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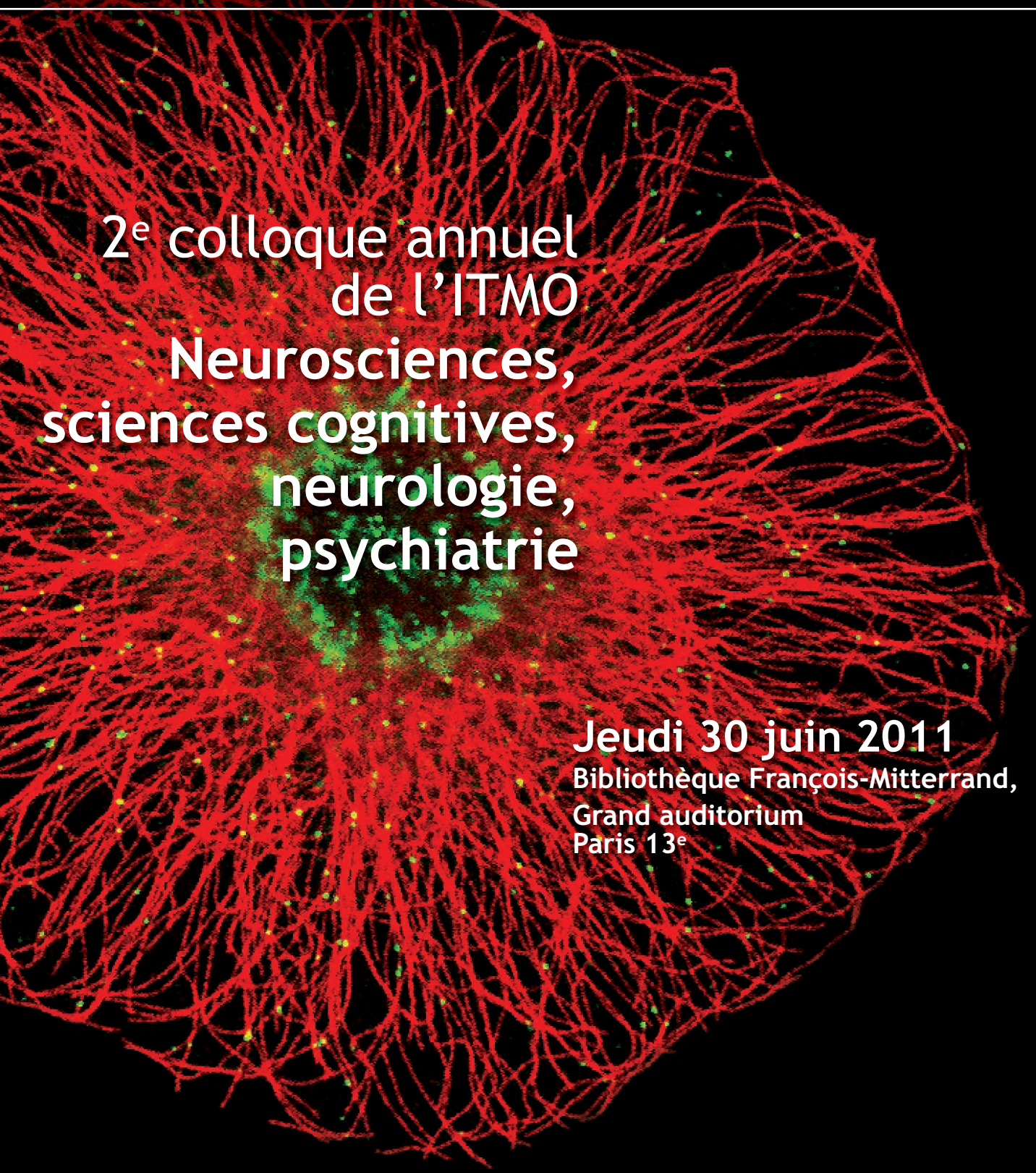

2e colloque annuel de l'ITMO Neurosciences, sciences cognitives, neurologie, psychiatrie

Jeudi 30 juin 2011
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Jeudi 30 juin 2011

2ème Colloque annuel

ITMO

NEUROSCIENCES, SCIENCES COGNITIVES, NEUROLOGIE ET PSYCHIATRIE

Grand Auditorium de la Bibliothèque Nationale de France
Quai François-Mauriac, 75013 Paris

9:00	**Café d'accueil**
9:30	L'Institut Thématique Multi-Organisme neurosciences cognitives, neurologie, psychiatrie : Actualités *The thematic multi-organization institute (ITMO) Neurosciences, cognitive sciences, neurology and psychiatry : News* - **Alexis Brice** et **Bernard Bioulac**, *Directeurs de l'ITMO Neurosciences*
10:15	Les neurosciences au rendez-vous de la première vague d'appels à projets des investissements d'avenir/*Neuroscience is one of the winners in the first wave of the call for proposals : "Investments for the Future"* - **Laure Sabatier**, *Directeur scientifique, MESR, Paris*
10:40	Alliance pour la recherche et l'innovation des industries de santé (ARIIS) : Focus sur les partenariats Public/Privé en Neurosciences / *Alliance for Research and Innovation in Health industry (Ariis): Focus on Public / Private partnerships in Neuroscience* - **Pierre Teillac**, *Président d'ARIIS, Paris*
11:05	Neuro-éthique/*Neuro-ethics* - **Jean-Michel Besnier**, *Professeur de philosophie à l'université de Paris IV- Sorbonne*
11:30	Des propriétés émergentes du projet "Blue Brain" au projet « Human Brain » / *From the Emergent Properties of Blue Brain to the Human Brain Project* - **Henry Markram**, *Blue Brain Project, EPFL, Lausanne, Suisse*
12:15	**Déjeuner - Buffet**
	Session scientifique
14:00	Restauration visuelle dans les dégénérescences rétiniennes, entre génomique, prothèses et optogénétique / *Visual restoration in retinal degeneration : genomics, prostheses and optogenetics* **José-Alain Sahel**, *Centre de Recherches Institut de la Vision UPMC-Inserm-CNRS, Paris*
14:45	Neuromodulation implantée en psychiatrie : stimulation haute fréquence de relais limbiques au sein des ganglions de la base / *Intracranial neuromodulation in psychiatry : high frequency stimulation of limbic relays in the basal ganglia* - **Luc Mallet**, *CRICM, Inserm UMR_S 975 - CNRS UMR 7225 – UPMC, Institut du Cerveau et de la Moelle épinière, CHU Pitié-Salpêtrière, Paris*
15:05	Le rôle de l'ocytocine dans le comportement social et dans le cerveau humain / *How oxytocin affects the human brain and behavior* - **Angela Sirigu**, *Centre de Neuroscience Cognitive, Lyon*
15:25	**Pause-café**
15:45	Réseaux de signalisation associés au récepteur 5-HT6 de la sérotonine : une nouvelle cible pour le traitement des déficits cognitifs de la schizophrénie / *Signalling network associated to serotonin 6 receptor : toward a new target for the treatment of cognitive deficits in schizophrenia* - **Philippe Marin**, *Institut de génomique fonctionnelle, Montpellier*
16:05	La question du choix dans les modèles animaux d'addiction / *Animal models of drug addiction* - **Serge Ahmed**, *Institut des maladies neurodégénératives, Bordeaux*
16:25	Nouveaux territoires pour les neurosciences de la rationalité / *New territories for neuroscience of rationality* – **Jean-François Bonnefon**, *CLLE, CNRS, Toulouse*
16:45	Neuro-éducation : comment la lecture et la scolarisation modifient-elles le cerveau humain ? / *Neuro-education : How learning to read and schooling change the human brain ?* - **Stanislas Dehaene**, *Collège de France, NeuroSpin, Paris*
17:30	**Conclusion**

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Résumés / *Abstracts*

Session scientifique / *Scientific Session*

RESTAURATION VISUELLE DANS LES DEGENERESCENCES RETINIENNES, ENTRE GENOMIQUE, PROTHESES ET OPTOGENETIQUE

VISUAL RESTORATION IN RETINAL DEGENERATION : GENOMICS, PROSTHESES AND OPTOGENETICS

José-Alain SAHEL
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Centre d'Investigation Clinique du Centre Hospitalier National d'Ophtalmologie des Quinze-Vingts;
Institute of Ophthalmology-University College London

With Serge Picaud, Thierry Léveillard, Saddek Mohand-Said, Michel Paques
(Institut de la Vision, Paris), ***Ernst Bamberg*** *(MPI Frankfurt)* and ***Botond Roska*** *(FMI, Basel)*

In retinal dystrophies, multiple gene mutations lead to degeneration of rod photoreceptor cells and secondarily cone photoreceptor cells, leading eventually to blindness. Gene corrective strategies are logical and have been efficient in selected situations. Importantly, retinal degenerations do not destroy the retinal inner circuitry, and, for often several years, cone photoreceptor cells, the later degenerating progressively through a secondary non cell autonomous mechanism. Thus, preservation and stimulation of remaining retinal neurons and circuits offers strong promise for avoiding blindness, as:

- Retinal prostheses can be implanted and restore useful vision in blind patients, by stimulating inner retinal neurons forming the optic nerve, following intensive rehabilitation programs,

- Delivery through gene therapy of channelrhodopsins and halorhodopsins to, respectively, inner retinal cells or remaining cone cell bodies restores visual functions in animal models and post-mortem human retinas,

- Such « dormant » remaining cone cells can be visualized with innovative high resolution, non-invasive, *in vivo*, imaging and layering, thereby enabling the selection of blind patients that can benefit from these strategies.

We shall try to demonstrate that a translational approach, integrating imaging technologies developed by astronomers, nanotechnologies and prosthetics, molecular pathobiology, optogenetics and gene therapies provides a spectrum of diagnostic, prognostic and therapeutic tools, enabling the fight against blindness from untreatable orphan genetic diseases.

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NEUROMODULATION IMPLANTEE EN PSYCHIATRIE : STIMULATION HAUTE FREQUENCE DE RELAIS LIMBIQUES AU SEIN DES GANGLIONS DE LA BASE

INTRACRANIAL NEUROMODULATION IN PSYCHIATRY: HIGH FREQUENCY STIMULATION OF LIMBIC RELAYS IN THE BASAL GANGLIA

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Deep brain stimulation (DBS), widely recognised in the treatment of Parkinson's Disease and other movement disorders, could also be used as a therapeutic procedure for sub-cortical dysfunction leading to emotional and other behavioural disorders. Its reversibility, adaptability and low morbidity rates suggest that DBS interventions on certain well-defined neural structures are likely to improve the symptomatology. By precisely targeting deep brain circuits implicated in psychiatric disorders, DBS offers hope for the alleviation of severe illnesses resistant to drug therapies; and, furthermore, provide a novel tool to investigate the neuroanatomic and physiological bases of certain disorders. Currently, DBS is employed or is in the course of development for the treatment of Essential Tremor, Parkinson's Disease, Dystonia, Epilepsy, Obsessive-Compulsive Disorder (OCD), Tourette's Syndrome (TS) and Major Depression, for which early results indicate positive therapeutic outcomes. OCD is characterized by persistent, intrusive and unpleasant thoughts, impulses or images, and recurrent, time-consuming behaviors which are performed in order to reduce the anxiety caused by obsessions. TS is characterized by motor and vocal tics and associated with self-injurious behaviors as well as compulsive behaviors. The pathophysiologies of OCD and of TS share dysfunctions of the associative and limbic circuits running between cortical and sub-cortical structures. Among the latter are the basal ganglia which consist of central grey nuclei which process motor, cognitive and emotional cortical information and send back a message to the frontal cortex. Functional imaging studies in OCD patients show an abnormal metabolic activity of the orbito-frontal and cingulate cortices, as well as of the anterior part of the striatum suggesting a dysfunction of the prefronto-basal ganglia circuits. Recent pathophysiological hypotheses suggest that TS symptoms result from a dysfunction of the basal ganglia circuitry, notably of the ventral striatum. These data are consistent with the supposed function of cortico-basal ganglia circuits in habit learning and routine performance of habits. Based on early reports indicating that high-frequency stimulation of structures along the prefronto-basal ganglia axis might be effective in alleviating OCD and TS symptoms, DBS is being tested across the world at several nodes of this circuit, including the subthalamic nucleus, pallidum, striatum, internal capsule/ventral striatum and thalamus. Increasing our knowledge of the functional organization of the prefronto-basal ganglia circuits and of their dysfunction in pathological repetitive behaviors would certainly contribute to better define the surgical therapeutic targets, thereby improving available treatments. Other psychiatric disorders (e.g. addictions) are also candidate pathologies for similar treatment – conditional on the formulation of precise hypotheses as to which neural networks are involved and on the severity and resistance of the disorder to non-invasive therapies. The development of such innovative treatment needs to be implemented in clinical research centres, in order to provide expert evaluation, selection, and management of these refractory patients. The implantation procedures and the closely circumscribed patient monitoring, particularly at the ethical level, have ensured that neurostimulation has become a valuable tool to clarify the neural bases of emotional disorders particularly in relation to the wider functions of the basal ganglia.

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LE ROLE DE L'OCYTOCINE DANS LE COMPORTEMENT SOCIAL ET LE CERVEAU HUMAIN

HOW OXYTOCIN AFFECTS THE HUMAN BRAIN AND BEHAVIOR

Angela SIRIGU
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Social skills require specific cognitive and emotional competences. Individuals with High Functioning Autism (HFA) cannot engage in social interactions despite preserved cognitive abilities. Recently, it has been suggested that oxytocin, a hormone known to promote affiliation and mother-infant bonds, may be implicated in the social deficit of HFA. We investigated the effects of intranasal oxytocin administration on the social behavior of HFA patients.

We used a double-blind, placebo-controlled within-subject design to study social behaviour of thirteen patients diagnosed with HFA after intranasal inhalation of 24 IU oxytocin compared to placebo. In one task, we developed a new social interaction paradigm, based on probabilistic algorithms, where participants interacted with fictitious partners. In a second task, we measured eye movement pattern, during examination of faces. Plasma oxytocin measures were performed using specific enzyme-immunoassay technique.

When participants interacted with fictitious partners, we found that after oxytocin inhalation, patients exhibited stronger interactions with the most socially cooperative partner, and reported enhanced feelings of trust and preference. Also, during free viewing of pictures of faces, oxytocin selectively increased patient's gazing time on the socially-informative region of the face, i.e. the eyes.

These findings suggest that oxytocin enhanced patients' capacities to process facial stimuli and to learn from social relevant cues to interact with other partners. Our results highlight the therapeutic potential of oxytocin through its action on core deficits of autism.

RESEAUX DE SIGNALISATION ASSOCIES AU RECEPTEUR 5-HT6 DE LA SEROTONOMIE : UNE NOUVELLE CIBLE POUR LE TRAITEMENT DES DEFICITS COGNITIFS DE LA SCHIZOPHRENIE

SIGNALLING NETWORK ASSOCIATED TO SEROTONIN 6 RECEPTOR: TOWARD A NEW TARGET FOR THE TREATMENT OF COGNITIVE DEFICITS IN SCHIZOPHRENIA

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Cognitive deficits are important symptoms in psychiatric disorders such as schizophrenia and are not efficiently treated by current antipsychotic therapies. The serotonin $(5\text{-HT})_6$ receptor, which is predominantly expressed in brain regions controlling cognition, has recently emerged as one promising target for treating cognitive dysfunction. 5-HT_6 antagonists are in clinical development in schizophrenia as cognition enhancing agents. However, the signalling mechanisms that mediate modulation of cognitive functions by 5-HT_6 receptors remain largely unknown. Using a shotgun proteomic approach, we demonstrated that 5-HT_6 receptors physically interact with several proteins of the mammalian target of rapamycin (mTOR) pathway, including mTOR itself, and that activation of 5-HT_6 receptors increases mTOR signalling in prefrontal cortex and striatum. Correspondingly, acute treatment of rats with the mTOR inhibitor rapamycin prevented behavioural deficits induced by peripheral administration of 5-HT_6 agonists as well as those observed in developmental models of schizophrenia in rodents. These findings provide novel insight into the molecular substrates of the control of cognitive processes by 5-HT_6 receptors and identify 5-HT_6 receptor-elicited mTOR signalling as a new target to alleviate cognitive deficits observed in the majority of schizophrenic patients. They exemplify the power of functional proteomics to decipher receptor-operated signal transduction underlying their role in complex physiopathological processes.

LA QUESTION DU CHOIX DANS LES MODELES ANIMAUX D'ADDICTION

ANIMAL MODELS OF DRUG ADDICTION

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The most perplexing aspect of cocaine addiction from a rational choice perspective is that addicted individuals apparently behave against their best interests and judgments. They continue to seek and to take cocaine despite an awareness of its harmful consequences and a desire to make a better. Everything happens as if individuals were unable to correctly evaluate the consequences of their choices, thereby systematically overestimating the expected value of future drug use. As a result, daily life and activities are centered on drug procurement and consumption, to the detriment of other, more beneficial courses of actions. One of the critical challenges for the neuroscience of addiction is to identify the neurobiological dysfunctions that explain why value-based decision-making is impaired in addicted individuals and biases action selection toward excessive drug choices.

One hypothesis that is currently gaining strength is that cocaine addiction would result from an underlying dysfunction in the orbitofrontal cortex (OFC), a phylogenetically conserved prefrontal cortical region that is also dysfunctional in other compulsive disorders. The OFC is a core component of the brain valuation system that automatically encodes, represents and compares the expected values of available actions. The resulting value information would then be sent downstream to the dorsal striatum to bias action selection toward the most valued. In cocaine addiction, the valuation and comparison functions of the OFC would be systematically biased in favor of drug use. This hypothesis is consistent with recent neuroimaging data showing decreased metabolic activation of the OFC during abstinence and increased activation during cocaine craving. However, because of limitations in the spatial and temporal resolution of brain imaging technologies and in the correlational design of human studies, the origin, nature and causal effect of this dysfunction remains poorly understood.

At this stage, further scientific advancement in our understanding of OFC involvement in cocaine addiction will require parallel experimental research on laboratory animals. Paradoxically, however, though cocaine addiction has long been conceptualized in reference to a rational choice framework, little research on animals has examined drug use in a context of choice. In virtually all previous research, animals had free access to cocaine with no valuable alternative actions. As a result, serious doubt exists about the pathological status of cocaine use in animals. Do animals take cocaine because they are addicted or simply by default of other rewarding activities? As it turns out, we recently found in rats – the most frequently used animal model in experimental addiction research – that when offered an alternative choice, most cocaine self-administering rats abstain from cocaine in favor of the nondrug pursuit. Only a minority continues to take the drug despite the opportunity of making a different choice and increasing stakes. This pattern of individual variation in rats (cocaine abstinence in most rats; cocaine preference in few rats) fits the known epidemiology of cocaine addiction which only affects a minority of drug users and thus suggests that only a minority of vulnerable rats would take cocaine by compulsion. The remaining majority of cocaine-self-administering rats would be resilient to addiction, taking the drug merely by default of other choices and abstaining when another valuable pursuit is available. The overarching goal of our research proposal will be to study the minority of drug-preferring individuals to elucidate what is awry in OFC functions that explain pathological decision-making in cocaine addiction.

NOUVEAUX TERRITOIRES POUR LES NEUROSCIENCES DE LA RATIONALITE

NEW TERRITORIES FOR NEUROSCIENCE OF RATIONALITY

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The main rational activities have already entered the realm of neurosciences: The neuroeconomics of decisions and the neuroethics of moral judgments are well-identified fields of research, and the classic tasks of the psychology of reasoning are undergoing systematic neuroscientific investigations. The new frontiers of the neuroscience of rationality should rather be sought within the themes that started their migration from the human sciences into experimental psychology or experimental economics. This migration process implies an effort of operationalization and systematic collection of empirical facts, which bodes well for the transition to a cerebral level of description. Two examples are considered in this presentation: Politeness effects in the coordination of collective rational activities, and the deleterious effects of mortality awareness on rational thought. In the two cases, a concept enshrined in non-experimental fields (politeness, mortality awareness) is identified as potentially having a transversal effect on the whole set of rational activities. In order to test that hypothesis, an experimental psychology program is deployed, which requires to define manipulations and measures of politeness and mortality awareness, and to integrate them with the protocols used to study rational thought. The deployment of such experimental programs is conducive to the transition to a neuroscientific approach.

NEURO-EDUCATION : COMMENT LA LECTURE ET LA SCOLARISATION MODIFIENT-ELLES LE CERVEAU HUMAIN ?

NEURO-EDUCATION : HOW LEARNING TO READ AND SCHOOL CHANGE THE HUMAN BRAIN?

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L'espèce humaine est la seule à augmenter ses compétences par l'éducation. Mon laboratoire mène des recherches qui visent à mettre en évidence la manière dont la scolarisation, et particulièrement l'apprentissage de la lecture, modifient le traitement de l'information dans le cerveau humain. Je présenterai une série de recherches qui comparent les performances et les activations cérébrales chez des personnes alphabétisées ou non. Les résultats montrent que l'apprentissage de la lecture modifie, non seulement la région que nous avons appelée « l'aire de la forme visuelle des mots » et qui code les chaînes de lettres, mais également de nombreux autres systèmes cérébraux : la représentation des visages dans les deux hémisphères ; l'aire visuelle primaire, dans sa partie qui code pour la zone horizontale où apparaissent les mots ; et la région du *planum temporale* qui représente la phonologie du langage parlé. Ces modifications de l'organisation fonctionnelle du cortex, visibles en IRM fonctionnelle, s'accompagnent de modifications comportementales. Elles sont compatibles avec l'hypothèse du *recyclage neuronal*, selon laquelle tout apprentissage scolaire doit s'appuyer sur la reconversion de circuits neuronaux responsables d'une fonction proche dans l'évolution. J'esquisserai certaines conséquences de ces recherches dans le domaine de l'éducation de l'enfant.

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