SEVENTH FRAMEWORK PROGRAMME

N€UROMED

Building Capacities for Mediterranean Neuroscience

Proceedings of the

IInd International meeting of the Mediterranean Neuroscience Network – N€UROMED

Fez – Morocco

June 10-11, 2010

neuromed

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Proceedings

Of the

2nd International meeting

Of the

Mediterranean Neuroscience Network – N€UROMED

June 10-11, 2010

Fez, Morocco

Organizing committee

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Table of Contents

N€UROMED organizes two kinds of scientific workshops: local workshops designed to create local, national networks on specific issues and International, consortium-wide workshops aimed at creating bilateral and multi-lateral interactions between N€uromed members.

The 1st N€uromed general workshop was organized in Marseille, at the kick off meeting in January 2010. Six months later, this 2nd workshop aims to bring the consortium members closer together around the four themes of the project.

The format of this workshop is as follows. There will be one session dedicated to each theme. Each session will start with a keynote lecture which provides participants with an up to date review of the state of current research. This will be followed by short presentations (10 minutes + 5 min discussion per presentation). At the end of each session, there will be a general discussion which will try to focus attention on the strengths for N€uromed - scientific or technical issues on which we can work to sustain collaborations, and apply for EU and other international funding.

A poster session is also planned. All members are strongly encouraged to visit the posters and discuss with their authors. Finally, the programme includes two special lectures: a public lecture on psychiatry, and an internal keynote lecture on history. The abstracts have been peer reviewed by independent experts, and are published online.[1]

Finally, a session entitled "open session" will be dedicated to new ideas and projects. This could be, in particular, research proposals that have emerged from permanent staff exchanges of the last six months, or any new scientific issues on which a member may wish to have input from the other members.

The chairwomen/Chairmen have a major role to play in the scientific success of this workshop: they are asked to read all the abstracts of their respective sessions in advance, chair the session and organize the discussion that follows it in order to come up with conclusions on how and where we can build sustained research networks.

We hope that this format will promote high quality discussion, create opportunities for new ideas and collaborations, and help our consortium build sustained scientific networks ready to apply for grants. N€uromed resource members will present opportunities offered by the 2010 heath call in FP7.

On behalf of the Organizing Committee and the SMC members, I warmly welcome you to this important event. Let us do everything possible to make it successful, and build the future!

Special thanks to the external referees who helped us with the abstract reviewing process.

Driss Boussaoud

[1] http://frontiersin.org/conferences/individual_conference_listing.php?confid=967&ind=1

Programme of the workshop

Thursday, 10 June - Venue: Palais des Congrès

8:30 OFFICIAL OPENING CEREMONY & WELCOME COCKTAIL

10:00 How to get funding to develop your research projects? **Joumana Sweiss**, Aix-Marseille University (Marseille, France) and **Hayat Benmoussa**, University Sidi Mohamed Ben Abdellah (Fez, Morocco).

Session 1: Brain diseases and their treatment – Chaired by Abdelhamid Benazzouz & Eman Khedr

11:00 Keynote speaker. Neurotoxicity, a major health concern in Morocco. **Nouria Lakhdar-Ghazal**, Mohamed V University, Rabat, Morocco.

11:30 Parkinson's disease: From pathophysiology to new therapeutical approaches. **Abdelhamid Benazzouz**, CNRS & University of Bordeaux, Bordeaux, France.

11:45 Cognitive functions and transcranial magnetic stimulations. **Eman Khedr**, University of Assiut, Egypt.

12:00 Learning by observation in schizophrenic patients. **Mohamed Agoub**, Hassan II University, Casablanca, Morocco.

12:15 Insight in bipolar disorder. **Marc Adida**, CNRS & Aix-Marseille University, Marseille, France.

12:30 Lunch

13:30 Cannabinoids transduction signal pathway in GT1-7 immortalized hypothalamic and AtT-20 cell lines. **Mohammed Errami**, University Abdelmalek Essaadi, Tetouan, Morocco.

13:45 Molecular Mechanisms of Neurological Alterations in Hepatic Encephalopathy. **Marta Llansola**, Centro de Investigacion Principe Felipe, Valencia, Spain.

14:00 Neurosteroids: emerging players in the pathophysiology of hepatic encephalopathy and other neurologic disorders. **Samir Ahboucha**, Cadi Ayyad University, Marrakech, Morocco.

14:15 General discussion: where are the strengths for N€uromed? (30 min)

14:45 Coffee break

Session 2: Adaptation to environmental stress – Chaired by Mohamed Najimi & Rabia Magoul

15:15 Keynote speaker. Corticosterone: a clock endocrine output involved in the circadian functioning of serotoninergic neurons. **Paul Pévet**, Strasbourg University, Strasbourg, France.

15:30 Water deprivation affects the neural and glial system in a desert rodent the Meriones Shawi. **Halima Gamrani**, Cadi Ayyad University, Marrakech, Morocco.

15:45 EM66-containing neurons in the hypothalamic parvocellular paraventricular nucleus of the rat: No plasticity related to acute immune and thermal stress. **Rabia Magoul**, Sidi Med Ben Abdallah University, Fez, Morocco.

16:00 Differential effect of stress on neurogenesis in rat adult central nervous system. **Mohamed Najimi**, Moulay Slimane University, Béni-Mellal, Morocco.

16:15 Arrhythmogenicity of Epinephrine-Induced Hyperadrenergic Activity: Applied evidence at the level of the organ and the organism. **Miran K. Rakha**, Suez Canal University, Ismailia, Egypt.

16:30 General discussion: where are the strengths for N€uromed? (30 min)

17:00 Public lecture - Chaired by Mireille Besson

Psychiatric diseases. **Omar Battas**, University Hassan II, Casablanca, Morocco.

Friday, 11 June - Venue: Hotel Menzeh Zalagh

Session 3: The plastic brain: implications for learning and education – Chaired by Marie Moftah & Halima Gamrani

8h30 Keynote speaker. Neuroplasticity and learning. **Driss Boussaoud**, CNRS & Aix-Marseille University, Marseille, France.

9:00 Subcortical cytoskeleton and neuroplasticity in hypothalamo-neurohypophysial system of rats and mice. **Latifa Dorbani-Mamine**, USTHB, Algiers, Algeria.

9:15 Experimental hyperthyroidism disrupts hippocampal long-term potentiation but not paired pulse facilitation in adult rats. **Seda Artis**, Medical Faculty of Erciyes University, Kayseri, Turkey.

9:30 Coffee break

10:00 Neurogenesis after complete spinal cord transection in *Pleurodeles waltlii*. **Marie Moftah**, Alexandria University, Alexandria, Egypt.

10:15 Organization of corticospinal projections in control and knockout-AC1 adult mice. **Mohamed Bennis**, University Cadi Ayyad, Marrakech, Morocco.

10:30 The musician brain as an excellent model of brain plasticity. **Mireille Besson**, CNRS & Aix-Marseille University, Marseille, France.

10:45 Evaluation of perceptual and mnemonic deficits in children. **Ahmed O.T. Ahami**, University Ibn Tofail, Kenitra, Morocco.

11:00 General discussion: where are the strengths for N€uromed? (30 min)

11:30 Plenary Lecture – Chaired by Nouria Lakhdar-Ghazal

History of mediterranean Neuroscience: The path to N€uromed. **Wail Benjelloun**, Mohamed V University, Rabat, Morocco.

12:30 Lunch

Session 4: Technological developments for neurosciences – Chaired by Fakhita Regragui & Yazid Cherfa

14:00 Dynamics of neuronal activity during mental training. **Fakhita Regragui**, LIMIARF, Mohamed V University, Rabat, Morocco.

14:15 Virtual Reality and Neuroscience. **Beatriz Rey Solaz**, LabHuman, Valencia, Spain.

14:30 Image processing for the detection of functional areas affected by stroke in the brain MRI. **Yazid Cherfa**, Saad Dahlab University, Blida, Algeria.

14:45 Diffusion fMRI and BOLD-fMRI: Towards a better Understanding of white and grey matter's function. **Said Boujraf**, University Sidi Mohamed Ben Abdellah, Fez, Morocco.

15:00 General discussion: where are the strengths for N€uromed? (30 min)

15:30 Coffee break

16:00-17h30 POSTER SESSIONS (1h30)

Session 5: Open session (1h30) – Chaired by Driss Boussaoud & Mohamed Errami

New ideas and collaborations (30 min)

Future events (15 min)

Summary and closing words (45 min)

19:00 Social events

----------End of the Scientific Sessions----------

Saturday, 12 June – Strategic Management Committee (SMC) meeting (9h-13h)

Poster titles

P001: Neurodegenerative diseases – Chaired by Eman Khedr & Mohamed Bennis

1. Therapeutic role of repetitive transcranial magnetic stimulation in obsessive compulsive disorder: randomized control trail. **M. Abdel-Rahman**[2], Assiut University, Egypt
2. Iron Deficiency Anemia Correlates with Cognitive Performances of Schoolchildren in Morocco. **Y. Aboussaleh**, A.O.T Ahami, M. El Hioui, S. Rusinek, F. Bonthoux. University Ibn Tofail, Kenitra, Morocco.
3. Anticonvulsant effect of butanolic extract of *Anacyclus pyrethrum* roots in rat. M. Ben el Fakir, Z. Sokar, M. Bennis and **S. Ba M'hamed**. Cadi Ayyad University, Marrakech, Morocco.
4. Psychomotor development of exposed mice offspring to fenugreek seeds. L. Khalki, Z. Sokar and **S. Ba M'hamed.** Cadi Ayyad University, Marrakech, Morocco.
5. *Perna perna* (Mollusca, Bivalvia): evaluation of pollution on the neuroseceretory cells of cerebroid ganglia and sexual cycle during an annual cycle. Klouche M.S., Idardare Z., Moukrim A., **Lakhdar-Ghazal N.**, **Benomar S**. Mohamed V University, Rabat, Morocco.
6. Impact of pollution in neurosecretory cells of ganglia nerves of Molluscan Mytilidae : Approach of the neuroendocrine control. **Benomar S.**, Aarab L., Klouche M.S., Moukrim A., Yacoubi B. and Mathieu M. Mohamed V University, Rabat, Morocco.
7. Chronic hyperammonemia induces tonic activation of NMDA receptors in cerebellum leading to a decrease of neuronal nitric oxide synthase activity. **N. El Mlili**, Carmina Montoliu, Hanan Ahabrach, Omar Cauli, Amparo Urios, Errami Mohammed and Vicente Felipo. Fundación Hopital Clínico and Centro de Investigacion Principe Felipe, Valencia, Spain; Univ. Abdelmalek Essaadi, Tetouan, Morocco.
8. Persistent effect of aluminum chronic toxicity on memory in adult Wistar male rat. **Azzaoui F-Z** and Ahami A.O.T. Unit of Clinic and Cognitive Neuroscience and Health, Laboratory of Biology and Health, Department of Biology, Faculty of Science, Ibn Tofail University, Kenitra, Morocco.
9. Calcitonin-induced sleep disturbance in rat when injected in the lateral ventricle and into the periaqueductal gray. R. Aboufatima, A. Zyad, J. Hafid, **A. Chait**. Faculté des Sciences Semlalia, Cadi Ayyad University, Marrakech, Morocco.
10. Clinical and genetic aspects of spastic paraplegia. **A. Benomar**, Mohamed V University, Rabat, Morocco.

P002: Neuroplasticity – Chaired by Marie Moftah & Driss Boussaoud

11. Neural correlates of observational learning in non human primates. Belmalih A., Thura D., Isbaine F., Brovelli A., Demolliens M., Meunier M. and **Boussaoud D**. INCM-CNRS & Aix-Marseille University, Marseille (France)
12. Lack of melanopsin in ganglion cells and its impact on retinal clock. Lahouaoui H., Dkhissi-Benyahya O. and **Bennis M**. Cadi Ayyad University, Marrakech, Morocco; Department of Chronobiology, INSERM U846, Bron, France.
13. Organization and functioning of the circadian clock of a diurnal rodent, *Lemniscomys barbarous.* **Ouarour A.**, Faculty of Science, Abdelmalek Essaadi University, Tetouan, Morocco.

[2] *Names in bold: presenting authors*

P003: Adaptation to environmental stress – Chaired by Paul Pévet & Seloua El Ouezzani

14. Neuronal adaptive mechanisms of desert vertebrates: Morphofunctional investigations. **Z. Barka**, A. Dekar and S. Ouali, USTHB, Algeria
15. Anorexigenic and orexigenic factors regulation in the rat dorsal vagal complex during stress-induced anorexia. **F. Chigr**, M. Najimi, F. Rachidi, C. Tardivel, J. Trouslard, E. Moyse. Sultan Moulay Slimane University, Béni-Mellal, Morocco ; CRN2M, Labo PNV, Aix Marseille Univeristy, Marseille, France.
16. Kisspeptin in the hypothalamus of the jerboa: sexual dimorphism and seasonal variation. Janati IA, Ansel L, Klosen P, Magoul R, Mikkelsen JD, Pévet P, Simonneaux V, **EL Ouezzani S**. Sidi Mohamed Ben Abdellah University, Fes, Morocco; INCI, Department of Neurobiology of Rhythms, Strasbourg University, Strasbourg, France.

P004: Technological developments – Chaired by Fakhita Regragui & Beatriz Rey

17. Comparative Study between Bias Correction Algorithms in Magnetic Resonance Imaging. **A. Cherfa** and Y. Cherfa. Laboratory of research in medical imagery, University Saad Dahlab of Blida, Algeria.
18. 3D MR Brain Images segmentation using fuzzy methods: FCM and BCFCM. A. Cherfa and **Y. Cherfa**. Laboratory of research in medical imagery, University Saad Dahlab of Blida, Algeria.
19. Brain MRI segmentation by snakes. Image processing for the detection of functional areas affected by stroke in the brain MRI. **Y. Yazid** and **A. Cherfa**. Laboratory of research in medical imagery, University Saad Dahlab of Blida, Algeria.
20. Original Molecule versus Generics of Antidepressants Commercialized in Morocco: A BOLD-fMRI Study in healthy subjects. **S. Farah**, J. Darwish, I. Kamaoui, S. Tizniti, F. Belahssen, S. Boujraf.

Abstracts – Oral presentations and Lectures

Session 1: Brain diseases and their treatment
Chaired by Adelhamid Benazzouz & Eman Khedr

Keynote Speaker: Neurotoxicity, a major health concern in Morocco

Nouria Lakhdar-Ghazal
Research Unit on Biological Rhythms and Environment, Faculty of Science, Mohamed V-Agdal University, Rabat, Morocco

The scientific community is facing a great challenge: the expansion of human populations on a very vulnerable planet. Throughout the world, there are programs trying to protect the environment by saving forests, soils, water resources, clean air and other resources, and by reducing pollution, thereby ensuring the balance of the eco-system. In the South of the world, however, awareness of these problems is recent and public authorities have only just begun to define strategies to preserve the environment. One key issue is brain health and the impact of environmental pollution on morbidity and death due to neurological and psychiatric pathology. The aim of this keynote lecture is thus to describe the impact of polluting particles and agents on brain health. I will refer in particular to the case of Morocco, stressing the importance of high level research and suggesting possible solutions.
In Morocco, traditional and modern industries such as metallurgy, art and crafts, and mining (lead, cobalt, cadmium, copper), combined with uncontrolled use of pesticides in agriculture, polluted food, and polluting vehicles, have led to widespread dispersal of neuro-tosins in the fields and in areas around urban centres. Neurotoxic agents enter the body through the skin, the nasal epithelium, as well as via food and water. Finally they pass the blood-brain barrier reaching the brain. Though this is still a controversial issue, studies are beginning to show a correlation between environmental neurotoxins and neuronal and cognitive pathologies. Morocco has a high incidence of child lead poisoning associated with alterations in learning and memory mechanisms subserved by neocortical and hippocampal functions. The incidence of atypical and idiopathic Parkinson's and Alzheimer's diseases and of cancer is also very worrying and could be related, at least in part, to poisoning by environmental toxins. The neuroscience research units in our University have started to approach these problems. Like others engaged in similar research in other parts of the world we have obtained some very interesting results. This findings show that innovative research into the impact of the environment on brain health should be a high priority for future work.

Parkinson's disease: From pathophysiology to new therapeutical approaches

Abdelhamid Benazzouz
Laboratoire MAC, CNRS-UMR 5227, Bordeaux.

Parkinson's disease (PD) is neurodegenerative disorder characterized by the manifestation of three cardinal motor symptoms: akinesia, rigidity and rest tremor. These symptoms are the consequence of a progressive degeneration of dopamine neurons in the pars compacta of substantia nigra, which results in a depletion of dopamine in the striatum and other brain structures. Functionally, the depletion of dopamine induces a disorganization of the neuronal activity in basal ganglia nuclei and especially in the subthalamic nucleus (STN), which plays a key role in the control of

movement. Several studies in rodent and non human primate models of PD have shown that the depletion of dopamine induced dramatic changes in the discharge pattern of STN neurons. The regular activity recorded in the normal situation was replaced by bursty and irregular pattern of activity, in the pathological situation. During the last two decades, deep brain stimulation (DBS) of the STN has proven to be highly effective in reducing all the cardinal motor symptoms in animal models of the disease as well as in parkinsonian patients suffering from a severe form of PD. However, despite these clinical achievements, the precise action mechanisms of STN-DBS still need to be fully characterized at molecular and cellular level. Our experimental studies have suggested that STN-DBS, at parameters improving motor symptoms, reduced the abnormal hyperactivity of STN neurons. Recently, DBS of other brain regions has proven to be capable of providing significant benefits for several complex motor neuropathologies as essential tremor and dystonia, and also some pharmaco-resistant psychiatric disorders such as Tourette syndrome, obsessive-compulsive disorder and severe depression.

Transcranial Magnetic Stimulation and Study of Human Cognition in Alzheimer patients

Eman Khedr
Neurology Department, Faculty of Medicine, Assiut University Hospital, Assiut, Egypt

Cognition is the ability to perceive, manipulate, integrate, and maintain information to be used in the future action. Cognitive disorder is any impediment of these functions and generally as a consequence of stroke or neurodegenerative disorders. rTMS has been increasingly used to improve deficits including cognitive disorders following damage to the CNS. rTMS studies report improved ability to name pictures after administration of rTMS to the anterior portion of the right homologue of Broca's area in aphasic patients. Stimulations of the right or left dorsolateral prefrontal cortex have been demonstrated to selectively improve picture naming in patients with mild to moderate Alzheimer's disease.
These studies suggest that rTMS may help to restore impaired abilities in physiological aging, in chronic aphasia, and in neurodegenerative disease. These effects appear to be due to rTMS-induced changes in cortical excitability, affecting the functional networks responsible for cognitive performance. Several mechanisms can account for these results; rTMS induces modulation of the neural threshold, or even a rearrangement, of synaptic efficiency (functional plasticity). It may be related to the direct change of activity in the areas immediately underlying the stimulation site, or at the level of connected neural networks. So the goal of the treatment may not be to restore the function of an impaired component, but rather to exploit preserved abilities to compensate for the deficit.

Learning by observation in schizophrenic patients

Mohamed AGOUB[1], Aida SAADOULI[1], Leila HASMI[1], Elisabeta MONFARDINI, Omar BATTAS[1], Martine MEUNIER[2], Driss BOUSSAOUD[2]
[1] Laboratory of Clinical Neurosciences and Mental Health, University Hassan II, Casablanca, Morocco.
[2] INCM-CNRS & Université de la Méditerranée, Marseille, France

Schizophrenia affects approximately 1% of the population, and begins mainly in late adolescence and early adulthood. The etiology and pathogenesis of the disorder are not entirely clear, but it is accepted that it has a multifactorial origin. Contemporary models conceptualize schizophrenia as

a neurocognitive disorder. Cognitive impairment is highly prevalent. The deficit is apparent at the first episode and is a stable, trait-related aspect of the disorder. Cognitive impairment is a predictor of social and occupational outcome as evaluated longitudinally.
Schizophrenic patients display a marked deficit in their ability to correctly attribute actions to self or to others. On this basis, we hypothesize that the inability to identify "who is the actor" could produce a secondary deficit in social, observational learning.
To test this hypothesis, we have conducted a study in a Moroccan sample of patients and controls, matched for age, gender and level of education. The study compared the performance of patients and controls when learning by observation and learning by trial and error. Our paper will discuss preliminary results, and their implications for the social deficits of schizophrenic patients.
Acknowledgment: This work was supported by the GDRI Neuro, CNRST (Morocco) and CNRS (France).

Insight in bipolar disorder

Marc Adida
Sainte-Marguerite Hospital, Department of Psychiatry and Institut de Neurosciences Cognitives de la Méditerranée (INCM), CNRS & Aix-Marseille University, Marseille, France

While the relationship between lack of insight in psychiatric disorders and anosognosia in neurological disorders has not been extensively studied, interest in examining psychiatric lack of insight has roots in advances in the understanding of the anosognosia. It is possible that both conditions share a common etiology in parietal and/or frontal lobe dysfunction, or they may represent two distinct entities with different etiologies, i.e., with predominance of brain dysfunction in anosognosia as opposed to the possible prominence of psychosocial factors in psychiatric lack of insight.
While it has long been recognized that insight is impaired in schizophrenia and other psychotic disorders, the topic of insight in bipolar disorder has been relatively neglected. In mania, impairment of insight is about as severe as in schizophrenia and probably is associated with poor prognosis. The neuropsychological and/or psychosocial roots of lack of insight in mania remain unclear even if we recently reported that lack of insight might predict impaired decision-making in manic patients. In bipolar depression, impairment of insight is less severe than in mania; however, psychotic depression is associated with less insight than non-psychotic depression. There is some evidence that insight in depression may be less impaired when depressive symptoms are more severe, possibly supporting the depressive realism hypothesis. In remission, bipolar patients seem to recover insight. Thus, lack of insight in bipolar disorder appears to be a state-related phenomenon, unlike schizophrenia.
Interest in studying clinical, neuropsychological and biological roots of insight in bipolar disorder, and their changes across different phases of illness, may improve our understanding of mechanisms underlying awareness of well-being in human.

Cannabinoids transduction signal pathway in GT1-7 immortalized hypothalamic and AtT-20 cell lines

M. Errami [1], H. Hoddah [1], L. Bakkali [1], E. Carbone [2] and M. Theodoropoulou [3]
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[2] Department of Neuroscience, Centre of Excellence, Turin, Italy
[3] Max Planck Institute of Psychiatry, Munich, Germany

Cannabinoids chemistry and pharmacology have been the object of thousands of publications over the last 40 years. The mechanism behind the effect of cannabinoïds on brain was investigated by our laboratories using two cell line models: GT1-7 immortalized hypothalamic cells and corticotroph-derived AtT-20 cells transfected with rat cannabinoïd receptors (CB1R).
In GT1-7 cells, we found that the CB1R /CB2R agonist, WIN55,212-2, inhibited the voltage-gated Ca^{2+} currents by about 35%. The inhibition by WIN55,212-2 (10 µM) was reversible and prevented by nifedipine (3 µM), suggesting a selective action on L-type Ca^{2+} channels (LTCCs). At variance with WIN55,212-2, the CB1R inverse-agonist AM251 (10 µM) caused 20% increase of Ca^{2+} currents. The inhibition of LTCCs by WIN55,212-2 was prevented by overnight incubation in pertuxis toxin (PTX) and by intracellular perfusion with Guanosine-5'-O-2- thiodiphosphate (GDP-β-S). The latter caused also a 20% Ca^{2+}current up-regulation. WIN55,212-2 action was also prevented by application of the protein kinase A blocker, H89, or by loading neurons with the cAMP analogue, 8-CPT-cAMP. Our results suggest that L-type Ca^{2+} channels in GT1-7 neurons are partially inhibited at rest due to a constitutive CB1R activity removed by AM-251 and GDP-β-S.
In the AtT-20 cells, the cannabinoïds agonist WIN55,212-2 (1µM) increased proopiomelanocortin (POMC) transcription by affecting several transcriptional factors which control POMC gene promoter. WIN 55,212-2 (1µM) increased the transcriptional activity of the Nur family transcription factors (Nurr1 and Nur77), and also increased the cAMP responsive binding element (CREB) transcriptional activity, while the cannabinoïd receptor inverse agonist AM251 had the opposite effect. The signal transducer and activator of transcription 3 (STAT3) was not affected by CB1 activation.
WIN 55,212-2 (1µM) increased CREB phosphorylation without affecting basal CREB protein levels and this effect was not blocked by PTX. This study suggests a new mechanism of action for CB1 on the regulation of signal transduction pathways at POMC level.
Acknowledgment: This work was supported by the Marie Curie Research Training Network "CavNET", the MIUR (grant COFIN no. 2005054435 to E.C.) and Max planck institute, Munich, Germany.
H. Hoddah was supported by an IMAGEEN European project and CNRST fellowships. L. Bakkali was supported by a DAAD, EMBO and CNRST fellowships.

Molecular Mechanisms of Neurological Alterations in Hepatic Encephalopathy

Llansola M, Cauli O, Monfort P, Agustí A, Abrahach H, Retnikov V, Hernandez V, Cabrera A, González A, Giménez C and Felipo V
Laboratory of Neurobiology, Centro de Investigación Príncipe Felipe, Valencia, Spain

Patients with liver diseases (e.g. cirrhosis) may present hepatic encephalopathy (HE), an alteration in cerebral function which is a consequence of failure of liver function. Patients with HE may present different neurological alterations, as impairment of cognitive or motor functions or altered sleep-wake cycle, which impairs their quality of live. Hyperammonemia is considered a main contributor to the neurological alterations in HE. Animal models of chronic HE (e.g. rats with portacaval shunts) or of ''pure'' hyperammonemia reproduce some of these impaired cerebral functions. Both hyperammonemia and neuroinflammation contribute to the impairment of cognitive and motor functions. We have found a good correlation between the learning ability and the function of the glutamate-nitric oxide-cGMP pathway in rat cerebellum in vivo. Treatment of rats with chronic HE or hyperammonemia by means of inhibitors of phosphodiesterase 5 (that increase levels of cGMP) restores the function of the glutamate-nitric oxide-cGMP pathway in cerebellum as well as the learning ability. The same beneficial effects may be obtained by treating

the rats chronically with an anti-inflammatory compound, ibuprofen. Ibuprofen also improves the hypokinesia in rats with portacaval shunts. Hyperammonemic rats also show altered circadian rhythms of activity due to the impairment of the circadian variation of the hypothalamus-pituitary-adrenal axis. Mechanisms involved in the effects of hyperammonemia and inflammation include alteration in glutamatergic and GABAergic neurotransmission in cerebellum and basal ganglia.
The study of these mechanisms in animal models of HE will allow the development of new and more efficient therapeutic strategies: for example, the increase of cGMP levels or anti-inflammatory molecules to improve learning and memory performance in individuals with HE.

Neurosteroids: emerging players in the pathophysiology of hepatic encephalopathy and other neurologic disorders

Samir Ahboucha
Université Cadi Ayyad, Equipe Neurosciences, Pharmacologie et Environnement, B.P./2930, Marrakech, Maroc

Neurosteroids (NSs) are synthesized in the brain mainly by astrocytes independent of peripheral sources (adrenals and gonads). Recently, NS are suggested to play a role in the pathogenesis of hepatic encephalopathy (HE). HE is a serious cerebral complication of both acute and chronic liver failure. In acute liver failure, astrocytes undergo swelling which results in increased intracranial pressure, brain herniation and death. In chronic liver failure, Alzheimer-type II astrocytosis is the characteristic neuropathologic finding. Patients with liver failure manifest severe alterations of their quality of life including sleep disorders as well as memory, learning, and locomotor abnormalities. NSs bind and modulate different types of neural receptors; effects on the γ-amino butyric acid (GABA)-A receptor complex are the most studied. For example, the NS tetrahydroprogesterone (allopregnanolone), and tetrahydrodeoxycorticosterone (THDOC) are potent positive allosteric modulators of the GABA-A receptor complex. As a consequence of modulation of these receptors, NS stimulate inhibitory neurotransmission in the CNS; the so-called "increased GABA-ergic tone" suggested recently as a new pathophysiological mechanism in HE. Moreover, some NS bind to intracellular receptors through which they also regulate gene expression, and there is substantial evidence confirming that expression of genes coding for key astrocytic and neuronal proteins are altered in HE. We will address findings consistent with the involvement of NSs in human and experimental HE, and will also address the increased evidence for the involvement of NSs in the pathophysiology of other neurologic and psychiatric disorders including brain injuries and neurodegenerative disorders.
Acknowledgment: Research activities of SA were supported by IBRO, ISN, and N€uromed

Session 2: Adaptation to environmental stress
Chaired by Mohamed Najimi & Rabia Magoul

Keynote speaker: Corticosterone: a clock endocrine output involved in the circadian functioning of serotoninergic neurons

Paul Pévet
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Disorders of rhythmicity are characteristic of, and may underlie, a variety of troubles. Sleep and circadian rhythms are often disrupted in neurological disorders and increasing evidence indicates that alterations in the sleep/wake cycle accompany (or may be responsible for) many types of neurological disorders. Develop strategies; to treat, prevent or delay such disturbances is a new challenge for medicine. The diurnal organisation of living organisms depends on a circadian network comprising circadian clocks, synchronizing inputs, various clock outputs as well as multiple peripheral self-sustained oscillators. In mammals, the focal point of this system is a master circadian clock within the suprachiasmatic nuclei (SCN) which has not only the capacity to build a circadian message, but can also distribute this signal to other structures. It is thus the complex interaction of neural, behavioural and hormonal outputs (e.g. corticosterone, melatonin) from the SCN that drive the circadian expression of events. It is in this context of a complex and partially redundant system that we will analyse the role of the corticosterone.
Corticosterone (CORT) is an efferent hormonal output of the circadian clock. The clock may thus use CORT signals to convey the circadian message to any system that can "read" it, i.e. to any structure/organ expressing corticoids receptors. In the context of the multi-oscillatory nature of the circadian system two modes of action have to be considered: 1) the hormone signal directly drives a rhythm; or 2) the hormone signal entrains peripheral oscillators. Beside its known capacity to synchronize individual oscillators in fibroblasts *in vitro*, we have demonstrated that CORT is also able to induce directly circadian functioning of neuronal structures. Tryptophan hydroxylase (Tph) is an enzyme involved in the synthesis of 5-HT especially in the Raphé nuclei. Tph2-mRNA displays a daily rhythmic expression in all Raphé subdivisions. The CORT daily pattern is responsible for the rhythm of Tph2-mRNA in the rat and hamster Raphé. After adrenaletomy Tph2-mRNA is expressed at constant level through 24h in the Raphé indicating that the CORT surge drives the rhythmic pattern of Tph2-mRNA. This issue is confirmed by the fact that the Tph2-mRNA daily pattern is fully restored in adrenalectomized rat and hamster after addition of CORT in the drinking water. Our studies provide clear evidence to a functional link between the rhythm of the 5-HT system and that of corticoids, whose we know the involvement and dysfunction in many psychological and neurological diseases such as mood disorders. However, the exact mechanism involved in CORT induction of Tph2-mRNA circadian expression is still not known.

Water deprivation affects the neural and glial system in a desert rodent the Meriones Shawi

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Water deprivation is a stress that has been associated with activation of several endocrine systems, including circumventricular organs of the central nervous system. The subcomissural organ (SCO), characterized by its glycoprotein secretion called Reissner's fiber has been suggested to play a role in the regulation of body water balance. Meriones shawi, a semi-desertic rodent characterized by its resistance to long periods of thirst was subjected to water deprivation for 1 and 3 months. Effect of water deprivation was evaluated immunohistochemically on 5-hydroxytryptamine (5-HT; serotonin) system and glycoprotein secretion of the SCO. Our findings demonstrate significant reduction of anti-Reissner's fiber immunoreactive materials within basal and apical parts of the SCO ependymocytes. These changes seem to be the consequence of reduced control by 5-HT fibers reaching the SCO as a concomitant and significant reduction of anti-5-HT immunoreactive fibers are also observed following water deprivation. 5-HT

immunoreactive reduction is seen in several regions in the brain including the neurons of origin within the dorsal raphe nucleus and the projecting supra and sub-ependymal fibers reaching the classical ependyma of the third ventricle. The extent of Reissner's fiber and 5-HT immunoreactive changes significantly correlates with the severity of water restriction. We suggest that water deprivation causes changes of the classical ependyma and the specialized ependyma that differentiates into the SCO as well as other cirumventricular organs such as the subfornical organ and the organum vasculosum laminae terminalis known to control drinking behaviors.

EM66-containing neurons in the hypothalamic paraventricular nucleus of the rat: No plasticity related to acute immune and thermal stress

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Neuropeptides, main neuroendocrine system effectors, notably regulate the response to different stressors via a secretory plasticity within their respective hypothalamic neuronal populations. Indeed, the hypothalamic response to an environmental stress implicates the corticotropin-releasing hormone (CRH) neuroendocrine system of the hypothalamic parvocellular paraventricular nucleus (pPVN) in addition to other neuropeptides coexpressed within CRH neurones and controlling the hypothalamo-pituitary-adrenal axis activity as well. The aim of the present study was to explore by immunocytochemistry the occurrence of the neuropeptide EM66 within the parvocellular neurones of the PVN of rat and its potential expression plasticity following stress.

The present results have shown that the secretogranin II (SgII)-derived peptide EM66 is strongly expressed within hypothalamic neuroendocrine areas such as the pPVN as well as the median eminence, suggesting a probable hypohysiotropic effect of this peptide. As a first approach to investigate such a role, we evaluated by immunocytochemistry EM66 expression within the pPVN following acute immune stress induced by lipopolysaccharide (LPS, ip) or interleukin – 1β (Il – 1β icv) injection in rat. The results showed that the number of EM66-immunolabeled cells did not fluctuate in this structure following LPS peripheral injection. In line with this observation, an intracerebroventricular injection of Il – 1β did not provoke any significant variation of the number of EM66 neurones in the pPVN. Furthermore, EM66 expression level did not change upon an acute thermal stress.

In conclusion, the present study revealed for the first time that EM66 expression within the neurosecretory hypothalamic pPVN is not responsive to central and peripheral Il – 1β. Consequently, EM66 does not participate in the phenotypic plasticity of hypothalamic parvocellular neurons in response to acute inflammatory or thermal stress.

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Differential effect of stress on neurogenesis in rat adult central nervous system

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The production of new neurons has until recently been considered to occur only during the embryonic and early postnatal periods with no significant role in the adult brain. It is now well accepted that neurogenesis occurs in several parts of the adult brain of mammals. Two regions have been defined as neurogenic niches, namely, the olfactory bulb and hippocampus. Recently, we have shown that also the dorsal vagal complex (DVC) in the rat brainstem displays adult neurogenesis. The new born neurons arise from neural progenitor cells located within the DVC itself. The DVC is considered as one of the key centres involved in food intake regulation. This function is highly sensitive to environmental influences like stressful conditions. Interestingly, stress affects negatively neurogenesis, notably in the hippocampus. However, how stress affects neurogenesis in DVC in relation to food intake regulation remains an unaddressed question. This represents the main goal of the present investigations. Using a homotypic and unpredictable stress paradigm (immobilization used repetitively during 3 weeks), we noticed that stress reduces significantly the rates of cell proliferation and differentiation in the DVC. The most dramatic influence of stress occurred in the area postrema, where the decrease reached about 50%, when compared to a 25-30% decrease in the nucleus tractus solitarius (NTS) and dorsal motor nucleus of the vagus (DMNV). Chronic immobilization stress induced a significant decrease of the total neurosphere number per rat DVC in both primary and secondary cultures, indicating that intrinsic neural stem cell frequency was decreased by chronic stress in DVC tissue. This stress paradigm elicits also a significant reduction of neurogenesis in the hippocampus (28%) whereas olfactory bulb seems to display an opposite response.

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Arrhythmogenicity of Epinephrine-Induced Hyperadrenergic Activity: Applied Evidence at the Level of the Organ and the Organism

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Epinephrine (adrenaline) is an endogenous stress hormone secreted by the adrenal gland, and it is a naturally occurring sympathetic neurotransmitter, which plays an important role in the sympathetic control of cardiac activity. Epinephrine can be a hidden menace in cases of hyperadrenergic activity at times of extreme stress or emotion when the sympathetic nervous system is over-active. On the other hand, epinephrine is clinically used as an exogenous sympathomimetic and β-agonist to treat cardiac arrest and cardiac dysrhythmias resulting in diminished or absent cardiac output. Recent advances in cardiac research have produced surprising and disconcerting results for the pharmaceutical industry and cardiologists. In particular, considerable problems were recently highlighted when extensive clinical trials revealed potentially lethal side effects of some drugs widely in use. Epinephrine, one of these drugs, is considered the most commonly available inotrope and in many cases the most appropriate drug to maintain blood pressure. However, tachycardia, ventricular arrhythmias, hypertension, hyperglycemia, and

even oxidative stress are recorded as side effects of this drug. Therefore, I have undertaken work to define and analyze the latest and most important information on the arrhythmogenicity of hyperadrenergic activity induced by epinephrine, at the level of the organ and the organism, using *in vitro* and *in vivo* experimental models. In both isolated hearts and intact animals, cardiac arrhythmias produced by epinephrine included; extrasystoles, tachyarrhythmias and bradyarrhythmias as well as abnormalities of both P-wave and ST segment. In intact animals, epinephrine induced a significant negative chronotropism accompanied by a non-significant negative dromotropism. A gradual and progressive positive inotropism and a non-significant increase in repolarization voltage were also obtained. Vasomotor dysfunction was recorded as an elevated venous blood pressure as well. Recently, I have introduced evidence for the anti-arrhythmic effect of natural wild honey against cardiotoxicity due to catecholamines, in particular epinephrine. More recently, I have proven that natural wild honey managed to reverse the side effects of epinephrine. Meanwhile, it preserved its powerful inotropic effect. So, with the advent of new technologies and great advances in cardiovascular research, more properly conducted clinical trials are needed to objectively substantiate the efficacy of natural wild honey as an important complementary biotherapy, besides epinephrine, as an inotrope, for the treatment of congestive heart failure. Especially, wild honey decreased the venous blood pressure which can reduce the pre-load of the heart and consequently may diminish the congestion in the venous system, the reason this condition is termed congestive heart failure. The outcomes of my latest scientific trials in order to suppress or attenuate the arrhythmogenicity of hyperadrenergic activity induced by epinephrine could result not only in the prevention of the deleterious effects of epinephrine, as an endogenous stress hormone and a chemical mediator, but also in novel anti-arrhythmia therapies against the adverse effects of epinephrine, thereby facilitating its safe use as an effective inotrope.

PUBLIC LECTURE

Les maladies psychiatriques – Psychiatric diseases

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Chaired by Mireille Besson

La santé mentale selon l'OMS est l'état de bien être dans lequel la personne peut se réaliser, surmonter les tensions normales de la vie, accomplir un travail productif et fructueux et contribuer à la vie de sa communauté. La santé mentale comporte trois dimensions : la santé mentale positive qui recouvre l'épanouissement personnel, la détresse psychologique réactionnelle qui correspond aux situations éprouvantes et aux difficultés existentielles et les troubles psychiatriques qui se réfèrent à des classifications diagnostiques renvoyant à des actions thérapeutiques.

Le champ de la santé mentale recouvre à la fois une dimension individuelle et une dimension sociétale. La maladie mentale a ceci de particulier qu'une réponse uniquement médicale ne suffit pas car le trouble psychiatrique touche et perturbe souvent la relation avec l'entourage (familial, professionnel et social).

Dans son rapport sur la santé dans le monde dédié à la santé mentale en 2001, l'OMS insiste sur le caractère universel des troubles psychiatriques qui se manifestent dans toutes les sociétés. La situation de la psychiatrie au Maroc se caractérise par une forte hétérogénéité régionale en

matière d'offres de soins et inégalité territoriale en termes de structures et ressources humaines et un déficit en lits.
Parmi les recommandations de l'OMS en matière de santé mentale : traiter les troubles, assurer la disponibilité des médicaments, associer les familles et les usagers, développer les ressources humaines, sensibiliser le grand public et soutenir la recherche. N€uroMed, en organisant cette conférence et un workshop sur les processus neurodégénératifs tente d'appliquer ces deux dernières recommandations.

Session 3: The plastic brain: implications for learning and education
Chaired by Marie Moftah & Halima Gamrani

Keynote Speaker: Neuroplasticity and learning

Driss Boussaoud
INCM-CNRS & Université de la Méditerranée, Marseille, France

Neural plasticity in relation to experience (i.e. learning) is one of the fundamental aspects of brain plasticity. It allows us and other animal species to acquire new perceptual and cognitive skills, to keep in memory tremendous knowledge, and overall to develop new behavioral capacities. Learning dependent plasticity leads to synaptic changes, both quantitatively and qualitatively (change in synaptic efficacy). These synaptic changes have consequences on information processing, which can be measured at single neuronal electric activity, and at the level of populations of neurons as well as large brain networks. This talk will attempt to link these different levels. I will address the results of recent studies in monkeys and human subjects that demonstrate that neurons and brain networks change during visuomotor skill learning. First, I will present the learning paradigm used, and present neurophysiological data showing that single neuronal activity changes during learning, and does so in one of two ways: (1) in one set of neurons recorded from the striatum (the major nucleus of the basal ganglia) the firing rate is highest early during learning, when the correct solution is not known, and it decreases as learning takes place. This change might reflect working memory. (2) In another set of neurons recorded from the same structure, the activity is weak early in learning and increases progressively as learning occurs. These changes are attributed to consolidation of correct, rewarded behavior, which leads to the storage of learned behavior in long term memory. In another series of experiments conducted in healthy human subjects using brain imaging techniques, with the same experimental protocol as in monkeys, we have shown that the basal ganglia and the cerebral cortex divide the labor during learning, with specific coding of errors and rewards in prefrontal cortex and ventral striatum (Brovelli et al., 2008). Overall, accumulated evidence suggests that skill learning correlates with neural changes that occur in large brain networks, and that specific sub-networks are involved in coding specific processes, namely error prediction and 1st correct response. Future work should investigate the question of whether these mechanisms of individual learning, are also the same in more social forms of learning, as when we learn from others.

Reference: Brovelli A, Laksiri N, Nazarian B, Meunier M. and Boussaoud D (2008). Understanding the neural computations of arbitrary visuomotor learning through fMRI and associative learning theory. CEREBRAL CORTEX, 18:1485-1495.

Submembranous cytoskeleton and neuroplasticity in hypothalamo-neurohypophysial system of rats and mice

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The regulation of water in the body is vital. It occurs due to the sensation of thirst, which itself is caused by intra- and extracellular dehydration. The baroreceptors and peripheral and central voloreceptors detect modifications of blood hyperosmolarity and hypovolemia and communicate with osmosensitive nerve centers that send efferents to magnocellular neurons. These hypothalamic neurons produce and secrete antidiuretic hormone, arginine vasopressin (AVp) and oxytocin (Ox) hormones. Secretion occurs by exocytosis of dense core granules in the neurohypophysial capillary surrounding space and then in the general circulation. The magnocellular neurons are closely associated with glial cells such as pituicytes in neural lobe and tanicytes in median eminence. The molecular processes that generate and regulate secretion are based mainly on the submembranous and cytoplasmic cytoskeletal and membranous domains components.
For the first time, we describe the distribution of dystrophins (Dp), utrophins (Up) and their associated proteins (dystrophin-associated proteins, DAPs) distribution in glial, neuronal and vascular endothelial cells of hypothalamo-neurohypophysial system.
Dystrophins are the products of the gene altered in Duchenne muscular dystrophy, a debilitating lethal disease. The utrophins are autosomal gene products homologous to dystrophins. These two family proteins have binding capacities even to cytoplasmic and membranous DAPs forming a molecular bridge between the intracellular environment by binding to actin filaments and the extracellular space through their interaction with extracellular matrix components.
Previous and present results obtained by immunohistochemistry, Western blotting and *in situ* hybridization approaches using rats, Dp71 knock out mice and their wild type have identified, in part, the molecular composition of these complexes in rat and mice hypothalamo-neurohypophysial systems compared to that of muscle, used as a reference. Otherwise, the distribution of these complexes is modified under dehydration conditions and suggests different roles as in receiving signals, by implication in the receptor clustering, in granules secretion. All these roles are accompanied with plasticity modifications, either of neurons or of glial cells.
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Experimental acute hyperthyroidism disrupts hippocampal long-term potentiation but not paired pulse facilitation in adult rats

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Manipulations of thyroid hormones have been shown to influence learning and memory. The main paradigm currently used to investigate hyperthyroidism is the administration of thyroxin to adult normothyroid animals. To date, however, there is a lack of electrophysiological data to

[Y] The authors are at equal level in this work

complement results from behavioral studies. In the present study, we therefore tested the effects of L-thyroxine on paired-pulse facilitation and long-term potentiation in rats.
The experiments were carried out on rats between the ages of 9-10 months and were approved by the Erciyes University Committee on Ethics in Animal Experimentation. The experimental animals were randomly divided into a hyperthyroid group and a control group (n=6 in each group). All rats in the hyperthyroid group were injected with thyroxine (0.1 mg/kg/day, ip, 14 days). At the 15th day, stimulating and recording electrodes were introduced in the medial perforant path and dentate gyrus, respectively. Field excitatory postsynaptic potentials (fEPSP) in response to electrical stimulation of perforant pathway were recorded from dentate gyrus using a voltage/current amplifier. fEPSP amplitudes were plotted relative to increasing current of the electrical stimulus to obtain input-output relationship. Paired pulse facilitation was measured from evoked responses of paired pulses with inter-pair intervals between 20-160 ms. Long-term potentiation was induced by four sets of tetanic trains after a baseline recording of fEPSP.
Compared to controls, the thyroxine-treated rats showed a significantly attenuated response during input-output relationship and lower efficacy of long-term potentiation. No significant differences were found in paired pulse facilitation.
These results provide *in vivo* evidence that administration of L-thyroxine leads to changes in the excitability of dentate gyrus neurons in adult rats. We hypothesize that this could be due to reduced expression of the NR1-NR2A subgroups of NMDA-type glutamate receptors, which are known to play a role in long term potentiation. To test this hypothesis it will be necessary to combine behavioral and electrophysiological measurements with studies of receptor binding or Western blot analysis.

Neurogenesis after complete spinal cord transection in *Pleurodeles waltlii*

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Following spinal lesion, connections between the supraspinal centers and spinal neuronal networks can be disturbed, which causes the deterioration or even the complete absence of sublesional locomotor activity. In Mammals, possibilities of locomotion restoration are much reduced since descending tracts either have very poor regenerative ability or do not regenerate at all. However, in certain lower Vertebrates such as Urodeles, there is spontaneous locomotion recuperation after complete spinal cord transection. This phenomenon depends on a translesional descending axon re-growth originating from the brainstem. On the other hand, cellular and molecular mechanisms underlying spinal cord regeneration resulting in parallel in locomotion restoration of the animal are not well known. Fibroblast Growth Factor-2 (FGF-2) plays an important role in different processes such as neural induction, neuronal progenitor proliferation and differentiation. Recent studies showed an up-regulation of this growth factor after complete trunk spinal cord transection in Pleurodeles. Nestin, a protein specific for intermediate filaments, is considered as a neuronal precursor early marker. It has been recently shown that Nestin expression increases after tail transection in Urodeles. Using this marker, our results show that the increase in FGF-2 mRNAs (grain count following *in situ* hybridization) and that of its protein during spinal cord regeneration (western blots) are correlated with an increase in neurogenesis (immunohistochemistry) in the Urodele Amphibian *Pleurodeles waltlii*. This study also confirms that axonal re-growth through the lesion site initially follows a rostrocaudal direction. In addition to its known role in neuronal differentiation, FGF-

2 could be implicated in the differentiation of ependymal cells into neuronal progenitors; thus promoting body spinal cord gap-replacement.

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Organization of corticospinal projections in control and knockout-AC1 adult mice

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Several guidance molecules are known to be involved at various decision points to regulate the projection of corticospinal axons. However, previous analyses of the corticospinal tract (CST) guidance defects in mutant mice lacking these molecules have suggested that there are other molecules involved in CST axon guidance that are yet to be identified. In this study, we investigate the role of cAMP signalling in the projection of motor CST axons in wild type and knockout-AC1 mice. To do so, we used in our study two different tracers: biotinylated Dextran amin (BDA) anterograde tracing of the motor CST axons and Fluorogold (FG) retrograde tracer to quantify the density of CST ipsilateral and controlateral projections on transverse sections at the level of high (C2-C4) and low cervical spinal cord (C5-C8).
Our anterograde tracers show that in both controls and knockout mice, in the cervical spinal cord, many axons branched out from the crossed CST (main tract) to the dorsal and ventral horn. Some of these axons crossed to the ipsilateral grey matter. CST axons branch toward the lateral and ventral white matter. However, in knockout-AC1 mice, the main CST contained high number of labelled fibres than thus observed in controls in upper as well as in lower cervical spinal cord. The same observation was made for the ipsilateral CST. Interestingly the result of our retrograde tracing did not show a similar phenotype of labelled motor neurons in the cortex between controls and knockout-AC1 mice. Corticospinal neurons seem to be denser and closer to the midline in the latter group.
It could be that *In Vivo*, the involvement of AC1 in the topographic organization of corticospinal tract is subtle, in contrast to what it has been shown for retinotectale and retinogeniculate systems. Although many questions remain, it is possible that other calcium-stimulated ACs, such as AC8, which is also expressed in the motor cortex, could be strongly involved in the organisation of these projections. It is evident that cAMP occupies a strategic position to control neuronal responses to a large variety of developmental cues that are important to investigate in the corticospinal tract axons *in vitro*.

The musician brain as an excellent model of brain plasticity

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Professional musicians spend hours every day practicing their instrument. Such an extended practice is known to influence the anatomo-functional organization of the brain. Interestingly, some of the brain regions that are modified by musical practice are also important for language processing. This led us to conduct a series of experiment to examine the influence of musical

expertise on several aspects of language processing (i.e., pitch and meter) in both adults and children. I will discuss the importance of these results for the domain-specificity of linguistic computations, for the learning of foreign languages and for using music training as a tool for the remediation of dyslexia.

Étude des déficits perceptifs et mnésiques chez des enfants d'âge scolaire

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Les troubles mnésiques constituent un réel handicap qui entrave le processus d'apprentissage chez le sujet et contribue à l'échec scolaire chez les enfants (Booth, 2007). Les évaluer est un enjeu majeur, car cela permet de repérer et diagnostiquer les troubles neurocognitifs qui passent souvent inaperçus aux parents voire même aux personnels éducatifs et sont lourds de conséquences sur la santé et le développement de l'enfant. (Ahami *et coll* 2006). Nous avons lancé une campagne d'évaluation des capacités mnésiques et perceptives chez des enfants âgés de 3 à 13 ans, et nous présentons ici une étude réalisée chez 70 enfants scolarisés, qui ont été examinés au niveau des écoles et garderies de la ville et région de Kénitra.
L'étude a été réalisée à l'aide du logiciel « Elian Expert » (Wallon, Mesmin, Jobert, 2009) du Centre Français de recherche sur le dessin (Crédage), qui analyse la dynamique d'épreuves graphiques (dessin de personnage, FCR, etc.) et mesure les capacités mnésiques, la perception visuelle, la manière d'organiser l'espace symbolique, la coordination visuomotrice, l'attention et la concentration.
Les premiers résultats de l'étude montrent des troubles perceptifs et des signes de déficits mnésiques chez plus de 27% des enfants examinés. On relève également d'importants signes d'angoisse et d'inhibition ainsi que de défaut de contrôle pulsionnel, ce qui peut se traduire par un comportement inadapté, une intolérance à autrui et un déficit scolaire.

PLENARY LECTURE

History of mediterranean Neuroscience: The path to N€uroMed

Wail Benjelloun
Mohammed V University, Rabat, Morocco
Chaired by Nouria Lakhdar-Ghazal

Throughout recorded history, the Mediterranean basin has been a cradle of civilizations and a receptacle for the knowledge developed by mankind. This is especially true in philosophy and in the physical and natural sciences. Among the latter, the neurosciences have occupied a special place in view of man's interest in his own functions and in the determinants of his actions. In Mesopotamia, 4 000 years before Jesus Christ, Sumerian "neuropharmacologists" resorted to poppy seeds to provoke euphoria. One thousand years later, the Edwin Smith papyrus described 48 clinical cases of spinal injury treated by the pharaonic priest Imhotep, who for the first time linked CNS insults (crushed vertebral nerves) to peripheral symptoms (incontinence, priapism). In Greece, Hippocrates (470-360 BC) wrote several volumes on brain surgery with detailed descriptions of spasms resulting from injury, contusions and cranial depression. With the advent of

Christianity, the Roman surgeon, Aulus Cornelius Celsus developed a reputation for the treatment of fractures resulting from cranial depressions. After the fall of Rome in 476, Europe entered the Dark Ages, an era of decline, low literacy, and hardship, in which the study of anatomy was prohibited. But the European Dark Ages were the golden age of Islam. Just a hundred and twenty years after the death of the prophet Muhammad in 632, Persia, Asia Minor, Syria, Palestine, Egypt, the whole of North Africa and the Andalus were under Islamic influence. The Muslims assimilated the cultures of the converted peoples and translated Greek, Roman and Persian manuscripts into Arabic, adding scholarly commentary. During this Muslim Golden Age, Muslim scholars contributed to all fields of knowledge, including, of course, medicine and the study of the nervous system. Avicenna, Al Razi, and Al Baghdadi all contributed to the study of pain, developing the use of plant anesthetics and ice. Avicenna described how to treat paralysis through cooling rather than the traditional Greek method of heating, and used eels to deliver shocks to epileptic patients, anticipating modern electroshock therapy. He also developed cataract extraction and described the diagnostic use of the pupillary reaction to light. Al Zahrawi described intra- and extra-cranial hemorrhages and developed craniotomy procedures using burr holes. Al Hazen described the optical pathways from the retina to the cranial hemispheres. During the European renaissance, many of these descriptions, discoveries and clinical methods were adopted by European physicians. Even if Granada, the last vestige of Muslim influence in Europe, had already fallen, the knowledge produced in the Muslim world did not disappear but lived on. This is what is still happening today: present advances in Mediterranean neuroscience are the product of a collective intelligence distributed around the Mediterranean countries, that in most cases has not only avoided the destruction of knowledge produced by others, but has adopted it for its own use. N€uromed and other forms of cooperation around the Mare Nostrum are the modern manifestations of an ancient tradition.

Session 4: Technological development of new methodologies for neurosciences
Chaired by Fakhita Regragui & Yazid Cherfa

Dynamics of neuronal activity during mental training

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Although there is converging experimental and clinical evidence suggesting that mental training with motor imagery can improve motor performance, it is unclear to what extent humans can learn actions through mental training despite the lack of sensory feedback from the body and the environment. In a recent study, we showed that mental rehearsal combined with physical practice leads to similar (or even better) performance than physical practice alone (Allami et al., 2008). Here, we investigate the changes in brain activity underlying improvement of performance during mental rehearsal. The scalp electroencephalogram (EEG) was recorded from two groups of subjects. In the first group (GEx) subjects physically performed a grasping task for 240 trials. In the second group (GIm), the subjects mentally rehearsed the same task for 180 trials (75% of 240) and then executed it physically for 60 trials (25%). Amplitudes and latencies of event-related potentials

(ERPs) were compared across the two groups and across learning. Interestingly, learning in both groups was accompanied by similar cerebral changes over the sensorimotor region of the brain (fronto-central electrodes), that lead to comparable patterns of EEG activity at the end of learning. To analyse the dynamics of changes during learning, we further processed the EEG signals on a trial-by-trial basis using a 5th order linear predictive model.
Under the assumption that EEG signal is a non stationary stochastic process, which means that its statistical properties (means, correlation) may change in time, the model considered is time dependant. For this reason, the model feature (coefficients) extraction was performed adaptively in such a way to enable the detection of any changes in the statistics that may occur in the signal while maintaining high speed of convergence. These changes, reflected as abrupt jumps in the curve representing the model coefficients' behaviour versus time followed, could be related to neuronal behaviour change. On the basis of this technique, for each trial, we estimated the time of occurrence of the first significant jump (TJ). Preliminary results showed that, in both the GEx group and the GIm group, the TJ parameter maintains in average a value of 385 msec during the training phase, diminishes rapidly during the 10 following trials before converging towards a value of 185 msec during the physical practice. Examination of the TJ curves obtained for these two groups revealed that they differ both in terms of leaning phase duration (much longer in GIm), and as TJ decreases, the slope is higher in the GIm group (twice the slope in GEx). This suggests that mental learning is slow, but increases the learning speed through physical experience.
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Virtual Reality and Neuroscience

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Virtual reality (VR) is one of the most challenging applications of computer graphics and is currently being applied in many fields. In neuroscience, VR can be used to create controlled Virtual Environments (VE) where participants can perform experimental tasks. For example, VR can help neuroscientists to create virtual versions of classical neuroscience tasks, such as the Morris water maze, making it possible to use these tasks with human subjects (i.e., Astur et al., 1998).
In reality, the relationship between VR and neuroscience is two-way. For neuroscientists, VR is more than just a tool: some aspects of subjects' VR experience, can be an object of study (Sanchez-Vives and Slater, 2005). VR researchers can investigate the processes that occur in the brain during navigation in VR environments and use the information to make their VR environments more compelling and effective. What they studying here is what has been called "presence" - an individual's subjective sensation of being in one place even she is physically located somewhere else. In recent years, many studies of presence have applied brain imaging methods. Baumgartner et al. (2006) used EEG to analyze neural correlates of spatial presence in an arousing virtual environment with no interaction. In a subsequent study (Baumgartner et al., 2008), the same group used fMRI to monitor subjects' brain activity. In recent work in our own group (Alcañiz et al., 2009; Rey et al, 2010), we have used transcranial doppler monitoring to analyze cognitive states related to presence during exposure to virtual environments providing different degrees of immersion and

different options for navigation. The findings suggest that two-way cooperation between VR and neuroscience can make a significant contribution to research in coming years.

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Image processing for the detection of functional areas affected by stroke in the brain MRI

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The aim of this work is to design a system applied to magnetic resonance brain images (MRI) that are multi-ponderable (T2, Diffusion, Flair), taken at different times according to changes in the pathology, from patients suffering from stroke.

The system is designed so as to take advantage of several complementary approaches. We opted for a 2D cooperative segmentation region/edge cuts, preceded by an adequate preprocessing phase suitable for MRI data. These operations aim at improving image quality and reduce the large amount of information contained in a cerebral image.

The following phase consists of a stroke geometric characterization, a 3D reconstruction of the image, a registration with a reference image, including functional areas in order to recognize the functional areas of the brain affected by the injury. The result of the mapping of the brain and brain segmented reference Broadmann, followed by determining the functional areas affected by stroke, has been validated by clinical examination of the patient.We used MRI images of subjects with stroke who have been appraised by clinicians

Tools such as mathematical morphology, anisotropic diffusion, image segmentation, cooperative techniques, and image registration were used for this task.

Our method can be used in the aid to diagnosis or surgery, or the temporal monitoring of the pathology according to a therapy.

Acknowledgment: We would like to thank the neurology department of the hospital in Grenoble for providing the images, and Catherine Garbay UJF of Grenoble for her help

Diffusion fMRI and BOLD-fMRI: Towards Better Understanding of White and Grey Matters Function

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Since early observations of the BOLD effect (1), fMRI has rapidly become a tool of choice for in vivo exploration of the functionality of the brain, with applications ranging from brain pathology

and plasticity to repair and functional recovery. BOLD-fMRI is especially useful for investigations of the cortex and of grey matter and is highly sensitive. However its spatial specificity is compromised by the diversity of vasculature present in the brain. Large draining veins, for example, are often distant from sites of neural activity (2). While significant progress has been made in understanding the functional role of grey matter regions, little is known about their relationship with underlying white matter structures. It is possible that these structures play an active role in mediating functional processes in the healthy and pathological brain. Study of white matter structures and the association between these structures and activated grey matter structures could thus add to our understanding of well-documented neural networks subserving functional processes.

As an alternative to the BOLD approach, Song et al. (3) have suggested a new contrast mechanism based on functional changes in the Apparent Diffusion Coefficient (ADC). In this early application of their approach, we studied the extent to which variability in the activation of task-related cortical areas depends on the presence of nearby white matter structures. Our study used a range of different diffusion tensor parameters including average diffusion (trace) and fractional anisotropy. Basically, diffusion fMRI is based on measurements of Intravoxel Incoherent Motion (IVIM) (3). IVIM models two major components in the diffusion signal: the first is generated by intravascular blood flow, the second by extravascular diffusion of water. The intravascular component signals high mobility and therefore persists only when using lower diffusion weighting. It can thus be used to map flow and volume changes in microvascular networks. Song (3) showed that the ADC increases with increases blood flow increases, regardless of whether vessel volume fraction increases or remains constant. In general, ADC depicts changes in blood volume and flow at the level of arteries, arterioles, and capillaries, while BOLD reflects changes in oxygenation in capillaries, venules and veins. The combination of the two sources of information can identify capillary activation, leading to enhanced spatial localization of the functional signal. The time course of the ADC-based functional signal precedes the BOLD signal by about 1 second, confirming that ADC contrast is sensitive to changes in blood volume and flow changes in the arterial and capillary network. We have found that high diffusion weighting produce a lag in the time course with respect to lower values. This implies that we can use diffusion weighting to tune sensitivity to vessels of different sizes. The ADC-fMRI method can be further refined by using flow-moment-nulling to compensate for the effect of changes in blood flow. In cases where the main changes are in volume, this improves the sensitive of the functional signal from smaller vessels (4).

Diffusion characteristics of peripheral white matter and application of ROI and connectivity analyses revealed the existence of connections worthy of further study. These findings suggested that studies of peripheral white matter morphology can make a useful contribution to our understanding of the brain. Such studies will require further refinements of the ADC method and its relation to functional, behavioral and structural indices.

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Abstracts – Poster Sessions

Session P001: Neurodegenerative diseases
Chaired by Eman Khedr & Mohamed Bennis

P001.1. Therapeutic role of repetitive transcranial magnetic stimulation in obsessive compulsive disorder: randomized control trail

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Obsessive compulsive disorder (OCD) is a condition characterized by distressing, irrational, time consuming, obsessive thoughts and compulsive urges. Lack of an efficient medical therapy for OCD led to frustration of both patients and physicians. This may in part be explained by the lack of understanding of the mechanisms underling OCD. The development of transcranial magnetic stimulation has provided new tool to study the cortical excitability in OCD and to use the repetitive stimulation to modulate this cortex to alleviate the symptoms.

The aim of the present work is: Phase 1: to assess the cortical excitability in OCD patients in order to understand more about its pathophysiological mechanisms, Phase 2: we will evaluate the impact of different frequencies of repetitive transcranial magnetic stimulation (rTMS) on OCD patients.

Material and Methods: Patients with OCD (according to DSM IV crieteria) that failed several standard medical treatments will participate in the study. They will be selected consecutively (through the first 3 months) from those attending the department of Psychiatry, Assiut University Hospital, Egypt. All subjects will give written informed consent. The protocol will be approved by the local ethics committee.

Assessment of cortical excitability (resting motor threshold (rMT), cortical silent period (CSP), transcallosal inhibition, intracortical inhibition anf facilitation (ICI and ICF) for each patient compaired with data of normal volunteer's age and sex matched.

Patients with OCD will be randomly classified to one of three groups; 1 Hz, 10Hz, and sham group with total 2000 pulses at 100% resting motor threshold per session on right pre-motor cortex for two weeks. The primary outcome of the treatment protocol will be the patients' own self rating of their symptoms using the Hamilton questionnaire for depression and anxiety, Yale Brown Obssive Compulsive scale (YBOCS), and Clinical global Impression-severity of illness at 3 and 6 months.

P001.2: Iron Deficiency Anemia correlates with Cognitive Performances of Schoolchildren in Morocco

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Iron deficiency anemia (IDA) has negative effects on cognitive development. Many studies have revealed this association. Some of them emphasized that the incidence of IDA at early age will have more deleterious consequences later in life. This aim of this study if to determine the association between iron status and cognitive scores of rural schoolchildren in North western Morocco.

All the 296 primary schoolchildren aged from 6 to 16 years old were observed in a rural setting. Iron status including Hemoglobin rate and serum ferritin were measured according to international standards. A battery of psychological and cognitive test was performed. Raven Progressive Matrix to measure the inductive component of intelligence and the bells barrage to determine visual attention and visual strategy. The maximum score attainable for Raven is 60 while it is 35 for the bells.

Results: Ferritin cut off point of 15µg/dl has showed that 76 children are iron deficient (ID) with 36 of them physiologically anemic according to their hemoglobin level under 11.5 g/dl. The respective prevalence was 20.4 % and 12% for ID and anemia.

Anemic children have performed less in Raven score (14.6 ± 9.7) than non anemic (18.4 ± 10.4) but have scored nearly the same average in Bells test (22.7± 7.3) and (22.7± 8.3) respectively. The results revealed that serum ferritin status is associated with school performance assessed by the average Math's score and the annual score with Pearson R- correlation values respectively 0.57 and 0.70. Theses correlations are statistically significant according the logistic regression test. Compared to the French population standards 77.9% of the anemic children might have an intellectual delay against 68.5% for non anemic children (p=0.035).

In conclusion, anemia needs to be treated and iron status should be adjusted in this school. Iron status is associated to the intellectual score but not to the visual attention in this study. A follow up study is planned with the partnership of the health services. Furthermore a fMRI study will be performed to determine the kinetics of iron in anemic children subjected to different cognitive tasks.

P001.3: Anticonvulsant effect of butanolic extract of *Anacyclus pyrethrum* roots in rat

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Popularly known as "pilletory", *Anacyclus pyrethrum* root is used since Unani system of medicine for the treatment of epilepsy. In the present study the anticonvulsive effect of butanolic extract of the plant roots (BEPR) was evaluated on the model status epilepticus (SE).

SE was induced in wistar rat by an intraperitoneal injection of kainic acid (KA). In the present study we used 4 groups of rats: 1: animals injected with 8 mg / kg of KA to induce epileptic activity, 2: animals injected intraperitoneally with 600 mg / kg of BEPR, followed, 40 min later, by injection of 8 mg / kg KA, 3: the third group received only BEPR, and 4: the last group received only a vehicle.

The animals were observed during 6h following injections. Latency and seizure severity based on the number of wet dog shakes (WDS) were measured.

The results showed that the pre-treatment of rats by the BEPR decreases significantly the number of WDS, and increases considerably the latent period between the injection of the KA and the

appearance of the crises. These behavioural results were confirmed by the immunohistochemical study at the level of the hippocampus, in which the Fos expression of the butanolic extract-treated animals largely reduced the number of labelled neurons with respect to the group, which received the KA alone. This suggests that the BEPR causes an anticonvulsive effect on rats, however the mechanisms remain to be determined.

P001.4: Psychomotor development of exposed mice offspring to fenugreek seeds

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It is recognized that some medicinal plants have harmful effects on maternal and fetal health. However, most clinical claims of medicinal plants, made available, to consumers do not have any scientific data support. The present study was undertaken to evaluate the prenatal effects of butanol extract from deeds of fenugreek on neurodevelopment behavior in mice.

The effect of prenatal exposure to fenugreek seeds extract on behavioral motor skills parameters in Swiss mice offspring was assessed. Pregnant mice were treated by gavages with 300 mg / kg / day of a butanolic extract dissolved in saline solution throughout the gestational period. Control animals received the vehicle for the same period. Before weaning, the pops were examined using the swimming behavior (PND10, 12 and 14) and the cliff avoidance test (PND 6).

In the treated offspring, swimming angle was significantly lower in scores than controls. Cliff avoidance test was significantly affected in treated group compared to controls.

These results showed a delay of early response development and motor coordination in the offspring of mice exposed to fenugreek seeds butanolic extract during all pregnancy period. We concluded that the fenugreek seeds consumption during pregnancy could be a cause of offspring developmental toxicity.

P001.5: *Perna perna* (Mollusca, Bivalvia): evaluation of pollution on the neuroseceretory cells of cerebroid ganglia

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Laboratory investigations on three mussel populations living along the Atlantic coast of Morocco were carried out i) to identify the different sexual stages throughout a year and specify spawning periods, ii) to determine numerical variations of neurosecretory cells (NSCs) positive to LHRH Luteinizing-hormone-releasing-hormone in the cerebroid ganglia of these bivalves, and iii) to assess the degree of pollution in each mussel bed via the study of several biomarkers (acetyl-cholinesterase, AChE; Catalase, CAT; Glutathione S-Transferase, GST, and Malondialdehyde,

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MDA). Mussel samples were collected from an unpolluted site, a bed polluted with domestic wastewater (Hay al-Fath), and another contaminated with industrial wastewater (Mohammedia). Three spawning periods were noted in the unpolluted site instead of two periods in the polluted beds. Compared to the unpolluted site, the gametogenetic waves in mussels were longer at Hay-al-Fath, and shorter at Mohammedia. The quantitative development of NSC in the cerebroid ganglia was correlated with the different stages of the sexual cycle. During gamete maturation, the number of NSCs increased whereas it decreased during spawning and/or sexual rest. In the site contaminated with domestic wastewater, the number of NSCs was significantly lower than those found in the bivalves from the other two sites. In all sites, the four biomarkers showed a seasonal cycle correlated to mussel sex. In polluted sites, high CAT and GST activities were generally found, while AChE activity was low, particularly at Hay al-Fath. High levels of MDA were noted even in the unpolluted site, but with variations according to the site studied. Pollution disrupted the sexual cycle of *P. perna* by reducing the number of resting periods and by changing the length of gametogenetic waves. In addition, it reduced the number of LHRH-positive NSC in the cerebroid ganglia of mussels living in the site contaminated with domestic wastewater.

P001.6: Impact of pollution in neurosecretory cells of ganglia nerves of Molluscan Mytilidae: Approach of the neuroendocrine control

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Histological and immunocytochemical investigations on the gonads and nerve ganglia of the African mussel: Perna perna, were carried out i) to follow the seasonal variations of the storage tissue during the sexual cycle of the mollusc and ii) to determine to determine the quantitative variations of neurosecretory cells (NSCs) in the nerve ganglia during the different phases of the sexual cycle. Studies were performed in two mussel populations, the first living in an unpolluted site (Cap Ghir) and the other in an area contaminated with domestic and industrial wastewater (Anza).

The number of NSCs, determinate by topographic staining (paraldehyde thionine, or Azan by Roméï's method) was significantly correlated with the sexual cycle and the reserve cycle. Two phases in increasing number of NSCs were observed in the two types of ganglia studied (cerebroid, and pedal ganglia) as well as in both mussel populations. The first (from December to June) preceded gonial mitoses and spawning, while the storage tissue decreased in volume. The second period (from July to November) was characterized by a greater increase in NSC numbers: it preceded a new gametogenetic wave and coincided with reconstitution of the storage tissue. However, at Anza, this second period was preceded by the development of the storage tissue which remained large up to the numerical decrease of NSCs.

In Cap Ghir mussels, the (Gonadotropin-releasing hormone) GnRH-positive NSCs in the cerebroid and pedal ganglia showed the same development in relation to the different phases of the sexual

cycle and the storage tissue. However, they were more numerous in the cerebroid than in the pedal ganglia. The number of GnRH-immunoreactive NSCs peaked in December in the cerebroid ganglia and this process preceded sexual maturation and spawning, whereas the lowest numbers were observed during sexual rest. However, during acinar development and the beginning of vitellogenesis, the positive CNS increased in numbers. In the same sampling site, the insuline-positive NSCs present in both types of ganglia did not have the same development from December to July: in the cerebroid ganglia, the number of these cells decreased, while the pedal ganglia contained twice more NSCs during reserve reconstitution. In contrast, during the second period, the increase of insuline-like NSCs was greater in the cerebroid ganglia, whereas the storage tissue decreased to its minimum.

Compared to Cap Ghir, the numbers of immunoreactive NSCs noted at Anza inversely evolved. If high numbers of GnRH-positive NSCs in the cerebroid ganglia were noted during the sexual cycle, such values were only found in the pedal ganglia during spawning, while the numbers of these cells were low in the latter ganglia during gamete lysis. The number of insuline-positive NSCs in the cerebroid ganglia steadily increased during the sexual cycle in spite of variations in this last cycle and the storage tissue. In contrast, in the pedal ganglia, the number of these positive cells did not change during storage tissue regression and increased when the tissue was reconstitute. The quantitative evolution of the NSCs showed a significant correlation with the sexual cycle and that of the reserves. It is likely that the products of secretion of the NSCs act on the target cells, of the gonad, the GnRH-like act on sexual cells, while Insuline-like would act on storage cells of Bivalve Mollusks.

P001.7: Chronic hyperammonemia induces tonic activation of NMDA receptors in cerebellum leading to a decrease of neuronal nitric oxide synthase activity

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Impaired function of the glutamate-nitric oxide-cGMP pathway contributes to cognitive impairment in hyperammonemia and hepatic encephalopathy. The mechanisms by which hyperammonemia impairs this pathway remain unclear. Understanding these mechanisms would allow designing clinical treatments for cognitive deficits in hepatic encephalopathy. The aims of this work were: 1- to assess whether chronic hyperammonemia *in vivo* alters basal activity of neuronal nitric oxide synthase (nNOS) in cerebellum and/or its activation in response to NMDA receptor activation; 2- to analyse the molecular mechanisms by which hyperammonemia induces these alterations; 3- to investigate whether tonic NMDA activation is increased in cerebellum in chronic hyperammonemia *in vivo*, and 4- whether this tonic activation is responsible for nNOS alterations in cerebellum. The findings show that hyperammonemia reduces both basal activity of nNOS and its activation following NMDA receptor activation. Reduced basal activity is due to increased phosphorylation of Ser847 by calcium-calmodulin-dependent protein kinases (CaMKII), which in turn is due to increased phosphorylation of Thr286. Inhibiting CaMKII, with KN-62 normalizes phosphorylation of Ser847 and basal NOS activity in hyperammonemic rats, leading to values similar to controls. Reduced activation of nNOS in response to NMDA receptor activation in

hyperammonemia is due to altered subcellular localization of nNOS, with reduced amount in post-synaptic membranes and increased amount in the cytosol. Blocking NMDA receptors with MK-801 increases cGMP and NO metabolites in cerebellum *in vivo* and in slices from hyperammonemic rats, reduces phosphorylation and activity of CaMKII and normalizes nNOS phosphorylation and activity. MK-801 also increases nNOS in synaptic membranes and reduces it in cytosol. This indicates that hyperammonemia increases tonic activation of NMDA receptors leading to reduced activity of nNOS and of the glutamate – NO – cGMP pathway.

P001.8: Persistent effect of aluminum chronic toxicity on memory in adult Wistar male rat

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Aluminum is the 3rd abundant metallic element in the nature after oxygen and silicon; it constitutes about 8% of the Earth's crust. It is present in numerous sources, including air, food, drugs, cosmetics, vaccines, household materials and water.

It was considered, for long time, as non toxic element and completely excreted out of the body by renal way. However, currently, its toxicity appears more and more threatening to exposed population and its principal target is the nervous system.

The aim of this study was to investigate the persistence of aluminum nitrate effect on short and long term recognition memory and object location memory of adult Wistar male rat. The intoxication lasted 10 months and the stopping of treatment was of 3 months. The memory abilities were evaluated using Novel Object Recognition memory test and Object location task. The results have shown that the effect of aluminum on memory abilities remained, even if, the intoxication was stopped. High significant decrease in the memory index of short ($p<0.01$) and long term ($p<0.001$) memory and in the location memory index ($p<0.01$) was registered in studied rats compared to the control ones.

P001.9: Calcitonin-induced sleep disturbance in rat when injected in the lateral ventricle and into the periaqueductal gray

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We have previously proposed that behavioral alterations induced by salmon calcitonin in the rat provide an animal model of depression. As depression is often paired with sleep disturbance and both interact in a quite complex manner, we examined the effects of microinjections of salmon calcitonin into the lateral ventricle and into the ventral PAG of the brain on sleep. The electroencephalogram (EEG) and Electromyogram (EMG) were continuously recorded during the first 8 hours postinjection. When injected in the lateral ventricle, calcitonin affect specially the total REM sleep. Calcitonin increases the total time spent in wakefulness, increases total NREM sleep and decreases considerably total REM sleep when injected into the ventral PAG.

P001.10: Clinical and genetic aspects of spastic paraplegia

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Hereditary spastic paraplegias (HSPs) are a clinically and genetically heterogeneous group of conditions characterized by the presence of lower limb spasticity and weakness. HSP is diagnosed on the basis of characteristic clinical symptoms, neurological examination, family history, or by identification of a pathogenic mutation in an HSP-causing gene. There is currently no cure or specific drug treatment. However new therapies are under investigation and clinical trials are in progress.

Our genetic research and development institution in Morocco has studied 38 families of uncomplicated HSP-AR of the uncomplicated type. The findings confirmed that 3 of the families were related. Hopefully, future advances will identify other genes associated with HSP, in addition to those already known. This would allow a better understanding of the pathogenic mechanisms underlying the disorder and contribute to the search for new treatments.

Session P002: Neuroplasticity – Chaired by Marie Moftah & Driss Boussaoud

P002.11: Neural correlates of observational learning in non human primates

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Numerous animal species, including human and non human primates, can learn either through their own experience (trial and error learning, TE) or through observation of their conspecifics. In this study, we address the question of how the brain of an observer encodes the outcome of others behavior, with particular focus on error and success signals. To do so, we trained two monkeys to learn one from another, in a task that requires the association of visual cues with the hand press of one of 2 or 4 targets on a touch screen. The experimental design allowed the monkeys to face each other, and to have access to the touch screen displayed face up between them. Only one monkey can perform the task at a time and had access to the touch screen: one monkey performs the task (actor) and the other observes (observer). To control that the observer actually looks to the touch screen during task execution by the actor, its gaze direction was monitored using an infrared camera (*Iscan Inc*).

A trial began with a white square (lever) indicating to the actor where to put his hand. Then a cue was presented at the center of the touch screen, together with 2 or 4 squares (targets) one in each quadrant. If the monkey pressed the correct target he received a drop of fruit juice (reward) after a green stimulus indicating that the response was correct. If incorrect, a red stimulus was displayed (error signal), and no reward was given. There were various conditions: observation of familiar or new cue-target associations, execution of new associations that were (observational learning) or were not (trial and error) observed.

Behavioral data showed that the monkeys learned by observation, and could gain up to 13.2% in their performance relative to TE learning. Neural activity was recorded from the dorso-lateral prefrontal cortex of the observer, an area known to play a key role in the processing of action and its outcome during learning. Preliminary data shows that, in parallel to the improvement in behavioral performance, some neurons (13 out of 39) encoded error and/or success signals. They may respond to the feedback signal of both self and other's behavioral responses (cognitive mirror properties), to feedback from self performance only, or to feedback from the actor's behavior. Taken together, the neuronal properties provide preliminary evidence that the monkey prefrontal cortex integrates signals about self and others successful and erroneous behavior. We suggest that learning by observation relies on two basic systems: the mirror system which allows the observer to process others' behavior and its outcome, and the reinforcement learning system which strengthens successful behavior. Ongoing experiments seek to confirm this tentative conclusion.

P002.12: Lack of melanopsin in ganglion cells and its impact on retinal clock

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The primary circadian pacemaker, in the suprachiasmatic nucleus of the mammalian brain, is photoentrained by light signals from the eyes through the retinohypothalamic tract. Evidence suggests that the entraining photoreceptors are retinal ganglion cells that project to the suprachiasmatic nucleus. The visual pigment for this photoreceptor may be melanopsin, an opsin-like protein whose coding messenger RNA is found in a subset of mammalian retinal ganglion cells.

Circadian clocks generate endogenous circadian rhythms throughout autoregulatory transcriptional-translational feedback loops comprised of a well defined set of clock genes.

The PER2 gene is a member of the Period family of genes and is expressed in a circadian pattern in the suprachiasmatic nucleus, the primary circadian pacemaker in the mammalian brain. The specific function of this gene is yet, unknown.

Our aim, in this study, was to investigate the localization and circadian rhythmic pattern of the protein expression of the PER2 clock gene in the retina of wild type (C57BL6) and transgenic melanopsin knockout mice.

Animals were housed at a constant temperature of 21°C under 12h light/12h dark condition (LD 12:12) at least two week before experiments. Just before enucleation, mice were housed under constant darkness (DD) for 2 days. Eyes were then enucleated at 0, 6 and 12 hours of subjective day and 2 hours of subjective night. Tissues were fixed in 4% paraformaldehyde, sucrose infiltrated and cryopreserved. Cryosections were examined by immunohistochemical procedure for PER2 protein.

In wild type mice, immunostraining of the ganglion cell layer and inner nuclear layers showed strong expression of PER2 protein. Levels of expression varied in line with circadian rhythm, with high levels at 0, 6 and 12 hours of subjective day and lower levels at 2 hours of subjective night under DD. The maximum level of expression appeared at 12 hours of subjective day under DD. In

knockout mice, by contrast, PER2 was expressed only at 0 hour of subjective day and only in ganglion cells. Levels of expression were lower than in wild type mice.

In conclusion: mouse retina contains PER2, a representative clock gene. The time dynamic of PER2 expression reflects a circadian rhythm. This expression appeared however linked to the presence of melanopsin photopigment, since the deletion of this later abolishes the expression of PER2 in all retinal layers.

P002.13: Organization and functioning of the circadian clock of a diurnal rodent, *Lemniscomys barbarous*

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Wheel-running activity was recorded in *Lemniscomys barbarus* exposed to different lighting conditions. This rodent shows rhythmic locomotor activity under natural twilight-light/dark (LD) as well as squared-LD cycles. A mean of 77% of the activity occurred during the light phase. Under different controlled photoperiods, the quantity of daily locomotor activity was relatively stable except for a lower level in the shortest photoperiod tested (LD 06:18). The duration of the active phase tended to increase with the duration of the light phase, especially in the longer photoperiods. Whatever the lighting conditions, *Lemniscomys barbarus* started running before lights-on and stopped after lights-off. The phase angle of activity offset relative to lights-off was stable in each squared-photoperiod, whereas the phase angle of activity onset relative to lights-on was significantly the highest under the shortest photoperiods. Recording of activity under constant lighting conditions showed that the daily rhythm of locomotor activity is fundamentally circadian. The endogenous period was slightly < 24 h (mean = 23.8 h) in permanent darkness and > 24 h (mean = 24.5 h) in continuous light. Re-entrainment of the locomotor activity rhythm after a 6 h phase advance or delay requires only four days on average. Moreover, the phase-responses curve to a 30 min light pulse (200 lux) in *Lemniscomys barbarus* kept in constant dark reveals large phase shifts according to circadian times (CT). With CT0 being defined as the onset of daily activity, maximum phase delay and advance shifts were observed at CT11 ($\Delta \Psi$ = -5.7 h+2.3 h) and CT21 ($\Delta \Psi$ = 4.9+1.2 h), respectively. Interestingly, the phase-response curve to light did not show any dead zone.

Immunohistochemical staining of the suprachiasmatic nuclei indicates that arginine vasopressin-immunoreactive cell bodies and fibers delimited a dorsal subregion that extends laterally and medially. The ventral subregion is rich in vasoactive intestinal peptide-immunoreactive neurones overlapping a smaller area containing gastrin-releasing peptide-expressing cells and receives numerous fibers labeled with neuropeptide Y antibody.

The results of this study clearly demonstrate that *Lemniscomys barbarus* is a diurnal species highly sensitive to the shifting effects of light. Overall, this rodent can be considered a new and interesting model for circadian rhythm neurobiology.

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Session P003: Adaptation to environmental stress – Chaired by Paul Pévet & Seloua El Ouezzani

P003.14: Neuronal adaptive mechanisms of desert vertebrates: Morphofunctional investigations

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The Saharan environment is an unstable biocenos because of its inhospitality due to the aridity and strong sunshine. Only the species well adapted can live in this extreme habitat.

In order to understand nervous adaptative mechanisms of vertebrates (Rodents and Reptiles) to these extreme conditions we examined two components of the brain: the hypothalamo-neurohypophysial system (HNS), involved in water balance, and the pineal gland and suprachiasmatic nuclei, involved in circadian rhythms responses.

In the HNS, we determined the cytoarchitectural particularities of the mean nuclei SON and PVN in these species: Numerous neuron-neuron appositions were observed in magnocellular nuclei system. Retraction of glial elements facilitates these appositions to enhance excitability and peptides release. To understand morphological interactions between astroglial and neuronal elements we performed electron microscopy and immunohistochemistry using polyclonal antibodies against the two neurohormones and glial fibrillary acidic protein (GFAP). Secretary activity of the HNS in desert animals is similar to that registered in experimentally dehydrated laboratory animals. By the same approaches, topography and cytological features of the pineal gland have been determined for diurnal and nocturnal rodents. Results show adaptative secretary profiles to the day / night cycle and to the seasonal photoperiods.

P003.15: Anorexigenic and orexigenic factors regulation in the rat dorsal vagal complex during stress-induced anorexia

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Food intake regulation in adult mammals is integrated mainly by two brain structures: the hypothalamus and the dorsal vagal complex (DVC), which involves a diversified array of neuroendocrine communications. Short-term regulation, which consists in reflex arrest of food intake under stomac filling or satiety reflex, is triggered by vagus nerve afferents to the DVC. Long-term regulation consists essentially in satiety reflex threshold modulation by "adiposity signals", which involve the hypothalamus and its reciprocal connections with the DVC. Stressful situations are well known to alter food intake and factors involved in its control. We showed recently that anorexia-inducing immobilization stress (IS) triggers different crain-derived neurotrophic factor (BDNF) recruitment patterns between DVC and hypothalamus. In the context of food intake, many

other gut hormones and factors act on hypothalamic and brainstem centres of appetite control, among them neuropeptide Y (NPY) and cocaine- and amphetamine- regulated transcript (CART). In order to investigate the involvement of the signalling of these peptides in the food control, notably in the context of food intake alterations (anorexia caused by stress), we analysed the hypothalamic and DVC expression of *NPY* and *CART* mRNAs. We showed, by using RT-PCR that the mRNAs of the two peptides display significant increases in stressed rats compared to controls, although with differential peaks. In hypothalamus, *NPY* and *CART* transcript up-regulation is observed at the end of IS and persists until 48-72h after IS. In the DVC, expression of the two transcripts peaks significantly at 24h post-stress and decline afterwards; NPY mRNA remains then significantly higher than in controls, whereas CART mRNA is down-regulated after 48h post-stress. The persistence of alteration of the expression of anorexigenic and orexigenic factors during the post-stress period could be highly related to the slow recovery of the hypothalamo-hypophyseo-adrenal (HPA) axis in IS and points to stress-induced plasticity in both nervous centres of food intake regulation.

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P003.16: Kisspeptin in the hypothalamus of the jerboa *(Jaculus orientalis)*: sexual dimorphism and seasonal variation

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In recent years, a substantial body of evidence has suggested that the hypothalamic peptide kisspeptin (Kp) and its receptor, kiss R, play a fundamental role in the regulation of reproduction notably for seasonal species.

The jerboa is a desert hibernator in which reproductive activity depends on seasons, being sexually active in spring-summer. The aim of this study was to determine the distribution of Kp neurons in the hypothalamus of adult jerboa in different seasons with a special attention to sex differences. Content of Kp was examined by immunohistochemistry using a highly specific polyclonal antibody (JVL-1) in male and female jerboas captured in the field of the Middle Atlas mountain (Morocco), either in spring or autumn season. The experiments were performed according to the recommendations of the local ethics committee, the approval of which is in accordance with international guidelines.

In animals captured during the spring season, neuronal cell bodies and fibers displaying Kp immunoreactivity were observed within the mediobasal hypothalamus along its rostrocaudal extent. In the anteroventral periventricular nucleus, the number of Kp- immunoreactive (ir) neurons was notably higher in female than in male jerboas; such finding confirms that the expression of Kp in neurons of this nucleus is sexually dimorphic, as previously documented in other mammals. In the arcuate nucleus, a sparse distribution of Kp-ir elements was noted. The median eminence, site of neurohormone release, exhibited a much higher density of Kp-ir fibers in the female as compared

to male jerboas indicating that these Kp-ir fibers may arise from the anteroventral periventricular nucleus. The seasonal study showed that the number of Kp-ir neurons in the caudal part of the arcuate nucleus was more than two-fold higher during spring than autumn.

In conclusion, this study reports the first mapping of Kp-ir neurons in the hypothalamus of a desert species. The results provide morpho-functional arguments in favor of a stimulatory control of Kp in ovary activity and in neuroendocrine events which regulate seasonal reproduction in jerboa.

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Poster Session P004: Technological developments – Chaired by Beatriz Rey & Fakhita Regragui

P004.17: Comparative Study between Bias Correction Algorithms in Magnetic Resonance Imaging

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Magnetic resonance images are often corrupted by an artifact called bias field or intensity inhomogeneity or shading artifact: a slow and smooth variation in the intensity of the image for the same tissue. The bias field is mainly due to non-homogeneity of the RF field, and increases significantly with increasing field strengths. It is generally modelled by a multiplicative field variable, which changes smoothly and slowly.

Bias field is unique to MRI. Given the brain's ability to correct image imperfections, it is virtually invisible to the human eye. However, it can cause errors in segmentation, and consequent misinterpretation. To avoid this difficulty, MRI images are often preprocessed to reduce the effects of bias before segmentation.

In our work, we make a comparative study of seven bias correction algorithms: the Eq algorithm from Cohen & al, the algorithm proposed by Mangin and al. incorporated in the Brainvisa software, Ashburner and Friston's algorithm, developed with SPM5, Styner and al.'s algorithm provided with the ITK library, EMS from Van Leemput and al. and finally Shattuck et al's BFC algorithm, available in Brainsuite. All these algorithms can be classified into two broad categories: those which aim only to correct the bias and and those which alternate correction and segmentation.

Our study was conducted in 3 steps:

- Estimation of corrected image bias and comparison with real bias present in images.

- Generation of histograms for corrected images and comparison with the ideal histograms for the images.

- Segmentation of corrected images and comparison with the ideal segmentation. We have tested these approaches on brain MRI corrupted with a known percentage of bias (40%).

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P004.18: 3D MR Brain Images segmentation using fuzzy methods: FCM and BCFCM

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In this work we present a method of 3D MRI segmentation, which allows physicians to have accurate information about the characteristics of the elements contained in the image. The method must be able to read 3D images, to display them slice by slice, and to perform some processing of three-dimensional nature. Among these processes, we propose a segmentation of volume images; the result is the extraction of the three core subjects makes up the brain, namely the gray matter, white matter and cerebrospinal fluid, knowing that they can be the seat of certain diseases such as stroke, tumors, etc. Due to the vagueness of a voxel belonging to a given class (brain structure), we chose fuzzy methods.We use two methods of fuzzy partitioning: algorithm averages fuzzy (FCM: Fuzzy C-Mean) and the fuzzy correction of the bias (BCFCM: Bias Correction FCM).

The FCM algorithm has been widely used for segmentation of brain images, whatever the modality and type of acquisition (single or multi-spectral). The modelling of vagueness on membership of a pixel (voxel) to a certain class is done by considering gradual boundaries instead of sharp boundaries between classes. The uncertainty expressed by the fact that a pixel has both attributes that assign a class to another. The fuzzy classification assigns, not a label on a single class for a pixel, but its degree of belonging to each class. These values express the uncertain membership of a pixel to a region, and are called degrees of belonging. The degree of membership lies in the interval [0,1], and the classes obtained are not necessarily disjoint.

The correction of the bias field can also be coupled to the segmentation process. Many methods are choosing this path, because the segmentation is often the ultimate aim to achieve. The technique is to standardize the MRI intensity in the same class: white matter, gray matter, CSF, and to alternate segmentation and bias correction. The BCFCM method proposed is based on the FCM algorithm. This algorithm including the immediate vicinity as the limit of adjustment to ensure that the estimated field is smooth. The BCFCM algorithm is insensitive to noise, but the volume of calculations is heavy.

This method is used to segment three-dimensional images.

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P004.19: Brain MRI segmentation by snakes. Image processing for the detection of functional areas affected by stroke in the brain MRI

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Segmentation by active contours is a special technique; its main advantage is that it provides an a priori guarantee that a contour will always consist of a string of points. This eliminates the need for monitoring algorithms to decide whether or not specific pixels need to be included in the contour. In other approaches contour points rarely form closed curves, and a closing step is usually is

necessary. A further advantage of the active contour technique is that it allows segmentation even when contours are not sharp.

In this article we describe the use of the technique to segment MRI images from the brains of healthy subjects and of stroke patients. We apply a number of different active contour models, focusing particularly on methods using a set of levels.

Deformable models are a very general tool used in fields as diverse as pattern recognition, animation, geometric modelling and simulation. Active contours are a class of deformable model, first introduced by Kass, that makes it possible to extract key visual features of images, such as the edges of objects or parts of boundaries. When applied to image segmentation, the active contours approach identifies boundaries among objects using intensity and geometric constraints associated with the objects concerned. The basic idea is to gradually deform an initial curve (2D) or surface (3D) producing the best possible fit with the boundaries of an object. The desired goals are integrated in the formulation of the model which guides the deformation process. In the classical model, the deformation process is based on the minimization of a functional, representing the geometric characteristics of the curve (or surface) and the image. This model has drawbacks that can be solved by applying "the geometric model". This model is based on equations describing the evolution of plane curves and surfaces, and their implementation as a set of levels. In this model, the desired contours or surfaces are considered as contours of a function defined over the whole support of the image.

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P004.20: Original Molecule versus Generics of Antidepressants Commercialized in Morocco: A BOLD-fMRI Study in healthy subjects

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The field of generic medicines underwent an immense development during the last decade. Antidepressants using inhibition and recapture of the serotonin mechanisms were also a subject of this development, especially the fluoxetine molecule that has 6 generics commercialized in the Moroccan pharmaceutical market. However the main issue is how efficient are these generics compared to the original molecule? In this study, we address this question using BOLD fMRI, using one of the most common molecules, the fluoxetine. Considering that fluoxetine generates motor and sensory hyperactivity by increasing the cortical oxygenation, neurogenesis, plasticity and excitability. We aim to compare the neurophysiological effects the original molecule (fluoxetine) and generic medicines that are extensively used for helping the treatment of ischemia.

Healthy volunteers (n=36; age 22-30 years old) were recruited among non-smoking subjects without a history of neurological and psychiatric diseases, and gave informed and written consent. They subjects were assigned to 6 different groups: one group received fluoxetine, 4 groups received one of 3 fluoxetine generics (G1, G2, G3) and one group received a placebo (P1). The

study was conducted using a double blind approach. A psychometric evaluation was achieved for assessing the depressive character of volunteers using BDI (Beck Depression Inventory) before the administration of the treatment. The functional MRI using BOLD measurement was performed before the administration of the treatment and 45 min after (half-life of different molecules). The subjects executed the motor task during 30 seconds alternated with 30 second off in block design. The BOLD-fMRI data was analyzed using "Statistical Parametric Mapping" package (SPM). An evaluation of maximal intensities and volumes of activation in all subjects before and after treatment administration was made.

The cerebral activations (intensity and volume) before the administration of the drug were similar in all groups of subjects, including the placebo group before or after treatment. However a significant difference in activation was found between fluoxetine and two generics: G2 and G3. However, in one generic molecule (G1), activation was not different compared to fluoxetine.

We conclude that antidepressant generics available in Morocco, which use inhibition and recapture of the serotonin mechanisms, do not have the same impact therapeutic value compared to the original molecule (fluoxetine). Especially when used for enhancing the oxygenation of the cortical area of brain after ischemia. This study suggests that generic molecules have to be tested for their bioequivalence before any promotion and prescription for patients.