us to explore new research fields involving more complex language functions such as pragmatics or prosody for example.

Contacts

xavier.deboissezon@inserm.fr & melanie.jucla@univ-tlse2.fr
& bkopke@univ-tlse2.fr