CRNL - Centre de recherche en neurosciences de Lyon

Rapport Hcéres

agence d'évaluation de la recherche
et de l'enseignement supérieur

Section des Unités de recherche

AERES report on the research unit

Lyon Neuroscience Research Center

From the

University Lyon 1

CNRS

INSERM

May 2010

agence d'évaluation de la recherche
et de l'enseignement supérieur

Section des Unités de recherche

AERES report on the research unit

Lyon Neuroscience Research Center

From the

University Lyon 1

CNRS

INSERM

Le Président de l'AERES	Section des unités de recherche
	Le Directeur
Jean-François Dhainaut	**Pierre Glorieux**

May 2010

Research Unit

Name of the research unit : LYON NEUROSCIENCE RESEARCH CENTER

Requested label : UMR_S INSERM, UMR CNRS

N° in the case of renewal

Name of the director : M. Olivier BERTRAND

Members of the review committee

Committee chairman

M. Jean-Jacques BENOLIEL, University Paris 6, France

Other committee members

M. Ole ANDREASSEN, University of Oslo, Norway

Mrs Anne BARON-VAN EVERCOOREN, University Paris 6, France

M. Niels BIRBAUMER, University of Tübingen, Germany

M. David CAREY, University of Aberdeen, UK

M. Serge CHARPAK, INSERM, Paris

M. Hervé CHNEIWEISS, Centre de Psychiatrie et Neurosciences, Paris, France

M. John EBERSOLE, University of Chicago Hospitals, USA

M. Matthias KOEPP, University College of London, UK

M. Christian LORENZI, ENS, France

M. David MOORE, MRC Institute of Hearing Research, University Park, UK

M. Friedemann PULVERMULLER, MRC Cognition and Brain Sciences Unit, UK

M. Emmanuel STIP*, Centre de recherche Fernand-Seguin, Canada

M. Mehdi TAFTI, University of Lausanne, Suisse

Mrs Irene TRACEY, University of Oxford, UK

Mrs Deidre WILSON, University College London, UK

M. Frank ZUFALL*, University of Saarland School of Medicine, Germany

* not present for the visit but contributed to the evaluation by sending writen report

Committee members suggested by CNU, CoNRS, CSS INSERM, CSS INRA, INRIA, IRD

M. Jean-Marie CABELGUEN, CNU member

M. Alain ESCHALIER, INSERM CSS member

Mrs Isabelle MAILLOCHON, CNRS member

Mrs Laure RONDI-REIG, University Paris 6, France

M. Lotfi SENHADJI, INSERM CSS member

Observers

AERES scientific advisor

M. Christophe BERNARD

University, School and Research Organization representatives

M. Lionel COLLET, University Lyon 1

Mrs Marie-Hélène LAFARGE, University Saint-Etienne

M. Amandine LHERITIER, CNRS

Mrs Marie-Josèphe LEROY-ZAMIA, chargée de mission Dpt Evaluation INSERM

M. Bernard POULAIN, DSA INSB CNRS :

Mrs Anne JOUVENCEAU , ITMO Neurosciences

Report

1 • Introduction

- Date and execution of the visit

The site visit took place in Lyon on february 1st, 2nd and 3rd 2010. The committee was constituted by an international team scientists with expertise in the area of scientific interest represented by the 14 teams of research being evaluated. Two experts (F. Zufall and E. Stip) were absent. However, they have sent their reports before the beginning of the visit.

- History and geographical localization of the research unit, and brief presentation of its field and scientific activities

The Lyon Neuroscience Research Center project includes 14 teams stemming from 11 laboratories (5 CNRS, 5 INSERM and 1 EA). The project is characterized by a multidisciplinary approach on integrative neurophysiology and its related disorders, with an important translational research facet.

The research center hosts 134 researchers (28 INSERM, 38 CNRS, 18 university, 38 university-clinician, 12 clinicians), 69 technical and administrative (28 INSERM, 19 CNRS, 21 university, 1 hospital) and 90 PhD students, post-docs and non-permanent personnel.

At the present time the teams are geographically dispersed. In 2013, 9 teams will join in a 6000 m2 new building, while the others will remain on their sites: the East-Lyon Hospital. This project, named NeuroCampus operation is financed (13.5 MEuros) by a State-Region program contract.

- Management team

The center will be directed by Olivier Bertrand and the leaders of team 4 and 5 will serve as Deputy-Directors. The board of team leaders consisting of all team leaders will meet with the Director and the Deputy-Directors on a monthly basis.

- Staff members

	Past	Future
N1: Number of researchers with teaching duties (Form 2.1 of the application file)	56	56
N2: Number of full time researchers from research organizations (Form 2.3 of the application file)	67	66
N3: Number of other researchers including postdoctoral fellows (Form 2.2 and 2.4 of the application file)	32	34
N4: Number of engineers, technicians and administrative staff with a tenured position (Form 2.5 of the application file)	71	64
N5: Number of other engineers, technicians and administrative staff (Form 2.6 of the application file)	13	7
N6: Number of Ph.D. students (Form 2.7 of the application file)	76	61
N7: Number of staff members with a HDR or a similar grade	91	91

2 • Overall appreciation on the research unit

- Summary

One of the 2 main research axes concerns the integrative and cognitive neurophysiology. It is focused on 3 scientific topics. The first one aims to study the neural substrate of perception (audition, vision, olfaction, pain), the influence of multiple factors (stimulus context, attention, expectation…) and the neurophysiology of action (motor and oculomotor control, perception-action-attention interactions, body representation). The second one is focused on memory and high-level cognition, including language, music, emotion and social cognition. The third one studies the physiological mechanisms underlying sleep and wakefulness. The second main research axis of the center involves the study of the molecular and cellular physiology and pathophysiology mechanisms. The main aim of this axis is to contribute to the better understanding of these mechanisms i) at different level of integrative neurophysiology (olfactory plasticity) ii) their dysfunctions in neurological disorders (sleep/wake, epilepsy, depression, brain tumours) iii) in the interactions between nervous and immune systems in neuro-inflammatory processes (multiple sclerosis, aging pathologies).

Thanks to the involvement of the university-clinicians, the two axes have important medical outcomes in terms of diagnostic and prognostic markers and innovative therapies.

To achieve their goals, various and complementary methodological approaches, available in the center, will be used in animals and human studies (electrophysiology, neuroimaging, psychophysics combined with behavioural measures, neuropsychology, brain stimulation, transgenic animals, pathological cell lines, radiopharmacological markers,…).

- Strengths and opportunities

- The committee has noticed the excellent leadership of the Director. He is internationally recognized in his field and has a strong support not only from team leaders but also from most individuals the committee members met during the specific meetings with researchers, technicians and PhD students and post-docs.

- The dynamics of the center was clearly apparent during the discussion with the staff. Indeed, the 3 meetings organized with the different categories of staff clearly demonstrated the enthusiasm of

researchers and technicians to create the center. All are convinced that the center and the new building will efficiently contribute to the visibility of Lyon Neurosciences and to better work conditions.

- The dynamics of the center was also highlighted by numerous translational projects involving several teams each. The main projects are focused on: cognition and neurodevelopmental disorders, adult and child epilepsy, Alzheimer's disease and innovative rehabilitation procedures. All teams are involved in one project, at least.

- The project is strongly supported by the university as shown by the meeting with the president of university Lyon 1 which has the ambition to create 2 centers of research, the present one and one in cancer.

- The committee considers that the technological platforms and the translational research are the main strengths of the scientific project

• Weaknesses and threats

- The dynamics of the center must be improved. From organization point of view, the present project seems to be the continuation of the IFR in Neurosciences. For instance, except for team 10 which results from the fusion of distinct units, the others have previously been constituted. Thus, a Scientific Advisory Board (SAB) must be rapidly created, that can make new recommendations on specific projects and interactions among different teams. The internal chart of the center was not communicated to the committee. Allocation of resources is not clearly defined.

- Until, at least 2013, the teams will be dispersed on different sites. Therefore, the policy in terms of recruitment of new teams remains fuzzy, and no specific plans are foreseen. Only 300 m2 will remain available in the new building for new teams. Moreover, in accordance with the SAB, it would be useful to identify which field is missing or must be reinforced.

- In general, the number of foreign PhD and post-docs is low. This raises the question of the international visibility of the teams.

- The size of teams is highly variable, some exceeding more than 10 researchers others with less than 5.

- Many studies are based on access to 3T human MRI scanner and it is unclear how this will be solved.

• Recommendations to the head of the research unit

Gathering together the existing teams with their heads does not create a real center. For instance, some teams, by their size and their dynamics, correspond perfectly to what is expected for a center. In contrast, in other teams, there are too many researchers who develop distinct axes in their projects, justifying that these teams could be split in 2 or 3 smaller but independent teams. Thus, the head of center must support the emergence of new leaders. The committee considers that an effort must be made to receive new teams with the idea to bring new technologies and/or thematic, such as modeling, biomathematics, molecular genetics, molecular neuroimaging. At least, the interactions between the teams could be improved by supporting transversal programs and interactions between Ph.D./postdocs across teams. In this context, the recommendations of the SAB will be very useful.

- Production results

A1: Number of permanent researchers with or without teaching duties (recorded in N1 and N2) who are active in research	122
A2: Number of other researchers (recorded in N3, N4 and N5) who are active in research	67
A3: Ratio of members who are active in research among permanent researchers [(A1)/(N1 + N2)]	1.0
A4: Number of HDR granted during the past 4 years	26
A5: Number of PhD granted during the past 4 years	87

3 • Specific comments in the research unit

The overall productivity is very good. During the past four years, the teams produced more than 900 publications, of which 41 with an impact factor >10 and 151 with IF between 6 and 10. Eighty seven PhDs have been defended.

As illustrated by the numerous recruitments of permanent researchers coming mainly from other laboratories in Lyon and of French post-docs the National and local attractiveness is very good. Moreover, they benefit from several grants from ANR (31) and PHRC (16). The center is considered as a highest priority by the university.

The members of the center have been awarded several medals from the CNRS.

The international visibility of the researchers of the center seems to be very good as reflected by the numerous invited talks (more than 400 in international conferences, workshops or seminars). However, the international attractiveness could be improved, given the present low number of foreign post-docs.

The industrial collaborations and transfers are very good. The center has filed 13 patents and 6 patent extensions during the past 4 years. The partnership with industry is strong (28 contracts for 1.4 MEuros). One start-up has been created in 2008.

Except the weaknesses mentioned above, the committee was satisfied with the management and life of the research teams. They have host a large number of speakers. 3 active journal clubs are well attended. Many actions are foreseen to reinforce the internal and external communication by promoting new journal clubs in emerging domains, by organizing the Annual Lyon Neuroscience, and by supporting the organization of International Workshops or Seminars.

To improve and optimize the international dissemination of knowledge, the first step of this process has been to identify the members ready to share their scientific and technical expertise. For this purpose, a questionnaire is accessible to all members via an internal website.

Several members of the center are strongly involved in teaching activities.

The meeting with ITA clearly showed that, whatever the affectation (specific teams or core facilities), they seem very satisfied. Their requests seem to be taken into account by the director. They are in charge of important tasks (health and security, for example). In terms of publishing policy, ITA are authors in most publications.

The present proposal is of high quality in the field of integrative and cognitive neurophysiology. The project is relevant and feasible within the next 4 years. It is based on powerful platforms. The CERMEP imaging platform have PET, 1.5 T MRI and MEG for human studies and micro-PET and 7T MRI for small animals. The micro-PET will be renewed in 2010. A new 3T MRI dedicated to behaving primate studies should be available in 2011. The "mouvement et handicap" platform has been created by members of the center. This platform is devoted to the human movement analysis (3D eye-hand coordination, visual-motor behavior, posture and gait, 3D kinematics analyses, real-time environment control). The clinical platform for intracranial stereotaxic EEG recording is devoted to the functional pre-surgery evaluation of epilepsy patients implanted with depth electrodes. It allows the access to the dynamics of functional brain networks involved in epilepsy pathophysiology, pain integration, auditory, visual and olfactory cognition, sleep and emotions. The "ProfilXpert" platform is devoted to the genomic analysis. This platform has obtained the IBISA certification in 2009 and offers fee-for-service to laboratories outside the center, including foreign laboratories. Finally the "Neurochem" platform has also obtained the IBISA label in 2009. It is devoted to in vivo, in vitro and ex vivo neurochemical studies.

Concerning funding, external grants represent 70% of total budget. The specific budget of the center will represent 8% of the total budget. It will be devoted to support new emerging platforms or services, scientific meetings, internal system of information, and to recruit a grant officer.

Team 1 : Dynamique cérébrale et cognition

Team leader : Olivier BERTRAND

- Staff members (on the basis of the application file submitted to the AERES)

	Past	Future
N1: Number of researchers with teaching duties (Form 2.1 of the application file)	2	1
N2: Number of full time researchers from research organizations (Form 2.3 of the application file)	8	9
N3: Number of other researchers including postdoctoral fellows (Form 2.2 and 2.4 of the application file)	6	6*
N4: Number of engineers, technicians and administrative staff with a tenured position (Form 2.5 of the application file)	6	6
N5: Number of other engineers, technicians and administrative staff (Form 2.6 of the application file)	0	0
N6: Number of Ph.D. students (Form 2.7 of the application file)	6	5
N7: Number of staff members with a HDR or a similar grade	8	5

- Appreciation of the results

The past work of this team is of highest international standing, greatest impact and full of translational perspectives. An impressive ~190 papers has been published between 2005 and 2009, many of them in high impact journals. Collaborative links have been built with centres Europe-wide and a range of grants, both national and international, could be secured. The team leader's international scientific standing and his visibility as one of the world's leading system neuroscientists stems from his pioneering publications on the neuronal and cognitive meaning of gamma oscillations in the human brain. Despite strong initial resistance from the neuroscientific community he and his collaborators were able to prove beyond any doubt that gamma oscillations are the process by which associative networks are connected and neuronal cell assemblies are built! To underscore the standing of this group in the top 5% of the world's human systemic neurosciences the scientific literature on gamma band exploded after Bertrand's publications, stimulating and creating a whole field. His papers in the J. Neuroscience and other high impact Journals on the meaning of gamma band are classics in the field. The extension of their immense expertise to Brain-Computer Interfaces and Disturbances of Consciousness will bring them to the forefront of the field. The most interesting New Neuroscience Journal (Frontiers in Neuroscience) made the team leader an Associate Editor acknowledging his world leading position. These projects on gamma waves should remain the focus of research of the group.

- Appreciation on the Project

The project lines 6 and 7 are clinically most promising if the behavioral principles of brain control developed in projects 1, 2 and 3 are used in projects 5, 6 and 7. I.e. the Epilepsy unit should use the neurofeedback approaches of the other projects and use neurofeedback also in implanted patients. Of particular relevance and importance in the Altered States project 6: a collaboration with other European groups (Belgium, Germany) should be realized: the widespread misdiagnosis and neglect of vegetative state, locked-in and apallic patients and their needs to be resolved. Only a thorough scientific investigation as planned here is the answer to this urgent health issue and ethical dilemma. Particularly Bertrand's knowledge and experience with gamma oscillations will be implemented in project 6.

Investigating perception, attention, social interaction, learning, dream sleep and epilepsy by looking at high frequency synchronous oscillations along with standard neurophysiological measures will, with great certainty, lead to a range of new theoretical insights along with translational impact.

- Weaknesses and Threats

They wish to include presently fashionable topics such as social cognition (see project 4) and the committee has strong doubts about its longevity, but this is a young project in the lab that will be reinforced by a newly coming researcher. They obviously wish to pursue this field for two reasons: for basic research on social interaction perception based on mirror neuron system, and for clinical application in Alzheimer's disease (early markers) and in autism.

The group is highly competitive and well organized. The funding of the whole project will increase the coherence and exchange between the 8 sub-projects and function as the "flagship" for the whole Lyon-Neuroscience Centre.

Team 2 : Neuroplasticité et neuropathologie du système olfactif

Team leader : Anne DIDIER

- Staff members (on the basis of the application file submitted to the AERES)

	Past	Future
N1: Number of researchers with teaching duties (Form 2.1 of the application file)	3	2
N2: Number of full time researchers from research organizations (Form 2.3 of the application file)	2	2
N3: Number of other researchers including postdoctoral fellows (Form 2.2 and 2.4 of the application file)	1	0
N4: Number of engineers, technicians and administrative staff with a tenured position (Form 2.5 of the application file)	8°	8°
N5: Number of other engineers, technicians and administrative staff (Form 2.6 of the application file)	1	0
N6: Number of Ph.D. students (Form 2.7 of the application file)	5	5
N7: Number of staff members with a HDR or a similar grade	3	3

°7 are shared with 4 teams (Didier, Gervais, Thai-Van, Tillmann)

- Appreciation on the results

The research emphasises the tie up between human and mouse research to cover the whole field from molecules to behaviour. While this is potentially a strength of the work, it also represents an enormous challenge. For example, the relation between hedonic aspects of olfaction, which is potentially a unique and positive reason for studying olfaction, is going to be very difficult to relate across such diverse species. Some unique aspects of olfaction – hedonics (as above), adult neurogenesis, accessibility of peripheral and brain structures, impact of experience, clinical relevance (e.g. aging and possible early diagnosis of Alzheimer's) – should be emphasised in both sides of the research (human, mouse), but the tie in between the two sides should be de-emphasised. Judging by the output of the senior researchers remaining with the team, their work is productive and evaluated by peers to be internationally leading.

The publication track record of this team is very good, both in terms of number and quality. There are several papers in leading journals (PLoS One, J Neurosci, Learn Mem), with others in the pipeline, as well as plenty of papers in more specialist journals. Other dissemination activities are at an appropriate level. Graduate student supervision is also appropriate.

A particular strength of this group is their industrial collaborations with the cosmetic and pharmaceutical industries. In addition, they list a number of national and international academic collaborations.

The level of international engagement (invitations to review papers and to present at meetings) is appropriate for a team with an international reputation. One CNRS bronze medal was obtained.

This team has recruited two very talented young scientists within the last 18 months.

A large number of funding sources is listed, including CNRS and EU (Curie Fellowship)

- Conclusion :

  - Summary

This is a very strong team doing cutting edge research with international impact. There are considerable scientific (interpretational) challenges to be addressed (as above and below. The high impact and productivity of the team speak for themselves.

  - Strengths and opportunities

This team is young and dynamic. It is a real team. The opportunity to collaborate within the newly formed team, which is clearly being taken, is a huge strength, together with the individual and collective productivity of the team members. The obvious opportunity is to establish and promote collaboration with other Centre members. The listed benefits of the Centre (clinical collaborations, other sensory modalities, imaging, neurobiology, learning deficits) are all interesting.

  - Weaknesses and threats

The main concern is the limitation to the strongly advocated linkage between the human and animal works because it is so strongly pushed. The individual components of the work are very strong.

Team 3 : Intégration Centrale de la Douleur

Team leader : Luis GARCIA-LARREA

- Staff members (on the basis of the application file submitted to the AERES)

	Past	Future
N1: Number of researchers with teaching duties (Form 2.1 of the application file)	4	4
N2: Number of full time researchers from research organizations (Form 2.3 of the application file)	3	3
N3: Number of other researchers including postdoctoral fellows (Form 2.2 and 2.4 of the application file)	6	6
N4: Number of engineers, technicians and administrative staff with a tenured position (Form 2.5 of the application file)	2	2
N5: Number of other engineers, technicians and administrative staff (Form 2.6 of the application file)	1	1
N6: Number of Ph.D. students (Form 2.7 of the application file)	6	8
N7: Number of staff members with a HDR or a similar grade	8	8

- Appreciation on the results

Highly original proposal that is rooted in excellent basic science translated to clinical pain conditions of significance relevance. The quality and impact of the work will be very strong. Further, they have proven track record of rapid translation of research into diagnostic and therapeutic methods. Excellent and integrated clinical links and collaborations.

Excellent track-record of high quality, high impact studies. 45 papers in past 5 years, 23 with IF>5 for 4 full-time equivalents. 20 papers cited more than 100 times, so very good citation indexes reflecting the high value the community places on their work. More than 60 invited lectures abroad during 2005-2009, Neurosciences Award from Institut de France 2009. Internationally recognised as leading team for EEG and cortical stimulation studies related to pain. Nine PhD theses and 6 postdocs in last 4 years. Laboratory recognised as an excellent training environment.

Quality and stability of partnerships is excellent, particularly the clinical partnerships and collaborations between Universities (two Hospitals, UCB Lyon and UJM St. Etienne).

The Neurosciences Award from Institut de France has been awarded to the team leader. Invitations abound for the team leader and others associated with this team to give lectures, run workshops, provide advice. It should be mentioned specifically that one PU-PH is a notable international figure of significant standing, which is impressive considering his demanding clinical duties. The younger members of the team are of the highest qualitybeing recognised as leading scientists. Their depth is good for succession planning as more senior members move towards retirement. There is however a need to recruit one or two young scientists.

International presence of post-docs and students is limited despite the potential attractiveness of the group. as proven by their international collaborations. Increasing recruitment from abroad should strongly be encouraged.

72% of funding comes from external sources and includes: 1 PHRC, 1 Ministère (collectivités territoriales), 1 from CHU Le Vinatier, INSERM/CHU, foundations FRM, IRME, CNP, APICIL, NRJ

This is a highly dynamic team with very strong leadership and management. There is a clear strategy with identifiable goals set. There is clear cohesion between all members of the basic research team and their clinical colleagues. Future areas of growth and development should be supported, so that there is long-term security for this team and area of research in Lyon. The committee recommends to increase the number of junior permanent members with skills in the cognitive and methodological/analysis domains of imaging related experiments.

The project proposed is innovative, ambitious and is likely to produce highly original results of considerable potential impact. It is divided in 3 mutually-enriching areas which are logically deduced from the previous work. The strengths are: a very good interface between researchers and clinicans, international recognition in human pain neurophysiology, a good synergy between the university and hospitals provides a unique opportunity of rapid translation of research into diagnostic and therapeutic methods. Complementary competences (neurosciences, clinicians).

While some aspects are risky (creation of animal model), as noted by the Head himself, they are worth pursuing as the results will be of considerable merit, irrespective of outcome, and of value to the community. The PET design could be more sophisticated and they might want to consider more fully examining the dopaminergic as well as the opioidergic system (if resources allow, as these are very expensive experiments), considering its increasingly recognised role in chronic pain states. For the empathy studies, care will be needed to appropriately control for the obvious emotional, motivational and cognitive influences that their specific design will elicit to varying extents in controls and patients, making causal interpretations of any pain modification to 'empathy' itself difficult to unravel. For the challenging surgical studies, which will require considerable effort, it might be worth considering using a parametric design and monitoring decision making in prefrontal/anterior cingulate regions at the point of pain for their involvement in driving the motoric response, in addition to delineating how S1-M1 regions are involved in driving the motoric pain response, as this will increase the novelty of information obtained. For the cortical stimulation studies, it is advisable to test prefrontal regions in more simple human models of ongoing pain before moving to patients, where arguably the brain structure might be altered and other factors make again interpretation difficult. Controlling for placebo effects will be necessary. For the LEP patient studies, the predictive capability of altered LEPs prior to patient report of pain is of considerable interest and value. For other aspects described, it is important to develop its capacity to deliver mechanistic information that is over and above correlating signals with the subjective report of heightened pain and therefore 'generalised' amplification of nociceptive inputs. It is important to identify how and specifically from where this amplification might occur, so that the information has true diagnostic value to allow appropriate targeting of treatments. For the sleep studies, it is advisable to consider recording in the brainstem too, considering the presence there and involvement of serotonergic systems relevant to pain (i.e. descending facilitation). Also, a 'brain-reading' approach to examine pre-nociceptive stimulus patterns of thalamo-cortical coupling that might predict nociceptive inputs being processed differentially (and leading to pain breakthrough) should be considered.

- Conclusion :

  - Summary

An outstanding group performing innovative research at the highest level.

  - Strengths and opportunities

Excellent strengths in the leadership, quality of the senior and junior staff, as well as clinical collaborators. Tremendous opportunities for further links and collaborations should the creation of a neuroscience centre occur. Opportunities to expand the functional imaging work should be encouraged with more staff and access to a designated human 3 T system, in addition to PET studies using novel ligands. The clinical work is excellent and the translational opportunities of their basic science findings should be further supported and encouraged with direct support of more staff. It will be of benefit to release one clinician from some clinical duties so he could focus more time for research.

– Weaknesses and threats

Threat is the one raised themselves regarding the age of the senior members of the team and therefore the need to consider further recruitment and development of younger members to take on leadership roles in future years.

The number of foreign PhD and post-doc is low.

Team 4 : Codage et mémoire olfactive

Team leader : Rémi GERVAIS

- Staff members (on the basis of the application file submitted to the AERES)

	Past	Future
N1: Number of researchers with teaching duties (Form 2.1 of the application file)	6	4
N2: Number of full time researchers from research organizations (Form 2.3 of the application file)	9	10
N3: Number of other researchers including postdoctoral fellows (Form 2.2 and 2.4 of the application file)	1	0
N4: Number of engineers, technicians and administrative staff with a tenured position (Form 2.5 of the application file)	8°	7°
N5: Number of other engineers, technicians and administrative staff (Form 2.6 of the application file)	1	1
N6: Number of Ph.D. students (Form 2.7 of the application file)	5	4
N7: Number of staff members with a HDR or a similar grade	6	6

- Appreciation on the results

The research team is active, specialist of olfaction and well known in France and internationally. It uses a wide range of techniques, from single cell recording (patch clamp recording, intra and extracellular recording, calcium imaging), multiunits and local field potential recordings (in anesthetized and freely moving animals) to fMRI imaging. The team is issued from a very large CNRS unit (UMR 5020) that comprised 6 teams. Of those, three have decided to apply independently, two teams studying audition and last one studying neuroplasticity in the olfactory bulb. The remaining three teams have decided to merge and present a single large team with fewer projects focussed on olfaction in both rodents and humans.

The past research has been successful and original. Most studies have been published in journals with moderate impact; however, a significant improvement has occurred in the last years, several studies being published in J.of Neuroscience, Human brain Mapping and Nature Neuroscience. These investigations covered the quality of olfactory receptor neuron responses to odor mixtures, the role and origins of oscillations in the olfactory bulb and pyriform cortex, the mapping of BOLD responses to odors in the olfactory bulb, the role of several brain regions of olfactory learning etc. In addition, the team has realized several technological developments: analysis software and odor delivery devices for fMRI.

During the last 4 years, the team has published about 60 papers, had about 25 invitations and numerous abstracts attesting of the team's visibility. (J Neurosci. 3, Nat Neurosci 1, Neuroimage 3, Eur. J. Neurosc. 5, J. Neurosci meth. 3, Cerebral Cortex 2, Human Brain Mapping 1).

The team recently attracted 2 CNRS researchers and plans to hire several young researchers.

The team has obtained 3 ANR grants and raised 540000 euros in the last 4 years. It has 8 international scientific collaborations.

- Conclusion :

  - Summary

The project for the next four years aims in two main directions: 1) olfactory coding and perception, 2) olfactory memory, both in rodents and animals. Among the subprojects, it is important to stress the originality of some of them, such as the study of the "accord" phenomenon at the cellular and behavioural level, the role of nutrition on odor perception, the use of multisite recordings to investigate episodic memory in the entire medial temporal lobe. Note that the team has a unique knowledge of in vivo multiunit recordings in the olfactory system in the world.

Overall, the project is perfectly relevant, original but not yet at the cutting edge although it is clearly getting near. Finally, the team's projects on human will strongly gain from the new center. Similarly, the other teams will also profit of the team's knowledge in vivo.

  - Strengths and opportunities

The team is unique in France in that it covers a large field of olfaction, from the physiology of olfactory receptor neurons to behaviour in rodents and humans. In addition, it has a strong technological know how, acknowledged in the world. The team leader plays a major role in neuroscience by taking the direction of the PhD neuroscience program in Lyon.

  - Weaknesses and threats

The team has decided to merge previous three teams in order to be stronger. The team is now rather big (10 researchers and 4 teaching-researchers) and this could slow down the emergence of young leaders. The actual leader is aware of the risk but has preferred to wait for the construction of the new center prior to push such emergence. The decision is questionable even though it clearly implicated all teams' researchers and was not decided by the team leader. Another weakness is that the team has published several studies in journals that were too specialized. Eliminating some subprojects would avoid the need for such publications and allow focussing on the most important ones.

  - Recommendations

A clear message should be given to ensure that smaller teams appear within the next few years.

The level of the research has strongly improved and the team should now systematically aim at publishing in the highest impact journals.

Team 5 : Neuro-Oncologie et Neuro-Inflammation

Team leader : Jérôme HONNORAT

- Staff members (on the basis of the application file submitted to the AERES)

	Past	Future
N1: Number of researchers with teaching duties (Form 2.1 of the application file)	13	13
N2: Number of full time researchers from research organizations (Form 2.3 of the application file)	8	6
N3: Number of other researchers including postdoctoral fellows (Form 2.2 and 2.4 of the application file)	4	4
N4: Number of engineers, technicians and administrative staff with a tenured position (Form 2.5 of the application file)	10	10
N5: Number of other engineers, technicians and administrative staff (Form 2.6 of the application file)	5	0
N6: Number of Ph.D. students (Form 2.7 of the application file)	9	3
N7: Number of staff members with a HDR or a similar grade	14	15°

- Appreciation on the results

The team made significant medical impacts in multiple sclerosis (epidemiology, therapeutics), paraneoplastic syndrome and brain tumors (diagnosis, impact on WHO classification, patent).

Contribution to common facilities:

I-Brain Platform using cellular and in vivo model of the blood-CSF barrier for both pharmaco-kinetic and fundamental studies of the blood-brain interfaces. It allows evaluating the bioavailability of drugs or antibodies in brain with a fee for service or research contract activity (pharmaceutical and biotechnology companies, public organizations).

NeuroBioTec. This Biological Resource Center, collecting human biological samples (blood, CSF or tissues), will increase its resources (tissue samples, DNA) and collections, namely for brain tumors, multiple sclerosis, paraneoplastic neurological syndromes, Alzheimer and other dementias, schizophrenia, epilepsy, autism, mental retardation.

More than 160 original publications, but mainly as collaborations within networks. However several are in the top 1% for neuro-inflammation and MS. Basic research need to get better results and publications.

Licensed patents

Some members are active in meetings organization

Great networking: Impressive efforts on partnerships with industrials (Nanobiotix, UCB, IDD-biotech), national partners (ANR (5), PHRC (2) ARH (2), AFFSAPS (1) European partnerships (Euronet and Neurobid) and valorization (7 patents with 5 of them subjected to PCT extension)

Several researchers of the team are recognized internationnaly as european program leader (MS) or head of learned sociaties and groups dedicated to specific pathologies (brain tumors). However, participation in editorial boards may be improved

Efforts were recently made to recruit foreign post-doc. Number of students might be increased considering the size of the group

They are very effective to raise funds: 2 european networks, 5 ANRs, 5 PHRC, 1AFFSAPS, Ministère, 2 GIS, 7 ARSEP, 1 ARC, 1 ELALigue C Cancer (5), Ligue SEP (1). The total was equal to 2. 789 K€ for 2007 and 3.358 K€ for 2009.

Their participation to international or national scientific networks and their ability to establish stable collaborations with foreign partners depends on topics and may be more in certain subfields (brain tumors, basic science on CRMPs).

Five topics adressed by groups from 2 to 9 peoples. Three clear axis appeared (MS epidemiology, blood/LCR barrier, CRMPs and brain tumors) and may lead hopefully, to some autonomy of these axes in the future. However, the responsibility of researchers is sometimes poorly outlined.

The leader is clearly acknowledged by the group as the coordinator. No particular cutting edge project or risk taking in the team project.

Several members are deeply involved in teaching. They are also implicated in scientific councils at the local level and in the organization of IFR 19. The team leader is also member of the steering committee of Neurodis (RTRS) and is head of the regional section "Neuro-oncology"

- Appreciation on the project

Any problem has been noted considering the grounds and fund raising. The existence and relevance of a policy for the allocation of ressources is very good. It seems from the passed experience that PIs request their own funds from external sources. As far as human ressources are concerned, 3 technical staff are being shared for histology, animal models and cell culture. Only aim/team 2 and 3 have technical staff, the 3 other ones do not.

Risk-taking is limited. No novel hypothesis or technic will be developped. A main strength is the availability of patients and the combination with clinical approaches. The project combines both basic and clinical approaches to identify new diagnosis and prognosis markers

(I) Guidance molecules (VEGF, CRMP and Syk kinases) determining neuronal polarity and regulating molecular mechanisms of axon and dendrite outgrowth may also participate to tumour and neuro-inflammatory processes

(II) The Blood-Brain and neuro-inflammation cerebral drug bioavailability

(III) Neural and hematopoietic precursors role in tumorogenesis and neuro-inflammation

(IV) Role of immune cells recruitment during neuro-inflammation and the effect of autoantibodies in Paraneoplastic neurological syndromes (PNS) and Devic's disease

- Conclusion :

  – Summary

A very broad project divided in 5 aims, some of which are complementary. The team is based on a solid pool of researchers and clinicians. Their entry in the Center will form a major core. Some of the subgroups have an excellent partnership strategy, a good publication and valorization policy. In addition, they have a good national and international visibility

All the subgroups and topics are not at the same level. Neuro-inflammation is among the top 10% at the international level. Other topics are good and solid and should be stengthened and developped to be more innovative and integrated in the glioma project.

- Strengths and opportunities

Very good fund raising

Very good networking

Very good interface with clinics

Very good interface with biotechs

Important facilities (CRB) and strong set of data that caan serve other projects

Bring a lot to the global project

- Weaknesses and threats

Size of the group

Very ambitious and widefield research project (neuroscience, oncology and immunology)

Heterogeneity of the group

- Recommendations

In terms of articles, they have to publish more from the real work and ideas of the group. Some researchers have to improve their scientific production.

An effort must be made to attrack students and foreign postdocs

In the future the three main axes may form individualized teams given that some of the researchers have the recognition and financial autonomy.

Team 6 : Physiologie intégrée du système d'éveil

Team leader : Jian-Sheng LIN

- Staff members (on the basis of the application file submitted to the AERES)

	Past	Future
N1: Number of researchers with teaching duties (Form 2.1 of the application file)	1	1
N2: Number of full time researchers from research organizations (Form 2.3 of the application file)	5	6
N3: Number of other researchers including postdoctoral fellows (Form 2.2 and 2.4 of the application file)	1	2
N4: Number of engineers, technicians and administrative staff with a tenured position (Form 2.5 of the application file)	6	5
N5: Number of other engineers, technicians and administrative staff (Form 2.6 of the application file)	0	0
N6: Number of Ph.D. students (Form 2.7 of the application file)	5	6
N7: Number of staff members with a HDR or a similar grade	5	6

- Appreciation on the results

This research team derives from the world-renowned original laboratory headed by Michel Jouvet and has a long lasting leading reputation originally in dissecting the mechanisms generating REM or paradoxical sleep and later on the discovery and the role of the histaminergic system in the vigilance states. The team leader has been pioneer in the recent and important role of the histamine neurotransmission and his own work is highly original, and has an important impact in the field of sleep research. He is considered worldwide as the best specialist in his expertise. The change from PS to systems regulating wakefulness is also very original because to the best of committee's knowledge no other lab in the world is focusing on this important topic. Nevertheless, since several researchers have been recently recruited, their past records cannot be considered at this stage.

The overall number and quality of publications remains at a good level. 20 or 22 out of the 56 peer reviewed publications listed are stemming from the lab, others are from newly recruited researchers and concern work done elsewhere. Although 6 PhD works are ongoing, only 2 have been completed during the last 4 years, again on the basic side since 4 others are listed but are most probably medical theses. The team leader is well represented at the international scientific level in terms of communication.

The group obtained 2 national and 2 European meeting travel awards. 1 national poster prize and 1 Young Investigator award at the EHRS meeting. 6 invited lectures at international meeting.

4 CR1 were recruited since 2007, one is a neurochemist and specialized in neurotransmitter detection by biosensors, one is a Drosophila specialist working on sleep (rest) in this model and coming from one of the leader groups in the field, one is a physiologist specialized in human metabolism and sleep and is recruited from abroad (Belgium), and one electrophysiologist a former PhD student in the same lab. 3 MDs are affiliated, one specialist in pediatric sleep with established reputation, two others are specialized in pediatric pulmonology and in geriatry. Although the expertise of a clinician specialized in narcolepsy sounds reasonable and will help further development and transfer of basic knowledge, the other medical collaborators seem somehow far from the main research topic of the lab. Recent developments of research activities include hypocretin (orexin) pathway and a researcher specialized in this field would be a great asset.

Although limited, the group seems to have the ability to attract both institutional and industry funds. A main focus should be a close collaboration with industry to develop a new class of anti H3 drugs as stimulants.

One member has 2 ANR contracts of correct size, other national partners are of small size, very recent (2008-2009) and mainly on human metabolism or sleep disorders. 3 European collaborations date back to 2002-20003 and only a recent one (2007) has been established with the Brain and Mind Institute (EPFL Lausanne). Overall collaborations with other labs seem very limited.

The major results concern the main expertise of the lab, which is the histaminergic role in wakefulness. This unique expertise puts the laboratory on the edge of a new and rapidly growing field leading to the next generation wake-promoting drugs acting through H3 receptors. This is a major asset for the lab to establish and transfer their knowledge with important socio-economic impact.

As mentioned above, the recent expansion of the team is difficult to assess since the lab starts to grow beyond its expertise mainly by adding a new model (drosophila), which is highly competitive (3 major American groups share almost all production in the field) and a new topic (metabolism) mainly in humans.

The team leader seems to be the only person having some teaching activity. Nevertheless the lab coordinates and houses 2 facilities of high quality, one in AniRA-Neurochem and one in 2-photon microscopy (not yet established).

- Appreciation on the project

Overall 5 projects are proposed. The first project is on the role of histamine and orexin in wakefulness and sounds like a follow up and further work on ongoing research. The major aim seems to make use of KO mice for histamine and orexin receptors and ligands. Although the histamine pathway is a trademark of the lab, the orexin pathway is a highly competitive field. Nevertheless, the proposed projects on orexin are original not only within this project but also in the second project on the mechanisms of cortical wakefulness and alertness. The second project is probably the most interesting, original and potentially productive one. The 3d project on an insomnia model is also original and relevant to the main topic of the team on wakefulness. Given that the model has been characterized by the former one member's lab, it is not clear how competitive this project may be in terms of the international competition in the field. Nevertheless these 3 projects are sound, feasible, and have the necessary infrastructure and funding. The 4th project is on sleep and metabolic disorders, led by one member recently recruited. The topic is of great interest recently to the community although controversial. The addition of potential animal models may be helpful given again the competitive nature of the topic. The project is well funded and feasible. The last project is on the treatment of sleep disorders with preclinical and clinical trials, making use of both available animal models and patients. The rationale of the proposed projects is weak and there seems not to be basically designed from scientific background but motivated by the attractiveness of such approaches.

The resources seem to be adequately allocated based on the proposed projects.

The work on histamine pathway is on cutting edge and some newer projects are well designed and highly competitive. Although not within the expertise of the lab (drosophila or metabolism) the recruited researchers have an established record in the field.

- Conclusion :

  – Summary

The team has focused its main project on the mechanisms of wakefulness, a topic that to the best of our knowledge is unique and highly original. The new developments of the team are difficult to evaluate at this stage since most are relatively far from the lab's expertise and new researchers have been very recently recruited. Nevertheless the projects proposed are of good quality. The scientific production is within the standards of the field, although higher impact papers could be expected. The team does not have international collaborations needed to reinforce their activities as well as to strengthen their leading expertise. Their funding is limited given the number of people and projects and outside funding such as ERCs would substantially improve their production.

  – Strengths and opportunities

The team has a world leading reputation in basic sleep research and histaminergic neurotransmission. They have moved from the cat to the mouse model at the right time and acquired the necessary expertise to use highly valuable transgenic models. With their expertise in neuroanatomy, electrophysiology, and pharmacology, they are well placed to play a leading role.

– Weaknesses and threats

The major weakness and threat might come from the new development including the metabolism in humans and sleep in drosophila. Whether these will remain competitive at the international level needs future evaluation. The proposed expansion towards sleep disorders does not seem focused and would have been better suited on a model disorder such as either narcolepsy or insomnia and not going from Parkinson's disease to sleep apnea. A second major threat is by dispersion the team may lose the leadership in the field of histamine and sleep-wake.

– Recommendations

- More focused projects and collaborations with clinicians.

- Increase research funding (European, Foundations, or through collaborative projects).

- Major effort in designing projects able to produce high impact papers within reasonable timeline.

- Develop international collaborations and be present where needed to keep the leadership.

Team 7 : Physiopathologie des réseaux neuronaux du cycle veille-sommeil

Team leader : Pierre-Hervé LUPPI

- Staff members (on the basis of the application file submitted to the AERES)

	Past	Future
N1: Number of researchers with teaching duties (Form 2.1 of the application file)	0	0
N2: Number of full time researchers from research organizations (Form 2.3 of the application file)	7	7
N3: Number of other researchers including postdoctoral fellows (Form 2.2 and 2.4 of the application file)	2	0
N4: Number of engineers, technicians and administrative staff with a tenured position (Form 2.5 of the application file)	5	4
N5: Number of other engineers, technicians and administrative staff (Form 2.6 of the application file)	1	0
N6: Number of Ph.D. students (Form 2.7 of the application file)	4	3
N7: Number of staff members with a HDR or a similar grade	5	5

- Appreciation on the results

This research team derives also (as team 6) from the world renowned original laboratory headed by Michel Jouvet and has a long lasting leading reputation originally in dissecting the mechanisms generating REM or paradoxical sleep (PS), a topic that the team leader kept expanding since the establishment of his lab. The major expertise of the original team has been neuroanatomy of the PS neuronal network, and the team remains at the forefront of the field. They have added electrophysiology and introduced a new technique to record neuronal activity in vivo. More recently they started to tackle the function of PS by recruiting 2 researchers specialized in memory and behavior. They have also found that MCH neurons within the lateral hypothalamus are involved in PS. Altogether the team benefits from a large scientific recognition and in addition to be world-wide renowned as experts in the mechanisms of PS generation, their work has a substantial impact in the field of sleep research.

38 peer-reviewed papers have been published by the team since 2005, some in collaboration but most from their own work. The team has published 7 peer-reviewed papers per year during the last 4 years with IF>10 for 1, >6

for 5, >3 for 17 (mean IF= 4.64, range 1.75-14.17). The quality is good to very good but the productivity of each researcher is variable. 6 PhD students completed their thesis and 4 are currently engaged. The lab had 14 temporary visitors both national and international showing the attractiveness of their work. Several members are well represented at international meetings.

2 members of the team are regularly invited and co-organizers of international symposia.

2 CR1 were recruited, both of high quality with strong backgrounds and publication records. The team has attracted post-docs (2) and visitors (7) from abroad.

Although limited, the group seems to have the ability to attract both institutional and industry funds.

The team has 2 ANR contracts and several national partners but no international collaboration is listed.

The team has made significant contributions starting with the identification of the sublaterodorsal tegmental nucleus as the major PS site. They also showed that GABAergic and glutamatergic mechanisms and not as believed so far monoaminergic systems are regulating PS. They have also been the first to report the implication of the hypothalamic MCH neurons in PS. Their recent interest in the functions of PS with special focus on learning and memory and the molecular correlates are highly promising. They have also engineered a new sleep deprivation device that is being transferred to industry for further development and commercialization.

The team is optimally organized and well managed

Several members of the lab are actively involved in local and international teaching activities.

- Appreciation on the project

2 major projects are considered. The first and the most important one concerns the major topic and expertise of the lab on the mechanisms of PS generation and regulation, supported by an ANR contract. This ambitious project is at the cutting edge of available methods and techniques including a high quality functional neuroanatomy making use of viral transfection, optogenetics, gene expression analysis, SAGE library sequencing, and multiunit multisite electrophysiology. The second project concerns the function of PS by studying its role in learning and memory. This project has a strong rationale based on unpublished preliminary data, although impressive in amount, generated by using gene expression before and after PS deprivation and after PS rebound. Genes identified have already been thoroughly investigated by qRT-PCR, immunohistochemistry, in situ hybridization, tracing methods and cFos labeling and indicate a major impact of PS on molecular machinery at specific brain sites such as the cortex and the hippocampus. Many of the identified genes are synaptic plasticity-related and induced by PS in limbic structures suggesting a major role for PS in learning and memory. This work should be rapidly published. Their new hypothesis that not only PS is involved in memory consolidation but also that slow wave sleep might be involved in erasing working memory is highly appealing and the recruitment of a specialist in the field of behavior and memory in rodents is highly valuable to further their efforts to dissect these important functions of sleep. The team has all necessary expertise and proposed projects are sound and feasible within the next 4 years, although they might need more support, especially in funding.

The resources seem to be adequately allocated based on the proposed projects.

The two main projects of the lab are highly original and at the cutting edge.

- Conclusion :

  – Summary

This group is the only one in the world with a specific topic aimed at dissecting the mechanisms of PS and its functions, while the majority of other sleep centers are concerned with slow wave sleep. The team is leader in the field with worldwide recognition. Their recent development and direction towards using new and state-of-the-art techniques is a guarantee of success. The scientific production although of high quality, remains still limited in terms of impact and can be substantially improved. Their funding is also limited and outside funding such as ERCs would improve their production.

  – Strengths and opportunities

As mentioned above, the lab and key researchers have a strong background and are leaders in the field. The team has a unique opportunity to reinforce its leading rank by conducting cutting edge and risky projects as proposed for the next 4 years.

– Weaknesses and threats

One major weakness of the team is long-term projects with limited production in terms of publication. Given their funding possibilities, ambitious projects such as SAGE library construction and sequencing or gene expression experiments take much more time than expected. The major threat is being behind the schedule in the international competition.

– Recommendations

- Increase productivity of some researchers.

- Increase research funding (European, Foundations, or through collaborative projects).

- Major efforts are needed to finalize two ongoing projects (SAGE and transcriptome analysis) to bring them to publication in high impact journals.

- Develop international collaborations in fields they are not yet strong enough such as the molecular analysis

- Develop rapidly optogenetic approches in order to photoactivate and/or silence the nuclei involved in PS.

Team 8 : Langage, Cerveau et Cognition

Team leader : Tatiana NAZIR and Anne REBOUL

- Staff members (on the basis of the application file submitted to the AERES)

	Past	Future
N1: Number of researchers with teaching duties (Form 2.1 of the application file)	4	3
N2: Number of full time researchers from research organizations (Form 2.3 of the application file)	8	8
N3: Number of other researchers including postdoctoral fellows (Form 2.2 and 2.4 of the application file)	2	1
N4: Number of engineers, technicians and administrative staff with a tenured position (Form 2.5 of the application file)	5	5
N5: Number of other engineers, technicians and administrative staff (Form 2.6 of the application file)	0	0
N6: Number of Ph.D. students (Form 2.7 of the application file)	9	7*
N7: Number of staff members with a HDR or a similar grade	11	10

- Appreciation on the results

This is a strong and active interdisciplinary team of researchers drawn from the humanities (linguistics, computational linguistics and philosophy), life sciences (cognitive psychology and neurosciences) and medicine (child psychiatry and neuro-pediatry). Their goal is to investigate the relations between high-level human cognition and its neural basis, disfunctions and rehabilitation taking a strongly theory-guided approach.

Leadership has recently passed to two mid-career researchers with complementary expertise and good track records in publication (40 books or papers in the last four years), grant getting (SRESR, ESF, Marie Curie, Fondation de France), conference organisation (5 conferences in the last 4 years) and research supervision. Both are long-standing members of the team, and they appear to work well and constructively together.

The team has generated 149 publications in the period under review, including 93 refereed journal articles, some of them in the most highly regarded international linguistics and cognitive science journals (Trends in Cognitive Sciences, Cognition, Mind & Language, Linguistics & Philosophy, Journal of Semantics, Pragmatics and Cognition etc.), and chapters in prestigious books – which are still a major medium of scientific communication in the humanities. The impact factors of linguistics and cognitive science journals are considerably lower than in neurosciences, but the journals listed are universally highly esteemed within their fields. It is noteworthy that the number of publications has increased by 30% during the period under review. It is also clear that the standards of thesis supervision are very high, with a significant number of good quality theses being produced in all areas of the project.

The team has had some success in raising funds competitively from both national and international sources, including 8 national grants, 6 European grants and one non-European grant. These include several major grants (e.g., ANR 350.000 euros for neuroreasoning, PHR 260.000 euros for research on fragile X, ESF 360.000 euros for experimental pragmatics) and many smaller grants. Both senior and junior members have maintained a high level of contributions to established national and international conferences (NELS, IPrA, Sinn und Bedeutung, Amsterdam Colloquium, Cognitive Science Society, European Society for Cognitive Psychology, etc.). Team members also gave invited talks at many top universities in Europe, the US and Canada (including Princeton, Rutgers, Brown, Johns Hopkins, Cambridge, etc.) and overseas (Japan, India, Guadeloupe, etc.).

One indication of the attractiveness of the team is its recent recruitment of two new permanent members (in neurosciences and linguistics), and the expressed wish of three postdoctoral researchers to join as permanent members (from the University of Michigan, the University of Barcelona, and the MRC in Cambridge).

The team has had some success in raising funds competitively from both national and European sources, including 8 national grants, 6 European grants and one international (non-European) grant. Some of these grants are for research training and others are for international collaborative research.

Members of the team are actively involved in several national and international scientific networks, including the European Science Foundation, the Marie Curie Research and Training Network, the Experimental Pragmatics network and the Interdisciplines web conference network.

Research by team members has led to concrete results in the domain of language modelling, detection and rehabilitation of learning deficits in healthy children, pharmaceutical testing of a molecule to improve cognitive and social behaviour in fragile-X patients, and in work on joint attention in children with autism. Many of these applications have involved collaborative research at local and national levels.

In a heavily interdisciplinary team such as this one, joint research does not happen automatically, and some overall strategy for collaboration and communication is essential. There is evidence that considerable thought and effort has gone into developing an overall framework to which all the sub-projects can contribute, and that this effort has been largely successful. In particular, it is clear that team members at the more theoretical end of the spectrum (in linguistics and philosophy) have been able to engage actively with those at the more empirical end (cognitive psychology, neurosciences, child psychiatry and neuro-pediatry), and vice versa, and that this engagement is beginning to pay off, both in terms of increased numbers of publications and increased impact factors. The team are to be congratulated on this.

The team has clearly put conscious effort into increasing internal and cross-disciplinary activity, as indicated by the number of weekly and monthly reading groups, yearly offsite strategy meetings and regular visitors from abroad.

Many team members are involved in individual teaching activities, and the team as a whole contributes to several Masters programmes (in cognitive sciences and neurosciences) at the Universities in Lyon. In the last four years, 25 doctoral theses supervised by team members have been completed or are in progress, leading to several publications and postdoctoral awards. Team members have also supervised five postdoctoral students.

- Appreciation on the project

Generally, there is a well-developed long-term project with a wide range of original sub-projects which match well with each other and with the overall themes of Centre (from gene to behaviour, and from bench to patient). Each sub-project is strongly interdisciplinary, with input from theoretical, empirical and medical levels. There is a

clear concern for clinical implications (e.g. for the management of autism and language/communication disorders). Several sub-projects are also strongly linked to the work of other teams at the Centre, sharing common topics (e.g. autism, comparison of human and animal processes), and increasing the chances of collaborative research.

The three main hypotheses to be tested are about the relation between 'situated' (environment-dependent) and 'non-situated' (environment-independent) processes, where situated processes are commonly shared with non-human animals and non-situated processes are not. Within this overall framework, a number of cutting-edge projects are proposed:

Project 1: to investigate perception-based aspects of conceptual abstraction in both typical and atypical populations and consider its implications for clinical practice and neurogenetics.

Project 2: to investigate the relation between motor processes and language, and in particular in language understanding. This project will probably have the highest impact internationally as the connections between brain systems for language and action have only recently been recognised to be crucial for language processing. This insight is presently leading to a revision of our views on the organisation of language in the human brain.

Project 3: to investigate the relation between situated and non-situated processes in social cognition. This will extend the team's world-class research in experimental pragmatics and psychology of reasoning, which has led to the development of an important new research field with significant implications for the theory of communication and the development and breakdown of communicative abilities. This is likely to have increasing impact as dedicated journals and research networks become established.

Project 4: to investigate the development of linguistic determiners and negation as prime examples of non-situated processes. This is a cutting-edge project on psychology of reasoning, and should benefit from the proposed new 'babylab' for investigation of early development.

Project 5: to investigate the relations between pretence, fiction, pretend play and theory of mind in pre-school children. This is a highly original project on an increasingly important topic, and will extend the group's work on brain imaging of logical reasoning.

The proposed Centre for Research in Neurosciences should offer unique facilities for carrying out this research in collaboration with other teams, and the proposal to set up a 'babylab' should bring important new opportunities for collaboration with local, national and international groups working on the development of language and communication.

- Conclusion :

  - Summary

The strengths of this project lie in the interdisciplinary connections between psychology, linguistics and neuroscience. Their scientific is impressive and documents good value for money. In the new programme, some established strengths (language-action links, experimental pragmatics, psychology of reasoning) are developed further in the cognitive neuroscience context and in collaboration with local teams. A range of planned work in sub-projects 2 and 3 are cutting edge. A highlight of the future plans are the language learning experiments which will have some impact in the field.

In the last four years, the team has established a good track record of original, high-quality interdisciplinary research, both theoretical and empirical, with increasing implications for clinical practice. This has been achieved through a conscious effort to develop an overall framework to which researchers from different disciplines can contribute, and through the willingness and ability of team members to engage actively with those from other disciplines. This strategy is likely to pay off increasingly as the Centre for Research in Neurosciences develops and new, more interdisciplinary research traditions become established.

  - Strengths and opportunities

An important strength is the successful collaboration between theoretical and empirical researchers from different disciplines. This pattern is becoming increasingly common internationally, and the quality of the resulting outputs is generally high. The Centre for Research in Neurosciences should provide many opportunities for further interdisciplinary collaborations within and across projects, and the development of the 'babylab' should offer new possibilities for further collaborative.

It has to be remarked that the number of researchers working on questions of higher cognition within the planned Lyon Neuroscience Centre is still low, somewhat below the critical mass of cognitive neuroscientists seen in competing centres and it may be wise, in future, to expand in this area of research.

– Weaknesses and threats

It is important to note the low impact factor of philosophy and linguistics journals as compared with those in some other disciplines, and the lack of journals specialising in interdisciplinary research. As evaluation moves increasingly towards the use of metrics, this presents some degree of threat. It is worth noting, though, that in the period under review, team members have published in the most highly regarded interdisciplinary, linguistics and cognitive science journals, and that this is extremely important to their standing and reputation in the field, and to the dissemination of their research.

The conceptual clarity of the proposal could perhaps be increased – especially when it comes to the relationship between situatedness, syntax, recursivity, logical reasoning and deception. Also, the neuroscience aspects of planned research on the "logical dimension of language", and generally in the domain of hypotheses 2 and 3, could have been outlined more clearly, for example by specifying experimental predictions and approaches along with brain mechanisms of the cognitive functions of interest in more detail.

– Recommendations

This a successful and energetic team doing important and innovative research, which deserves full support. However, they should use input from electrophysiologists (Team 1) to reinforce the EEG part.

Team 9 : Espace et Action

Team leader : Denis PELISSON

- Staff members (on the basis of the application file submitted to the AERES)

	Past	Future
N1: Number of researchers with teaching duties (Form 2.1 of the application file)	5	8
N2: Number of full time researchers from research organizations (Form 2.3 of the application file)	6	4*
N3: Number of other researchers including postdoctoral fellows (Form 2.2 and 2.4 of the application file)	4	5
N4: Number of engineers, technicians and administrative staff with a tenured position (Form 2.5 of the application file)	7	6°
N5: Number of other engineers, technicians and administrative staff (Form 2.6 of the application file)	2	1
N6: Number of Ph.D. students (Form 2.7 of the application file)	9	7
N7: Number of staff members with a HDR or a similar grade	10	10

- Appreciation on the results

The research of this team is highly focused on the interface between perception and action, at different levels of organization (sensori-motor, automatic, attentional & cognitive). It is probably fair to say that the work of the group on sensorimotor control and its various pathologies, in particular its work on optic ataxia and related disorders is not only world-leading; it has helped to re-energise study of these fascinating patients whose deficits have much to say about models of eye-hand coordination as well as the functional architecture of the cerebral cortex. In addition, the work on eye movement abnormalites in any patient group is extremely challenging to do and clearly is producing world class results. These French scientists are carrying on a long tradition of sensorimotor work but are extending it

into perceptual and attentional domains, usually the province of mainstream cognitive psychology. Work on attention and how it interacts with sensorimotor systems is similarly very important. Many motor scientitsts are uninterested in cognitive, perceptual and attentional effects interaction with eye and hand movements. Indeed even some neuropsychologists tend to ignore whole swathes of research questions because they over-emphasise the perception-action dichotomy.

The originality of this team also relies strongly on its ability to conduct translational research, with clinical applications in neurology, neuro-ophtalmology, neuropsychology, and rehabilitation. Over the last 4 years, this team has conducted coherent research sub-programmes on six closely-connected topics (visuo-motor adapation, control of eye-movements in patients, mechanisms of saccadic adaptation, mutisensory integration, optic ataxia and unilateral neglect) that led to significant advances in each field. The work on prism adaptation in hemineglcet syndromes alone is extrememly influential: the technique is being used in at least 20 different laboratories worldwide.

Over the last 4 years, this team (composed of 13 permanent members: 6 researchers, and 7 academics/clincians) has published 125 articles in international, peer-reviewed journals, among which 80 have been published in fundamental neuroscience, cognitive psychology and cognitive neuroscience journals, and 45 in clinical (neurology) journals (10 additional papers appeared by the time the evaluation team visitied Lyon in February). Remarkably, nearly 60% of the publications of IMPACT are based on work with patient populations, which is extremely impressive given the challenges these participants face in performing in experiments. These 88 neuroscience/cognitive psychology articles have been published in journals of high-to-excellent impact, all extremely relevant to the present field of research (e.g., Brain, J. Neurosc, J. Neurophysiol., NeuroImage, J Cog Neurosci., J Vision, Exp Brain Res, Neuropsychologia, etc.). It is noteworthy that papers have been published in Nature Neurosci, Curr Biol, Brain and PNAS. The scientific productivity of this team can therefore be considered as outstanding. In addition to that, 9 Ph.D. theses and an Habilitation (HDR; L. Pisella) have been completed over these 4 years.

- Quality and stability of partnerships

Most articles have been co-authored by two or more than two team members, demonstrating the ability of these 9 permanent members to work as a team.

This team has a solid, international reputation on the study of the anatomo-functional organization of action. The attractiveness of the team is clearly demonstrated by its ability to attract new groups (1 INSERM AVENIR team). This team has also developed a wide range of scientific collaborations with local (mostly Hospitals), national (eg, INPG, CNRS), and international partners (50% of articles co-authored with foreign scientists) during these 4 years.

The group have made 63 presentations to national and international conferences from 2005. Extremely impressive and probably stronger than many of the other themes. One reseacher has obtained the Bronze CNRS medal.

The attractivity of the team is clearly demonstrated by its ability to attract 4 leading, senior visiting scientists and 9 postdoctoral scientists over these 4 years.

This team has demonstrated an outstanding ability to raise funds (4.3 M€) in a 4-year period, from different national or international funding agencies (ANR, DGA, clinical clusters, EU FP7, Human Frontier Science Prog, ESF, etc).

This team is involved in European (eg, FP7) projects and collaborates with foreign teams (30% of articles co-authored with foreign scientists).

Participations to various clinical trials and clinical clusters and a CIFRE grant supported by a cochlear-implant manufacturer indicate that the team has conducted translational research, and attempts to develop links with industrial partners.

The transfer of team leadership is extremely well adapted for ensuring intellectual guidance, cohesion and expansion of this group, and dissemination of their research at national and international level over the coming years. The 6 thematic axes with a single named leader is appropriate and manageable. The team meets quite frequently, including biweekly scientific meetings and weekly administrative sessions which include the theme leaders only.

The team has recently initiated the PRIMAGE project (comparative study of human and non-human primates) to restart an ambitious research program (neuroimaging and neurophysiology) in the monkey. The new Centre de Neurosciences de Lyon will help setting up this PRIMAGE project. Stengthening the theme's utilisation of neuroimaging in human participants seems sensible given international developments in cognitive neuroscience as well as advances in methodology which allow for at least some movement within the scanner under controlled circumstances, accurate measurement of eye emovements, etc.

Most members of this team are academics and teach in Medical schools in Lyon. The other members teach at the master degree level in Neuroscience or neuropsychology local, national or European training programs.

The new research program will stay extremely focused on the study of perception-action interactions, with new priorities planned over the next 4 years on 1) multisensory integration in grasping, 2) sensory competition and attentional modulation, 3) oculomotor control and plasticity, 4) visuomotor adaptation, and 5) the study of normal and pathological development. The project is original, ambitious but feasible, all skills required to conduct successfully this project being clearly masterized by the 10 permanent members of the new IMPACT team.

The human, technical and financial ressources that will be necessary to conduct the various projects of the team are well identified and well specified.

In addition to the excellent research paradigms continuing to produce high quality publications, two cutting edge projects which build on the existing research base have been highlighted: (1) neuroimaging studies with nonhuman primates (the only one in France) and (2) neuropsychological studies on normal and pathological development. In this latter instance, comparing and contrasting oculomotor and skeletaomotor systems is useful for appreciating common principles of control, as suggested by the project description. In addition, differences between eyes and hands serve as natural "independent variables" which can be informative. Inertial properties of the eye in saccadic eye movements are trivial in comparison to limb dynamics, interactions with trunk muscles during reaching etc., so extending some of the work on eye-hand relationships to head movements is another exciting direction for this gorup to purse.

- Conclusion :

  - Summary

This is a solid team, which has a well-established international reputation in the field of "cognitive neuroscience of action", and which has conducted translational research projects with applications in clinical neurology. Its scientific productivity is outstanding.

  - Strengths and opportunities

(1) Outstanding scientific productivity, (2) capacity to attract postdocs and senior scientists for long periods, (3) capacity to raise important fundings from various agencies, (4) Strong capacity to conduct translational research with clinical applications.

  - Weaknesses and threats

None visible.

Team 10 : Recherche translationnelle et intégrative en épilepsie

Team leader : Philippe RYVLIN and Laurent BEZIN

- Staff members (on the basis of the application file submitted to the AERES)

	Past	Future
N1: Number of researchers with teaching duties (Form 2.1 of the application file)	3	7
N2: Number of full time researchers from research organizations (Form 2.3 of the application file)	1	1
N3: Number of other researchers including postdoctoral fellows (Form 2.2 and 2.4 of the application file)	0	5
N4: Number of engineers, technicians and administrative staff with a tenured position (Form 2.5 of the application file)	5	5
N5: Number of other engineers, technicians and administrative staff (Form 2.6 of the application file)	0	2
N6: Number of Ph.D. students (Form 2.7 of the application file)	2	3
N7: Number of staff members with a HDR or a similar grade	3	3

- Appreciation on the results

This team is a newly created group derived from UMR5123 and UMR_S821. It emerged from the past three years of fruitful collaboration among epileptologists, geneticists, and neurobiologists in the CTRS program, "Cognitive Development in Epilepsy".

The group issue from the unit U821 concentrated its research activity on three areas: Cognitive Dysfunction in Epilepsy, PET imaging of 5-HT1A receptors using [18 F] MPPF and patients suffering of sudden unexpected death in epilepsy SUDEP. This group also participated in several clinical trials of anti-epileptic drugs. Thus, they determined that children have a greater response to placebo than do adults. They described the electroclinical concept of temporal plus epilepsy in which there is co-involvement of orbito-frontal, frontal, or insular cortical regions.

The studies of the group issue from UMR5123 from 2005 to 2009 was devoted to the study of hypoxic stress and neuroprotection using animal models of epilepsy, in particular the pilocarpine model in rats.

Since 2005 this team has published a total of 257 papers (an average of 3 papers per investigator per year). Fifty-five percent of these papers have one of the team members as first or last author. Eighteen papers have an impact factor greater than 10 and 73 have an IF greater than 5. It should be noted that many of these are clinical manuscripts concerning epilepsy syndromes, their diagnosis, and treatment rather than preliminary work in the research topics that will be continued.

Six Ph.D. theses have been defended during this period. The members of the team are on the editorial board of three epilepsy-related journals.

The group have made many presentations to national and international conferences from 2005 to 2009. One member is "Lauréat du 3ème Tremplin Recherche Sénat".

Two students from Erasmus University Rotterdam have been recruited. Moreover, the TIGER group has already successfully recruited a well-known pharmacologist to join their team and assist in studies of and clinical trials involving anti-epileptic drugs. National and international co-operation is already seen in several such ongoing studies such as Mortemus.

The team leaders participate in various national and international collaborations. They have numerous national and international grants, both as PI/cp-ordinator as well as national leaders in European consortia. Fortunately this group already has 97% funding for future activities from a variety of sources.

The team is probably unparalled in France, and possibly Europe, in the way they are scientifically connected.

Both teams spent significant amount on teaching. The advent of IDEE has significantly re-structured research at the local level.

This team will focus on the pathophysiology and improved treatment of two major co-morbid conditions and/or complications of epilepsy, namely cognitive dysfunction in children and sudden unexpected death in epilepsy (SUDEP). In both cases, coordinated animal experiments and clinical studies will be performed to test specific hypotheses that cognitive dysfunction is related to delayed regional maturation and that the primary cause of SUDEP is serotonin-dependent post-ictal central apnea.

The formulation of TIGER will underpin on-going collaborations and translational research activities between these two groups. The goal of research for the TIGER group during the 2010-2014 period is to understand two pathological processes/conditions that accompanying epilepsy and afflict some patients with seizure disorders. These projects do not address epilepsy itself, its pathogenesis, physiology, or treatment, but both are of highest relevance in epilepsy. Both axis are ambitious, but the outlines of projects are feasible.

Both axis include cutting-edge projects, in particular brain maturation in children with epilepsy, cognitive rehabilitation, and the proposed clinical trials and PET studies.

- Conclusion :

  – Summary

The epilepsy team has a well-deserved international recognition and is well- published. The basic science team is showing promising work, but is less well-published or known than the clinical partners. The projects, although not directed at epilepsy per se, involve the elucidation and treatment of two serious complications of seizures, are well defined, original and combine sophisticated imaging techniques of brain structure, function and connectivity with cutting-edge neurophysiological approaches (high-frequency oscillations). The combination of functional/neurological/neuropsychological/ psychiatric, and electrophysiological methods, and structural and functional neuroimaging methods will allow to deliver the planned research within the proposed time frame.

  – Strengths and opportunities

The strength of TIGER are its people. The established collaborations guarantee the feasibility of this project. The principal applicants of these projects have published very important papers, are involved in many studies conducted in patients with epilepsy and other disorders, and have an extensive experience using the methods planned for these studies. They could be considered as key opinion leaders in epilepsy, neurophysiology and soon also to be in SUDEP. Joining a focused basic science group with a large active clinical group and addressing the same topics will allow direct translation from bench to bed and vice-versa.

  – Weaknesses and threats

The publication record within the group is unbalanced, but this should change with stronger collaborations with the clinical team. There is a multitude of problems inherent in clinical trials, and in particular, longitudinal imaging studies, which are necessary to answer the relevant questions about brain development and maturation. The applicants are aware of the pitfalls, including recruitment and retention of participants. The large group of clinical

collaborators could be the solution to the recruitment of the required large number of patients, but also a real threat in maintaining focus in view of competition with many other projects of this group.

There are minor methodological problems or concerns about a number of the projects, but none of these cannot be overcome or should eliminate a useful outcome.

There is some-risk taking, given their single hypotheses, but the efficiency of this narrow focus will make the successful completion of clinical investigations more likely.

– Recommendations

The research proposal is clinically important, scientifically highly original, but realistic. Results will benefit patients with epilepsy and contribute substantially to ongoing scientific discussions within neurology, psychiatry, and cognitive neuroscience.Some projects only starting

Concerning the animal studies, interactions with specialist in apnea is strongly suggested

Team 11 : Schizophrénies débutantes et résistantes: de la physiopathologie à la thérapeutique

Team leader : Mohamed SAOUD

- Staff members (on the basis of the application file submitted to the AERES)

	Past	Future
N1: Number of researchers with teaching duties (Form 2.1 of the application file)	3	2
N2: Number of full time researchers from research organizations (Form 2.3 of the application file)	1	1
N3: Number of other researchers including postdoctoral fellows (Form 2.2 and 2.4 of the application file)	2	3
N4: Number of engineers, technicians and administrative staff with a tenured position (Form 2.5 of the application file)	0	0
N5: Number of other engineers, technicians and administrative staff (Form 2.6 of the application file)	1	1
N6: Number of Ph.D. students (Form 2.7 of the application file)	3	1
N7: Number of staff members with a HDR or a similar grade	4	4

- Appreciation on the results

The group has been involved in very relevant research, investigating core features of the severe mental disorder, schizophrenia. Some parts are very original such as TMS treatment in schizophrenia, however, it is unclear if this has been replicated in other groups.

The research strategy translating clinical characteristics into objective phenotypes and measures is promising, but not unique. This is a fruitful approach that the group are competent in, and some aspects of it is pretty original and has provided high impact findings, such as PET investigations.

Around 8 international publications per year (range 3-10) for a small group suggest a good productivity. In general, reasonably good publications, some case reports, but mostly medium quality. Some high impact publications (Brain, Biol Psychiatry, Mol Psych) are noticed but these works are attributed to collaborators more than to the team.

A single relevant publication in Biol. Psych. in 2005 is from the team and concerns one of the first reports of potential effectiveness of TMS in Schizophrenia. Nevertheless, this original finding lacks major positive replications (except another original one), leaving the approach and its future doubtful at this stage. A reference to a publication in Am. J. Psychiatry concerns a letter to the editor.

Good and stable collaboration with clinical units at hospital, as well as close collaboration with other neuroscience groups at the Neuroscience center.

Few or under-reputation in terms of awards and invitations to conferences. An effort seems appropriate.

Lack of recruitment of basic scientists in a clinical set up.

3 PHRC and 2 contracts with industry have been obtained.

Involved in collaboration with a major researcher (Netherlands) in schizophrenia field. This has also resulted in publications. A special advantage is the group's membership in FondaMental collaboration – collection of a standardized dataset of a large sample of patients.

They contribute to a better understanding of the psychopathology of schizophrenia, to help patients in their daily life.

Small team that seems to be not fully mature

The project description was vague and little details of research plan was provided. Therefore, it was difficult to assess the plan.

Six PhD have been defended, 3 are in progress. The teaching activities are fairly good. This team brings to the center its expertise in psychometry and psychiatry and gives access to human samples and patients cohorts.

- Appreciation on the project

Although the project seems interesting and some parts may include innovative approaches, the document provided includes very little information and the site visit revealed inconsistent presentation. There seems to be a large access to patients, but without large resources from the clinicians, the group has not enough resources or personnel to run long-term follow up projects.

The axis 1 includes more patients together with the FondaMental network. This is a very interesting and important effort, and may provide new interesting findings. However, the project involving large scale explorative projects regarding the FondaMental database is not specified, and the role of the team in this effort, except data collection, is unclear. The dopaminergic hyper reactivity of schizophrenia hypothesis, as stated, did not convince the committee, especially there were concerns regarding a peripheral measure of dopaminergic reactivity to stress as relevant for any central implication. The study design, especially regarding genotyping was somwhat unclear, since none of these candidate genes have been replicated as susceptibility genes for schizophrenia in recent large scale studies. The GABA dysfunction as a biosignature of prodromal or pre-psychotic states is potentially interesting, but the feasibility of the study can be questioned. Especially access to patients from a university health care center, seems to be a limiting step. Further, in order to develop a reliable biomarker for schizophrenia subjects, a series of samples must be investigated, and the resources available make it less feasible. In addition, markers in prodrome subjects will not necessarily be transferable to the general schizophrenia population. The design of the imaging protocol and the specific hypotheses to be tested in this project were unclear.

The studies of axis two are based on the rTMS intervention, and it is unclear if the effect of this method in schizophrenia has been reliably replicated, although the study seems to be well designed. The cognitive rehabilitation project is a very interesting approach in modern schizophrenia research. For these studies, the clinical resources will be used, which is a great advantage. The mechanism of therapeutic change is an interesting approach, but it all depends on the effect of rTMS, which is still doubtful.

The concept of searching for critical steps for development of schizophrenia in axis 3 is a valid approach, but there was too little information about how to perform the research. How many subjects will be recruited, which phenotypes will be assessed, how are they going to analyze the data (statistical expertise), and what is the power of the different samples in order to identify these critical steps? The committee noted that the report from the team clearly indicates several weak points that seriously question their projects. Amongst these are:

Lack of expertise in neuro-imaging, design of protocols and data processing.

Lack of appropriate skills in statistics and epidemiology and therapeutic trials.

Relatively low impact factor of publications.

Drop out of animal studies due to low critical mass and logistic support

The current major topics of the research plan are in line with what a modern clinical research unit in schizophrenia is involved in. The novelty lies in the collaboration with other Neuroscience and imaging groups in Lyon, and these projects have a potential for becoming cutting edge quality, but at present they are not. There seems to be some lack of both overall scientific strategy and specific plans for boosting this potential and reaching the forefront of international research.

- Conclusion :

  - Summary

Medium to high productivity, interesting and important research area, but some major limitations with research plan and expertise.

  - Strengths and opportunities

Focus on early phase – potential for prevention

Access to patients, closely integrated with clinic.

Translational approach, good collaboration with other neuroscience groups locally.

National collaboration, especially FondaMental partnership

  - Weaknesses and threats

Low quality of research plan, lack of overall scientific aims, unclear hypotheses and plans for implementation,

Lack of expertise in statistics, epidemiology, and therapeutic trials

Difficult to achieve enough know how in many research areas together (genes, phenotyping, imaging, clinic etc.)

Need access to 3 T MRI scanner.

High impact journals are in collaboration with other groups.

Lack of expertise in the group, the interview suggested under-experienced leader.

– Recommendations

The main advantage of this team is the access to patients and expertise in psychiatric nosology and assessments. Close integration with clinical psychiatric departments will be very important for the translational aspects of the Lyon Neuroscience center.

Further, psychiatric patients will be essential for a series of future neuroscience research fields. It is also an area were more knowledge about underlying disease mechanisms are highly needed. Thus, it is important for the Neuroscience Center to maintain a close connection to clinical psychiatric units.

Team 12 : Audiologie

Team leader : Hung THAI-VAN

- Staff members (on the basis of the application file submitted to the AERES)

	Past	Future
N1: Number of researchers with teaching duties (Form 2.1 of the application file)	7	7
N2: Number of full time researchers from research organizations (Form 2.3 of the application file)	1	1
N3: Number of other researchers including postdoctoral fellows (Form 2.2 and 2.4 of the application file)	0	0
N4: Number of engineers, technicians and administrative staff with a tenured position (Form 2.5 of the application file)	4°	7°
N5: Number of other engineers, technicians and administrative staff (Form 2.6 of the application file)	0	0
N6: Number of Ph.D. students (Form 2.7 of the application file)	6	4
N7: Number of staff members with a HDR or a similar grade	6	9

°Shared with 4 teams (Didier, Gervais, Thai-Van, Tillmann)

- Appreciation on the results

This recently reorganized auditory research team has permanent members (academics and ENT clinicians), with expertise in neurophysiology, brain imaging, psychoacoustics, clinical audiology, and signal (speech, audio and neural signals) processing. The previous team had a track record of innovative and high impact research, particularly for its work on plasticity of the efferent system (a very timely and appropriate area of research) and, later on, for its work on auditory training and plasticity connected with cochlear implants. Significant findings included (i) demonstrations of perceptual changes in frequency discrimination close to the cut-off frequency of the audiogram for listeners with high-frequency hearing loss, before and after auditory rehabilitation with a conventional hearing aid, (ii) tonotopic reorganization of the primary auditory cortex following cochlear implantation, and (iii) cortical control of cochlear activity using electrical stimulation of the auditory cortex.

This is a new group that emerged only in the last couple of years. Previous productivity appeared quite strong, but was somewhat limited by publications in poor quality clinical journals. Over the last four years, the team published 36 papers in international, peer-reviewed journals. Of these, about 25 papers correspond to significant contributions to the team's main research sub-programmes (auditory plasticity and top-down control), indicating a

clear interest from the hearing science community. The demonstration of corticofugal modulation of cochlear activity in humans may be considered a significant breakthrough in auditory neurophysiology. The remaining papers have been published in clinical journals (of good-to-high impact in their respective fields). These 25 papers corresponding to significant contributions have been published in relevant journals of good-to-high visibility (e.g., Otol NeuroOtol, Int J Audiol, Clin Neurophysiol, Hear Res, JSLHR, Cereb Cortex, Brain, J Neurosci, J Neurosci Methods, etc) at international level in the corresponding disciplines. In addition to this, six Ph.D. theses and an Habilitation (HDR) were completed over the last four years.

In past work, a number of articles were co-authored by two to three permanent members, demonstrating their ability to work as a team. This group is one of the few to point to interactions within the Centre (e.g. with team 1 and 9) as a part of their research plan.

This team has a well-established national and international reputation in the field of auditory neurophysiology (role of the medial efferent system and auditory plasticity following auditory deprivation and rehabilitation with hearing aids or cochlear implants). They have developed strong links with other fundamental research teams in neurosciences or psycholinguistics in Lyon (eg, UMR_S821 INSERM, UMR CNRS 5596), and ENT clinics and industrial partners (hearing aid and cochlear implant manufacturers, etc.) conducting applied and clinical research on auditory neurophysiology, audiology and cochlear implantation in France. The role of the team in some national research programmes isn't clear. They have collaborated internationally with teams in the UK (Cambridge), USA (NIH, Minnesota Univ, House and Ear Inst, LA, etc.), Canada (McGill), Japan (National Tokyo Medical center), South Korea (Seoul National University, College of Medicine). The key partnership with Minnesota Univ, House and Ear Inst (USA) is mentioned above and needs to be validated. The attractiveness of the team is demonstrated by the 6 Ph.D. students, completed during the last 4 years, and a crop of new students. At the academic level, the team seems well placed in local and national teaching institutions (Degree and Master level in Biomedical Engineering, Medical Schools), ensuring the ongoing recruitment of master and Ph.D. students.

Three young permanent members received various local and international distinctions (e.g. Lilly grant) over the last years. The reputation of the team was helped by their contribution to the organization of 3 international symposia on audiology or auditory neurophysiology, and 7 national meetings on auditory rehabilitation (cochlear implantation or hearing aids). It is also demonstrated by their participation in the editorial board of an international journal publishing audiological research (Audiol and NeuroOtol), and expert reviews for national (ANR) and international (NSF, MRC, Israel Science Fundation, National Inst for Health Res UK) research institutions.

This is a particular area of concern as the group appears to lack senior basic research scientists and no postdoctoral scientist joined the team over the last 4-5 years. Recruitment of two new assistant professors has been promised in 2010 and it should be a high priority for these to be research experienced. A number of current doctoral students are mentioned in the proposal.

Funding appears to come from regional, clinical and industrial sources. European funding was available in the previous work. The group relies heavily on funding from private sources, particularly hearing instrument makers (4 CIFRE grants, various contracts with hearing aid & cochlear implant manufacturers, audiology consortia, etc.). This latter point is clearly a strength of the team.

This team has been involved in national and European clinical trials, epidemiologic studies, multi-centre research programs (eg, collaboration with Institut Pasteur, Paris; eg RTRS Fondation Voir & Entendre; GDR CNRS GRAEC). This team collaborates with foreign research teams in the USA (NIH, Haskins Labs, Yale Univ), canada (McGill) or in Japan.

The translational activity of this team is evidenced by its ability to raise funds from clinical clusters (e.g., PHRC) and from industry and other private partners. Some recent findings by this team have triggered interest in audiovisual training for children with language impairment and hearing aids using frequency transposition algorithms.

The team receives benefit from positioning in a clinical environment, giving access to large cohorts of patients with hearing deficits.

Team leadership has been given to a young auditory scientist (Ph.D., HDR, PU-PH) and ENT clinician. This leadership should ensure cohesion and expansion of this group at the interface of fundamental and clinical research.

However, team organization appears to have a weak point, with lack of day-to-day scientific leadership. One member is listed as contributing 30% of his time, clearly unrealistic in light of his other responsibilities.

The team has organized or co-organized locally various meetings (n=11) of national visibility designed to promote research on experimental and clinical audiology.

The team is heavily involved in teaching a range of medical and paramedical professionals.

The research project of this team has been re-organised into two main sub-programmes focusing on rehabilitation plasticity and top-down control of the auditory system. However, there does not appear to be a clear long-term strategy or vision emerging from the wide mixture of proposed small projects.

Allocation of resources was not presented as a policy. Future public and private funding sources are listed in the proposal, including national Clinical Research Hospital Programs, Cluster Région "Handicap, Vieillissement, Neurosciences", CIFRE grants, Medtronic France, Siemens Audiology France and patients association "France Acouphènes".

The former team leader has essentially left, passing the baton to a younger clinician and research worker who does not yet enjoy the same international reputation. Nevertheless, he has proposed an ambitious program, consisting of studies of rehabilitation in cochlear implant (CI) recipients and studies of the efferent auditory system. The proposed methods involve cross-modal rehabilitation of CI users, focusing on somatosensory (proprioceptive) aspects of speech production and development and balance control. In the medial olivocochlear efferent system (MOCS) the focus is on functional asymmetry, with particular reference to children with learning and auditory processing deficits. Proposed investigations include auditory brainstem and cortical response recording to speech stimuli and transcranial magnetic stimulation (rTMS). These methods address important and highly applied questions and appear to be very novel. However, it isn't clear that the basic premise of the CI research is sound. The results of tilting children who are CI users (stimulating several systems) would be difficult to interpret. Balance deficits in profoundly deaf children may be due to vestibular involvement causing direct problems. A CI, designed for auditory stimulation, may provide almost random input to this damaged system. The proposal rests heavily on collaboration with the developer of the somatosensory method, but a crucial issue is whether that method would work in congenitally deaf children. An Alzheimer's disease proposal looks like therapeutic intervention, not research as such. A speech ABR proposal lacks a clear hypothesis or aim. In the efferent work, it isn't clear how asymmetry is judged, what it's significance might be, or what to do about it. The idea that cortico-cochlear control is involved in reading acquisition is complex and appears not to have been well thought through. Spatial localization in 3D, and its relation to efferent feedback and learning, is highly complex. There was no clear understanding shown by the team of this complexity (e.g. the difference between localization and lateralisation). Poor learning for localization may also be a problem. rTMS as a way of studying efferent processes is of interest, but its relationship to tinnitus is not known nor spelt out in the proposal. Also, in questions, the ability to use rTMS on auditory cortex had not been fully considered. Thus, while the proposed research is relevant and original, the quality and impact of the methods and results may be limited.

- Conclusion :

  - Summary

This is a multi-disciplinary team with a research program focusing on the neurophysiological investigation of auditory plasticity and top-down modulations of cochlear activity. The future work is based on a history of interesting and internationally known research demonstrating auditory plasticity following cochlear lesions and auditory rehabilitation by hearing aids or cochlear implants, and corticofugal modulations of cochlear activity. Interesting work on language disorders has also been conducted. However, the current team needs to develop its international visibility and the research projects, whilst novel and potentially translational, are not very clearly presented. They are not strongly supported by findings from outside this team or a recent history of high impact publication. The leadership should ensure that the team will increase its national and international visibility and expand over the next years. However, it will be essential to develop the scientific leadership and close interaction with other appropriate auditory scientists.

– Strengths and opportunities

There is a strong, almost total, clinical orientation to the research of this group. They are well connected clinically and have access to students and others locally who support the research. In a profession (ENT) that has a very poor culture of research, internationally, the team leader's work is a rare exception of a clinician leading a research programme. Access to neuroscientific and clinical platforms, as well as exposure to high quality basic science in the new Center will specially help this team.

– Weaknesses and threats

The lack of dedicated and full-time scientific leadership within the group and the apparent lack of connection with other strong and relevant French and international teams of auditory scientists. A consequence of this apparent isolation is the disconnected and speculative nature of the research proposals. They have not been well written and could have benefited greatly from critical review.

– Recommendations

This team needs an opportunity to spell out clearly where they are going and how they are going to get there. They need a clear, unified vision and a plan of close collaboration and mentorship with other active research teams in audition and in other areas of neuroscience. As such, they could benefit a lot from being members of the Centre, possibly under the guidance of a senior investigator (e.g. leader of team 1).

Team 13 : Cognition Auditive et Psychoacoustique

Team leader : Barbara TILLMANN

- Staff members (on the basis of the application file submitted to the AERES)

	Past	Future
N1: Number of researchers with teaching duties (Form 2.1 of the application file)	1	1
N2: Number of full time researchers from research organizations (Form 2.3 of the application file)	2	2
N3: Number of other researchers including postdoctoral fellows (Form 2.2 and 2.4 of the application file)	3	2[1)]
N4: Number of engineers, technicians and administrative staff with a tenured position (Form 2.5 of the application file)	5°	5°
N5: Number of other engineers, technicians and administrative staff (Form 2.6 of the application file)	0	0
N6: Number of Ph.D. students (Form 2.7 of the application file)	3	1[3)]
N7: Number of staff members with a HDR or a similar grade	1	1[4)]

°Shared with 4 teams (2, 4, 12)

- Appreciation on the results

This team has developed a sound expertise in "Auditory Cognition", a relatively novel field of research (investigating higher-level auditory functions, such as attention, memory or consciousness) that has received increased interest from the 'Hearing Science' community over the last decades (little is currently known on these topics, compared to Vision Science, for instance). Empirical studies on auditory, speech and music perception are conducted by this team on human listeners showing either normal hearing or central auditory deficits (amusia). The general methodology is based on behavioral procedures used in psychophysics and cognitive psychology, and noninvasive electrophysiological procedures. These three sets of techniques are extremely well masterized by the 3 permanent members of the team. The team leader has also some expertise in connexionnist modelling, that complements these approaches. Over the last 4 years, this team has developed elegant and original paradgims to investigate the effects of auditory expectations on hearing, and made significant and even influential contributions to their field by demonstrating a role of temporal and cognitive expectations (at both conscious and non-conscious levels) on sound detection, pitch perception, or even auditory scene analysis (segmentation of sound mixtures). This team has also developed elegant paradigms to investigate auditory scene analysis using sequences of speech sounds (vowels). This team is internationally renowned for their demonstration of so-called "harmonic priming" effects, and their elegant use of this effect to unveal central auditory processing of music or language. This team is also well know for their contribution to the understanding of the auditory cues and mechanisms involved in auditory scene analysis.

The scientific production of this team is clearly excellent. Their results have been published in the international, peer-reviewed journals most relevant to the different fields covered by their investigations, namely (i) experimental psychology, (ii) psychoacoustics, and (iii) cognitive neuroscience (J Exp Psychol: HPP, J Exp Psychol: LMC, Cognition, Memory & Cog, Psych Res, Percept & Psychophys, Hear Res, J Acoust Soc Am, CerebCortex, NeuroImage, J Cog Neurosci, Neuropsychologia). Despite the general low IF of such journals (1-2), these journals are considered as providing the best and most rigorous peer-review process in their respective areas. J Acoust Soc Am is also considered as "archival" in psychoacoustics (Journal created a century ago). Over the last 4 years, the 3 permanent members of this team have published 40 papers, among which about 35 are of high significance in these journals. Scientific production is also extremely regular. Some papers have add clear impact in the field (e.g., many of Tillman's papers; Gaudrain et al., Hear Res, 2007).

The 3 permanent members of this team clearly show complementary skills (cognitive psychology & modelling; signal processing, psychophysics, audiology; cognitive neurosciences, neuropsychology). A number of articles (published or submitted) are co-authored by the 3 members, demonstrating their strong partnership. For these reasons, this team seems to be built on solid grounds.

This team has gained a national and mostly international reputation in the 'Auditory Cognition' field, with a clear leadership position in this domain at the European level. They have developed strong links with the two other national teams conducting research on auditory cognition (Lille III, Dijon- CNRS; Caen Inserm), and a wide range of scientific collaborations with foreign teams of high to extremely-high scientific reputation (USA, Canada, ...). The attractivity of the team is demonstrated by the attraction of 5 Ph.D. students (3 completed during these 4 years) and 2 postdocs. Finally, at the academic level, the team seems well inserted in the local and national teaching institutions (Degree & Master level), ensuring the ongoing recruitment of Ph.D. students.

The reputation of the team is clearly demonstrated by their contribution to the organization of 3 international symposia on music perception, and participation to several editorial boards of important journals or international research institutions (NSF, ESF, Canada, etc).

The attractivity of the team is demonstrated by the attraction of 5 Ph.D. students (3 completed during these 4 years) and 2 postdocs.

The team has demonstrated a clear ability to raise important fundings from local/regional (n=4), national (n=7, eg, ANR, CNRS) and international (n=4; eg, FP7, ESF, Australian Res. Council) funding agencies, and from the industry or from private partners (CIFRE grant).

This team participates actively to national (through multi-sites ANR projects such as multistab) and international (n=2; Europe (EBRAMUS project) & Australia) networks and have developped collaborations with foreign partners (eg, Europe, Australia) supported by various grants.

The team has produced a CD Audio ("Fonds sonores") providing acoustical material for clinical investigations of hearing & hearing loss, that is increasingly used in foreign, but mostly French-speaking countries (eg, Canada).

This team has successfully managed to produce a coherent and well-focused global research programme focused explicitly on auditory cognition, and the behavioral study of top-down influences on hearing. Each sub-program (i.e., investigation of auditory, speech, music processing and the possibility of implicit processing) is split in a clear manner between PIs within the team. The team has also succeeded in finding diversified forms of fundings at local, national and international levels to support this global research programme.

Team leadership is extremely well adapted for ensuring intellectual guidance, cohesion and expansion of this group, and dissemination of their research at national and international level over the coming years.

The team has organized or co-organized locally various meetings (n=4) of national visibility designed to promote research on auditory cognition. The team is also deeply involved in the promotion of Hearing research in the Société Française d'Acoustique (SFA). Finally, the team has contributed locally to a national initiative designed to promote and fund research in cognitive sciences over the next years (PIRSTEC project).

At the academic level, the team seems well inserted in the local (Lyon) and national (eg, Paris) teaching institutions (Degree & Master level), ensuring the ongoing recruitment of well-trained, Ph.D. students.

- Appreciation on the project

Over the next 4 years, the team will naturally carry on investigating the effects of cognitive expectations on speech and non-speech (eg, music) perception to provide additional evidence for top-down modulations of auditory processing. The team aims to investigate further the neural correlates of these top-down (eg, cortical) influences and develop novel rehabilitation strategies for people with central auditory processing disorders. The new neuroscientific and clinical facilities offered by the Lyon Neurosciences Research Center will clearly allow this team to conduct successfully their investigation of the neural bases of cognitive influences and the two cutting-edge clinical projects listed below.

The human, technical and financial ressources that will be necessary to conduct the various projects of the team are well identified and well specified.

Two novel and ambitious projects may lead to important breakthroughs in Hearing Sciences and more specifically, Cognitive Neurosciences of Hearing. The first project aims to use of SEEG in epileptic patients to investigate the neural correlates of unconscious auditory processing and the role of neural synchronization across brain structures. The second project aims to test whether clinical applications based on a specific musical training may rehabilitate language processing in people with either brain damage or specific learning disorders. These two cutting-edge projects will strongly benefit from the clinical platforms & ressources offered by the Centre de Neurosciences de Lyon.

- Conclusion :

  – Summary

This is a small, multi-disciplinary team with a well-focused research program on auditory cognition that has gained a strong international reputation over the last years. This team has recently conducted original and elegant behavioral work demonstrating quite clearly cognitive (top- down) influences on auditory perception with speech and music material. This work has been supported by various local, national and international funding agencies, and published regularly in the international journal most relevant to their field. A strong leadership ensures that this team will increase its international visibility and expand over the next years. Clearly, this is an outstanding team that deserves strong support from the new Centre de Recherche en Neurosciences de Lyon.

– Strengths and opportunities

Main strengths: 1) well-focused research program on a maintream topic, 2) scientific productivity of high quality, with clear international visibility & leadership, (3) clear complementarity between the 3 PIs, 4) strong leadership 5) access to neuroscientific and clinical platforms in the new Center.

– Weaknesses and threats

Main weakness: small size; No apparent links with the Audiology team (team 12).

– Recommendations

(1) Recruitment of a 4th PI with conjugated expertise in cognitive psychology, cognitive neuropsychology, cognitive neurosciences, and auditory psychophysics; (2) Develop collaborations with the Audiology team, focusing also on top-down modulation of auditory processing.

Team 14 : Neuropharmacologie et imagerie des troubles de l'humeur

Team leader : Luc ZIMMER

- Staff members (on the basis of the application file submitted to the AERES)

	Past	Future
N1: Number of researchers with teaching duties (Form 2.1 of the application file)	4	3
N2: Number of full time researchers from research organizations (Form 2.3 of the application file)	6	6
N3: Number of other researchers including postdoctoral fellows (Form 2.2 and 2.4 of the application file)	0	0
N4: Number of engineers, technicians and administrative staff with a tenured position (Form 2.5 of the application file)	6	6
N5: Number of other engineers, technicians and administrative staff (Form 2.6 of the application file)	1	1
N6: Number of Ph.D. students (Form 2.7 of the application file)	4	4
N7: Number of staff members with a HDR or a similar grade	7	6

- Appreciation on the results

The team leader has made significant contribution in the field of pharmacology and imaging of the serotoninergic neurotransmission, with a significant amount of works on 5HT1A. The translational research from the animal models of disease to radiopharmaceuticals or therapeutics for the patients seems grounded and sound. New concepts in molecular imaging such as PET and receptor internalisation, PET and agonist imaging illustrated by the high citation of certain articles plus head of the plateform ANIMAGE indicate a substantial interest. Micro-PET instrument will be renewed in 2010. It will be used for in vivo imaging of serotonin receptors (depression, Alzheimer) in rodents (conventional and transgenic mice, rats). The team leader has a methodological expertise internationally recognized in PET radiopharmacology and in vivo microanalysis (capillary electrophoresis).

Contribution of the other axis of the team is more difficult to evaluate since no precise focus appeared during the site visit. The project on anxiety/depression model that this group claims to be the only one to develop makes probably reference to selected mouse lines for depression. Nevertheless, and although a high impact publication (Sience 2006, 311:77-80) was produced with collaboration, there seems no attempts to further this project by gene

mapping (QTL analysis). The work on the rat prefrontal cortex concerns classical coupling between pharmacology and electrophysiology that does not seem to raise cutting edge questions (though the commission recognized that deep brain stimulation in patients may be promising).

More than 80 papers but no major publication even if they contributed to a few ones in high IF journals as collaborators in the middle of the multiple names (Nat Neurosci, JCO, Neuron). The team leader contributed to a majority of these papers, mostly also through collaborations or in methodological journals when last author. The formation of the team (2007) is most likely too recent to allow a real evaluation from their common publications. They previously collaborated on papers published in high impact factor journals by the groups of Lazdunski and Debonnel. Of note encouraging are two papers in 2009 published together in Progr NeuroPsychopharmacol Biol Psychiatry and in Neurobiol Aging. Finally, 2 researchers of the team have co-authored a study presently that was indicated in press in PLoS Biol. But no clear information was given to the committee on this paper. The paper is now out but credited to the Institut de pharmacologie moléculaire et cellulaire of the University of Nice.

Information in terms of awards and invitations to conferences in the last two years are missing.

The team has integrated researchers (1 INSERM researcher, 1 CNRS researcher, 1 professor and 1 lecturer) between 2007 and 2009

- Appreciation on the project

- Behavioural techniques and animal models: The project is focused on evaluation of depressive and anxiety behaviors and development of original animal models: the animal model was questioned since a basic characterization such as genetic deep sequencing or CGH-array was not done. Coherence with the hypothesis based on 5HT receptors are not clear, for instance the level of expression of 5HT4 or 7 were done evaluated in the Rouen model.

- In vivo electrophysiology : exploration of neuronal activities and synaptic plasticity. In vivo electrophysiology allowed them to collaborate in works published recently in high IF journals, such as Neuron and Nature Neurosci. However, the Committee wondered about the attractiveness of exploration of neuronal activities and synaptic plasticity in the proposed general context of the new team. Link to PET is difficult to see. The interest of developing in parallel a rat and a mouse model was not clearly understood by the Committee.

- In vivo neurochemistry: intracerebral microdialysis and measurement of the extracellular neurotransmitters; ex vivo neurochemistry of proteins involved in neurotransmission: quantitative analysis of receptors and transporters. This should be developed.

- Neuro-anatomical techniques: pathway tracing; evaluation of the expression of plasticity associated marker proteins and hippocampal neurogenesis. Connection to PET and imaging are difficult to see

- PET neuroimaging: development of new brain radiotracers and small animal positron emission tomography is sound.

- Innovative therapies non-pharmaceutical neuroscience-informed rehabilitation therapies. Through intracranial neurostimulation in the prefrontal cortex for depression or mood disorders. This is out of the scope of expertise of the team, which is already too dispersed.

Unclear and insufficient information regarding the use and handling of ressources.

They present original therapeutic targets in depression targeting 5-HT7, 5-HT4, glutamate receptors with a particular focus on the prefrontal cortex. A deep thought is needed to choose the best models for this challenging goal.

A potential medical transfer in diagnosis or in therapeutics: from a preclinical radiotracer to a PET radiopharmaceutical, from a drug candidate to a therapeutic.

- Conclusion :

  - Summary

Heterogeneity between a solid technical knowledge in methods linked to neuronal dynamics, particularly in innovative PET tracers and animal models, and some standard descriptive basic methods.

More hypotheses than strong results characterize the team. There are discrepancies between the targets (5HT1A,4 and 7) and the model used (Rouen mouse). There is unclear strategy as a group.

Indeed, cooperation between members of the group was not obvious

  - Strengths and opportunities

Targetting delay of action of antidepressant is a major scientific goal.

Capacity to design and obtain original pharmacological compounds (such as receptor ligands) thanks to close collaborations with chemists.

An interesting association of two disciplines considered to be complementary, although rarely associated: neuropharmacology and neuroimaging

Original concepts on 5HT4 and 7 involving also glial cells in the PFC

Pharmacological expertise

Two members are heads of platforms essentials for the future Center (Animage department in the CERMEP and NeuroChem)

  - Weaknesses and threats

Fusion of the heterogeneous researchers within a single major cooperative project was not done.

The ressource seems insufficient to characterize correctly the mouse “Rouen” model or develop genetic analysis.

Relevance of the “Rouen” mouse model of depression is questioned. The model lacks detailed characterization, particularly at the genetic level.

The low average impact factor of some publications. could be better if more focused and supported by multidisciplinary approaches

Local collaborations with clinicians like psychiatrists are currently insufficient.

Granting is not sufficient to support the research

No genetic approach

Too much “old fashion” pharmacology and not enough functional genomics.

  - Recommendations

The evolution for the last 2 years may have been promising but need still to make demonstration of the basic hypothesis.

The scientific hypotheses, although interesting, seemed multiple and not strongly grounded as presented to the Committee.

Turn to forces: PET tracers and animal facilities. To be integrated in the Center as supporting the plateforms may help and give time to merge toward more coherent scientific approaches of the mouse model of choice.

Models and techniques are too disperesed to creat a cohesive team. The team should focus on some and leave others for the sake of coherence. The committe did not consider that the team would explore : the role of prefrontal cortex by deep brain stimulation, pharmacology, rat and mouse models, lesions, 5HT1A, 5HT4, 5HT7, adding anxiety models, neurogenesis in hippocampus, glutamatergic, GABA-ergic, and mGluR systems, and finally neuroimaging. There are too many hypothesis, techniques, models, and objectives for a relatively small team.

Note de l'unité	Qualité scientifique et production	Rayonnement et attractivité, intégration dans l'environnement	Stratégie, gouvernance et vie du laboratoire	Appréciation du projet
A	A	A	A+	A

Nom de l'équipe : DYNAMIQUE CÉRÉBRALE ET COGNITION

Note de l'équipe	Qualité scientifique et production	Rayonnement et attractivité, intégration dans l'environnement	Stratégie, gouvernance et vie du laboratoire	Appréciation du projet
A+	A+	A+	A	A+

Nom de l'équipe : NEUROPLASTICITÉ ET NEUROPATHOLOGIE DU SYSTÈME OLFACTIF

Note de l'équipe	Qualité scientifique et production	Rayonnement et attractivité, intégration dans l'environnement	Stratégie, gouvernance et vie du laboratoire	Appréciation du projet
A	A	A	A	A+

Nom de l'équipe : INTÉGRATION CENTRALE DE LA DOULEUR

Note de l'équipe	Qualité scientifique et production	Rayonnement et attractivité, intégration dans l'environnement	Stratégie, gouvernance et vie du laboratoire	Appréciation du projet
A+	A+	A+	A+	A+

Nom de l'équipe : CODAGE ET MÉMOIRE OLFACTIVE

Note de l'équipe	Qualité scientifique et production	Rayonnement et attractivité, intégration dans l'environnement	Stratégie, gouvernance et vie du laboratoire	Appréciation du projet
A	A	B	A	A

Nom de l'équipe : NEURO-ONCOLOGIE ET NEURO-INFLAMMATION

Note de l'équipe	Qualité scientifique et production	Rayonnement et attractivité, intégration dans l'environnement	Stratégie, gouvernance et vie du laboratoire	Appréciation du projet
A	A	B	A	A

Nom de l'équipe : PHYSIOLOGIE INTÉGRÉE DU SYSTÈME D'ÉVEIL

Note de l'équipe	Qualité scientifique et production	Rayonnement et attractivité, intégration dans l'environnement	Stratégie, gouvernance et vie du laboratoire	Appréciation du projet
A	A	A	A	B

Nom de l'équipe : PHYSIOPATHOLOGIE DES RÉSEAUX NEURONAUX DU CYCLE VEILLE-SOMMEIL

Note de l'équipe	Qualité scientifique et production	Rayonnement et attractivité, intégration dans l'environnement	Stratégie, gouvernance et vie du laboratoire	Appréciation du projet
A	B	A	A	A

Nom de l'équipe : LANGAGE, CERVEAU ET COGNITION

Note de l'équipe	Qualité scientifique et production	Rayonnement et attractivité, intégration dans l'environnement	Stratégie, gouvernance et vie du laboratoire	Appréciation du projet
A	A	A	A	A

Nom de l'équipe : ESPACE ET ACTION

Note de l'équipe	Qualité scientifique et production	Rayonnement et attractivité, intégration dans l'environnement	Stratégie, gouvernance et vie du laboratoire	Appréciation du projet
A+	A+	A+	A+	A+

Nom de l'équipe : RECHERCHE TRANSLATIONNELLE ET INTÉGRATIVE EN ÉPILEPSIE

Note de l'équipe	Qualité scientifique et production	Rayonnement et attractivité, intégration dans l'environnement	Stratégie, gouvernance et vie du laboratoire	Appréciation du projet
A	A+	A	A	B

Nom de l'équipe : SCHIZOPHRÉNIES DÉBUTANTES ET RÉSISTANTES: DE LA PHYSIOPATHOLOGIE À LA THÉRAPEUTIQUE

Note de l'équipe	Qualité scientifique et production	Rayonnement et attractivité, intégration dans l'environnement	Stratégie, gouvernance et vie du laboratoire	Appréciation du projet
B	B	B	B	B

Nom de l'équipe : AUDIOLOGIE

Note de l'équipe	Qualité scientifique et production	Rayonnement et attractivité, intégration dans l'environnement	Stratégie, gouvernance et vie du laboratoire	Appréciation du projet
B	B	B	B	B

Nom de l'équipe : COGNITION AUDITIVE ET PSYCHOACOUSTIQUE

Note de l'équipe	Qualité scientifique et production	Rayonnement et attractivité, intégration dans l'environnement	Stratégie, gouvernance et vie du laboratoire	Appréciation du projet
A	A	A	A	A

Nom de l'équipe : NEUROPHARMACOLOGIE ET IMAGERIE DES TROUBLES DE L'HUMEUR

Note de l'équipe	Qualité scientifique et production	Rayonnement et attractivité, intégration dans l'environnement	Stratégie, gouvernance et vie du laboratoire	Appréciation du projet
B	B	A	B	B

Université Claude Bernard Lyon 1

Le Président
Lionel Collet

Villeurbanne, le 15 Avril 2010

M. Pierre GLORIEUX
Directeur de la section des unités de l'AERES
20 rue Vivienne

75002 PARIS

Monsieur le Directeur,

Je vous remercie pour l'envoi du rapport du comité de visite concernant l'unité de recherche :

«Centre de Recherche en Neurosciences de Lyon» rattachée à mon établissement.

En tant que Président de l'Université Lyon I, je tiens à rappeler à l'occasion de la venue du comité de visite de l'AERES que la création du Centre de Recherche en Neurosciences de Lyon, que j'ai souhaitée et qui est le cœur de l'opération « Neurocampus » inscrite au Contrat de Plan Etat Région, se place dans une dynamique de structuration forte du Pôle d'Enseignement et de Recherche en Santé de Lyon-Est dont un des objectifs est de renforcer les activités de recherche translationnelle.

A cet égard, l'émergence de deux Centres de Recherche, en Neurosciences et en Cancérologie, et la mise en place d'une Structure Fédérative de Recherche, dont ils constitueront les principaux piliers, permettra de développer les synergies en tirant partie d'un ensemble de plateformes technologiques de premier plan.

Je tiens à réaffirmer mon total soutien à la création du Centre de Recherche en Neurosciences de Lyon qui est d'une importance stratégique pour l'Université Lyon 1.

Je vous prie de croire, Monsieur le Directeur, à l'expression de ma meilleure considération.

Le Président de l'Université

Lionel Collet

Reply to the AERES report on the LYON NEUROSCIENCE RESEARCH CENTER

Project Leader: Olivier BERTRAND

May 2010 *(Note: in blue and italic are the comments from the AERES report)*

The members of the Lyon Neuroscience Research Center, and particularly its director and the team leaders, would like first to thank the members of the AERES committee for their evaluation work during the visit and in the report.

1 - Comments on the overall appreciation of the Center

We appreciated that **a certain number of strengths of our Center project have been acknowledged**: the strong involvement of university-clinicians resulting in high-level translational research, the emergence of new transverse and structuring projects along the translational axis, the quality of the technological platforms, the very good level of publications, the numerous recruitments of permanent researchers, the very good level of industrial collaborations and transfers, the strong involvement of the members in educational responsibilities, the great enthusiasm of all categories of members to create the Center, and, finally, the excellent leadership of the director.

However, we regret that there were only very few comments on the overall scientific and strategic projects proposed in the Center organization (both pointed out in the written project and during the visit), namely:

- to break the walls between disciplines for studying the brain at multiple scales, with a truly multidisciplinary approach, increasing individual team capacities.
- to implement this scientific strategy, from gene to cognition, and from bench to patients, in order to increase conceptual and translational efficiency of the team projects.
- to gather and organize the teams on the Neurocampus, having research laboratories, specialty hospitals, and technological platforms at walking distance, with a strong research concentration of teams in a new dedicated building in 2013, thus increasing scientific interactions, facility sharing, and translationnal collaborations.

All these actions aim at reinforcing the overall scientific efficiency, visibility, and attractiveness of the Teams in the Neuroscience Center.

2 - Reply to the specific comments on the Center

(1) Scientific strategy and cross-team synergies: *"From a scientific point of view, the present project seems to be the continuation of the IFR in Neurosciences"*

Indeed, the Center capitalizes on the 15 years of shared efforts of the Teams within the IFR in Neurosciences (very positively evaluated in 2007). This has been instrumental for sharing facilities, for organizing common scientific events, and for setting up a Master and a doctoral training program.

However, the Neuroscience Center dynamics has allowed to start building up a true common scientific strategy supported by a more efficient transverse organization, and this will be continued and strongly promoted in the future, namely through:

- **Transverse themes**: strengthening adult and child epilepsy research (a new team and the IDEE project), and emergence and support of new translational transverse projects with multi-scale approaches (neurodevelopmental disorders, Alzheimer's disease, and neuroscience-informed rehabilitation, with, in some cases, a clinical coordination organized thanks to the Center dynamics).

- **Emerging platforms and shared expertise**: the recent acquisition of a biphoton microscope, the emergence of a baby-lab for behavioural and electrophysiological studies in infants, the implementation of an EEG-TMS-neuronavigation platform, all projects being initiated by several teams willing to combine their expertise in a common endeavour.

- **Transverse personnel**: the implementation of missing methodological expertise by dedicated transverse personnel with advisory and technical support missions across teams (already implemented for molecular/cellular biology and for neuropsychological patient testing).

- **Joint ventures**: The Centre, before actual taking off, already propelled several joint ventures (new collaborations between teams, joint grant proposals to the ANR calls or to calls for research networks).

These are already our first actions demonstrating the much higher potential of a Center organization as compared to the mere federation of units.

(2) Size of the teams: *"The size of teams is highly variable ... For instance, except for team 10 which results from the fusion of distinct units, the others have previously been constituted. Thus, a Scientific Advisory Board (SAB) must be rapidly created, that can make new recommendations on specific projects and interactions among different teams."*

It should be first noted that there has been several team reshaping: Team 10 resulting from the fusion of distinct units; Teams 2, 4, 12, and 13 were derived from the split of a large research Unit. Among those new teams, several have been positively evaluated by the Committee.

The fact that several units join the Centre without being re-shaped is a deliberate choice. It has been motivated by sake of prioritizing scientific success and logistic functionality.

- Some of the teams are composed by researchers who proved very productive in the last four years thanks to a high degree of internal coherence. It has been our collective choice to prioritize internal coherence at expenses of generating new teams in the first step towards the constitution of the Centre.

- Differently sized teams are sometime motivated by the different topics tackled, requiring to keep together complementary competences.

- Only some of the previously constituted (but geographically dispersed) research units will jointly move to the Neurocampus building where they shall preserve, thanks to a favourable logistic, close scientific connections and exchanges. These units, indeed, were among those who proposed to generate new teams. Note also that all these units have been evaluated positively only 4 years ago and a re-shaping of the unit contours was therefore not considered timely.

The creation of a SAB proposing constant counsels on the Centre activities, as indicated in the submitted project, has been scheduled at highest priority in the post-AERES evaluation period. In the context of the NeuroCampus building, i.e., in the next 4-year contract, the Centre will carefully consider, promote and select the emergence of new teams, in agreement in particular with the SAB advice.

If other restructuring plans could have been possible for the future, it was simply not realistic to propose a scientifically and logistically efficient reshaping of many units as long as they were not located on the same site (the NeuroCampus building).

(3) Critical evaluations: Three teams have received various degrees of negative appreciations.

- With regards to the two clinical teams (Teams 11 in psychiatry and 12 in audiology), in spite of an insufficient number of full-time researchers in these teams, we consider their scientific expertise (acknowledged by publications and invited talks) and their structured clinical research logistics (assessed by several clinical research grants, PHRC) as highly beneficial for developing translational projects through mutual exchanges with several teams in the Center. The importance of such domains in the Neuroscience Center has been acknowledged by the Committee.

- With regards to Team 14 (mood disorders), it should be noted that this team has been ranked A by the AERES two years ago, thus generating high-level recruitments and personnel mobility based on its attractiveness in neuropharmacology combined to neuroimaging.

(4) Internal Chart: *"The internal chart of the center was not communicated to the committee."*

The Internal Chart has not been communicated because it was not clear whether it should be included in the submission (not clearly specified in the AERES guidelines, rather suggesting a limited number of pages for the submission).

We consider the Chart as an important founding milestone and we would like this chart to be validated by our institutions (INSERM, CNRS, Lyon 1 University).

This Chart has been discussed in the meeting of the committee with the research staff, and, as indicated in the written submission, it has also been extensively discussed between all Teams' members, and includes the policies and criteria for resource allocation. As indicated in the project submission, **a chart committee has been created in 2009** and it is working to propose a final chart by the end of this year (2010). Additionally, the work in progress on the Chart has been conceived of as extremely open and transparent: the provisional form of the Chart is available on-line to all members of the future Centre on the internal website.

All the governing principles were indicated in the project document (executive team, Center Council, Board of Team leaders, and Scientific Advisory Board). As for the budget, in the first year of the Center, we anticipate 8% of the total budget (recurrent budget and grants) to be devoted to shared platforms, incentive calls, common scientific events, and all actions contributing to the structuration of the Center.

(5) Recruitment of new teams: *"Until, at least 2013, the teams will be dispersed on different sites. Therefore, the policy in terms of recruitment of new teams remains fuzzy, and no specific plans are foreseen. .... Moreover, in accordance with the SAB, it would be useful to identify which field is missing or must be reinforced."*

A general agreement has been made (and again, included in the Chart) clearly stating that recruitment policy of individual researchers is, at least in the initial phase, left to the individual teams. In parallel, both the recruitment of new teams and the emergence of new research themes from internal resources will both be promoted by the Direction (also based on SAB reports) to fulfill specific research domains that may be left uncovered and new needs that will inevitably occur in the future.

As indicated in the written project and during the oral presentation, several domains of expertise have already been identified either as urgently needed (**computational neuroscience and complex system statistics, neurophotonics**), or as existing but to be reinforced (**molecular neurobiology, neurogenetics**).

Specific actions are already undertaken to recruit young researchers in these fields through the RTRS NeuroDis Foundation, and through Avenir/Atipe INSERM/CNRS positions. Contacts initiated with local Engineering Schools will also contribute to the improvement of missing expertise.

(6) Interactions between teams: *"At least, the interactions between the teams could be improved by supporting transversal programs and interactions between PhD/postdocs across teams."*

We fully agree that the interactions between the teams are essential for a true development as a Center. For that very reason, we have already implemented in the IFR of Neurosciences annual scientific internal calls since 2007 to promote joint projects between teams or between teams and platforms. In 2010, boosted by the dynamics of the creation of the Center, the number of submissions to this call has doubled. These incentive actions will be continued and even further improved in the Center.

PhD and Post-docs are already interacting through very effective transverse Journal Clubs (Oscillations, Cognition, Sleep). They have not only allowed to discuss recently published scientific results but also to present foreseen experimental protocols, freshly obtained results, and difficulties encountered in data analysis/interpretation. It also offers lively interactions with and among senior researchers. It thus goes far beyond the classical journal club format. This successful meeting format will be promoted in the Center in new domains (e.g., neuroimaging, ...).

Finally, a yearly scientific meeting supervised by docs and post-docs will be organized by the Center to promote interactions.

The multiscale and translational projects, supported by excellent platforms, already provide solid grounds for improving the cross-teams interactions.

(7) Foreign PhD and post-docs: *"In general, the number of foreign PhD and post-docs is low."*

Although there is a clear visibility of some of the teams, the overall international visibility of them was one of the major concerns and motivations for the creation of the Lyon Neuroscience Research Centre. We believe that the number of foreign PhDs and post-docs (**20% of the 125 PhD students, and 50% of the 60 post-docs, in the 2005-2010 period**) will significantly increase thanks to the increase in visibility that will be granted to all the teams by the creation of the Centre. **Already among the 18 new students starting their PhD in 2009 in the Center, 7 were foreigners**.

The "Neuroscience and Cognition" doctoral school (led by one of the deputy-director of the Center) will strengthen its international policy through the NENS (Network of European Neuroscience Schools). Foreseen actions, strongly supported by the Neuroscience Center, will consist in organizing international summer or winter training courses in Lyon for PhD students and post-docs.

(7) 3T MRI: *"Many studies are based on access to 3T human MRI scanner and it is unclear how this will be solved."*

A 3T MRI scanner, fully dedicated to research, is already funded and will be operational in 2011 (for both human and non-human primate research). The management of the MRI facility will be co-directed by the CERMEP imaging platform and Centre members.

The acquisition of a second human 3T MRI scanner, also fully dedicated to research, is foreseen and actions have been undertaken to fund this new instrument based on the recent governmental initiative to support public research in France ("Grand Emprunt National").

3 – Replies to the specific comments on the Teams

3.1 – Team 01 (O. Bertrand)

We would like to thank the committee for its very positive appreciation of our team.

We notice that the committee mentions doubts about the social cognition topic.

First, we would like to stress that this domain has been successfully studied for more than ten years by our group. This is attested by 28 publications (between 1998 and 2009) presenting with an average of 46 citations per paper. We believe that the planned projects address well-defined questions that avoid the pitfall of being "too" fashionable. The feasibility of the applications to be developed in Alzheimer's Disease and in autism is ensured by a strong clinical network organized within the Neuroscience Center, and there is no doubt about the importance of studying social cognition deficits in these pathologies.

Second, as mentioned by the committee, this theme will be reinforced by an incoming researcher who will explore the role of the mirror neuron system into the understanding of social interactions. We therefore feel very confident about the longevity of this theme as tackled by our group.

Lastly, this project, jointly with those of other teams, will contribute to two transverse strategic axes of the Center, "Neurodevelopmental disorders" and "Alzheimer's disease".

3.2 – Team 02 (A. Didier)

We would like to thank the committee for its very positive appreciation of our team.

The sole point raised by the committee members is about the link between human and mouse studies which they thought was too much emphasized. Our project was build indeed in order to focus on the same topics (olfactory hedonics, and effects of aging and experience on olfactory perception), both in

human and mouse. However, we are aware that species differences make difficult direct between-species extrapolations and we acknowledge that the way our project was presented may have been misleading.

Our objective is rather to go further in the understanding of olfactory plasticity through parallel studies in human and animals with the goal of constantly adjusting the animal models and paradigms to best fit to the main issues raised in human (for instance, developing an animal model to study odor preferences or new mice models combining amyloidal pathology with noradrenergic deficits, to get closer to the human pathology). This opportunity to develop complementary human and mouse studies in our group is a strength that has been recognized by the committee and has already been fruitful both in terms of publication and fund raising.

Finally, we would like to stress that our group has a very strong involvement in academics and teaching, which was not pointed out by the committee. Beyond their full time teaching duties, the two university staff of the group have academics responsibilities: A Didier is in charge (with a colleague from the Physiology department) of the Master 1 “Physiology and Neuroscience” since 2007 and will be responsible for the Master 2 “Neuroscience” in 2011. F Jourdan is the director of the Federative Institute of Neuroscience in Lyon (IFNL) and of the Doctoral School in Neuroscience and Cognition since 2007 and until the end of 2010. Both researchers of the group perform significant teaching.

3.3 – Team 03 (L. Garcia-Larrea)

We thank the Committee for the highly appreciative comments on our past work and our project, and attentively consider their recommendations for future developments. Two of their suggestions have particularly raised our interest, namely the importance of dopaminergic PET studies in chronic pain states, and the importance of pre-stimulus patterns of thalamo-cortical coupling that might predict nociceptive inputs being processed differentially. The latter is indeed being pivileged in the group and we expect to provide relevant results in a near future.

Although we do agree with the Committee that increasing recruitment from abroad should be encouraged, may we note that, in the past four years, 5 out of 6 post-docs and 2 of 4 PhDs did come from abroad (Brazil, Lebanon, Spain, Belgium and Germany). We will try of course to further improve these figures in the future.

3.4 – Team 04 (R. Gervais)

All members of the team thank the reviewers and the committee for their constructive critical comments. We are pleased to see that our scientific axes have been appraised to be relevant. Also the committee pointed out some specificities of the team as being the sole in France in covering a large field in olfaction neurophysiology and having a unique knowledge of in vivo multiunit recordings in the olfactory system in the world. We would also like to underline the fact the group possesses a strong expertise in olfactory functional neuroanatomy in humans with PET and fMRI (about fifteen papers since 1999). There are only 3 other groups in Europe and 4 other groups in the rest of the world running such experiments (chemical senses: olfactory, gustatory, or trigeminal).

We acknowledge the recommendation of the committee concerning our publication policy. The main strategy of the new team which results from the merge of smaller groups of the present laboratory is based on the principle of intra-team collaborations. As a result, the new team will certainly gain in visibility in order to increase the impact factor of the journals in which we will publish. We point out that ongoing ANR grants already include internal collaborations. They will also be facilitated until 2013, since all members of the new team will be housed in the same building in the Gerland Campus and share experimental facilities. This will allow interactions on a daily basis.

By 2013, our team will move in the new Neurocampus building in which other teams of the Neuroscience Center will converge. This will offer realistic new opportunities for reconfiguring the

contour of the Olfaction team in order to promote emergence of new team leaders. As recommended by the committee, this reflection will be conducted early in the next quadrennial period.

3.5 – Team 05 (J. Honnorat)

We would like to acknowledge the committee for its insightful comments and suggestions. Overall, while committee members found that our "team is based on a solid pool of researchers and clinicians", that "Some subgroups have an excellent partnership strategy, a good publication and valorization policy" and "in addition, they have a good national and international visibility", they raised some points that we would like to address.

(1) We are surprised by the statement that we developed *"no novel hypothesis or technic"*:

a) Our research is based on the original concept that the alteration of molecules and signaling pathways shared between immune and nervous systems lead to neuro-inflammatory diseases such as Multiple Sclerosis (MS) or Paraneoplastic Neurological Syndromes (PNS) and that the same molecular pathways are involved in tumor growth. A lot of novel hypothesis concerning the choice of shared molecules and their role are mentioned along the project namely concerning CRMP proteins family, VEGF and semaphorins.

b) Concerning the technics: production of transgenic mice, development of animal models of pathology or of the unique model of in vitro blood-brain interfaces and the establishment of transcriptomic and genomic platforms as well as collection of biological resources from cohorts of patients demonstrate a real technical inovation.

(2) The committee mentioned that *"their participation to international or national scientific networks and their ability to establish stable collaborations with foreign partners depends on topics and may be more in certain subfields (brain tumors, basic science on CRMPs)"*. We would like to underline foreign collaborations in rare brain tumors lead us to propose and published new WHO classifications in pineal and pituitary tumors and to identify new prognostic markers. Concerning CRMPs molecules, we collaborated with well known US and Japanese teams which lead us to publish numerous articles (J Neurosci x2 ; Gene to cell; Mol Psy; FASEB J…) and to develop three CRMP knock-out mice (CRMP1, CRMP3, CRMP5)

(3) The statement that *"in terms of articles, they have to publish more from the real work and ideas of the group"* is questionable. Indeed, since 2005, we published 164 research articles and more than 70 had at least one member of the team as first or last author. Among them, a majority had an impact factor higher than 5 with well recognized journal such as New Engl J Med, Blood x 2, FASEB J x 2, Mol Psy, Stroke, Neurology, Annals Neurol, Arch Neurol, J Cereb Blood Flow, Glia… Furthermore, we published 29 more articles since September 2009 and while our Inserm unit has been created in 2007, we have some major articles under revision (Brain ; J Neurosci x 3) or under review (Nature Neuroscience).

(4) One major remark of the committee is about the *size of the group*. We planned during the first discussion of the Lyon Neuroscience Center to split the Unit in two parts, but an unforeseeable event with one team leader lead us precluded this as a first step. The split of the group into three teams is not realistic and would be deleterious to the scientific consistency, since first because our research is based on multiparametric analyses (epidemiological, clinical, anatomopathological, molecular) needing a close collaboration between clinicians and scientists and second the same molecules are studied by the researchers working on neuro-inflammatory diseases or brain tumor.

(5) We will improve the number of students and foreign postdocs, but in the last 5 years, 9 PhD (one co-directed with Italy) and 17 Masters2 have been defended with in addition 4 students from Ecole Pratique des Hautes Etudes (EPHE) and 2 from "Ecole de l'Inserm". In the last three years, 5 post-docs (one from Finland) were in the team and three new have been recruited in 2010.

(6) We agree that *"the participation in editorial boards may be improved"*. However, we would like to strengthen that several members of the team are in the editorial or advisory board of French as well as foreign journals such as "The cerebellum" or "J Neurol Neurosurg Psychiatry".

3.6 – Team 06 (J.S. Lin)

We appreciate that the reviewer recognized the importance of our research topic, wakefulness, and that he highlighted not only our unique expertise and world leading reputation, but also the pertinence of our major projects.

However, we would like to emphasize that, our strength is due to the fact that we have not only identified the function of histamine on waking, but also demonstrated its deficiency as the direct cause of somnolence, encountered in various sleep-wake disorders and other brain pathologies. The dissection of molecule/function relationships has allowed us to develop a multiple-scale approach from molecule and cells to behavior and therapy.

This strategy is highly appreciated by INSERM commissions, as demonstrated by the recruitment of 4 researchers (CR1) during the last 2 years. This is an exceptional performance in view of the highly competitive context, emphasizing the validity, vitality and attractiveness of our project. We are surprised that such a performance was qualified "*difficult to evaluate*" or even "*dispersion*"!

The concern on clinical studies is unfounded since we fortunately have been the first to propose and test the histaminergic therapy at a highly competitive level (Clinical phase III trial, Lin et al.,2008).

In summary, we have developed a unique opportunity to combine molecular functional approaches and associated pathologies in a context where the required competences are available in our team from genetic tools to behavior and therapy including original animal models and clinical trials.

(1) We wish to make some rectifications concerning our activity:

Publications. 65 papers instead of 56 in the reviewer's report, were published between 2005-2009 by team members joining the lab before 2009 (L.Seugnet not included). 2 of them have an IF >10, 10 an IF of 6-10 and 14 an IF of 4-6. 38 have been published by members after their recruitment in the team (including 1 Nature Rev. Endocrinol.) and 29 concern results that were produced, at least partly, in the lab, including 3 J. Neurosci.

Funding. While we are working towards improving funding, it is important to note our increasing external funding from 48 k€ in 2005 to 289 k€ in 2009, i.e., 78% of our current total budget. Notably 2 ANRs (413 k€/4y), 1 *Crédit de recherche clinique translationnelle* (94 k€/2y) and 1 Eu grant (75 k€/3y).

Our overall international collaborations were clearly underestimated in the report. A few examples: 1) H.L. Haas (Dusseldorf), a renowned specialist of histamine: sharing common Eu contract (2002-2005), PhD and Post-doc students, 5 common papers in which, 2 J. Neurosci. in 2009; 2) M. Yanagisawa (Texas), member of USA Academy of Science, prestigious scientist in orexin, 2 common papers; 3) H. Ohtsu (Sendai, Japan); prestigious specialist of histamine, 4 common papers. Moreover, the new recruits are working synergistically with their former teams, constituting important collaborations and outreach of our team and therefore placing us in a position of strength faced to international competition.

Other rectifications: 1) In addition to a "Young Investigator Award", a "Sleep Research Society's Outstanding Scientific Achievement Award" was attributed to K Spiegel in 2007; **2)** 20 invited lectures at international meeting instead of 6; **3)** Not only the team leader, but also Dr P. Franco (associated professor, 30% ETP devoted to teaching) and K Spiegel (CR1) have been actively involved in teaching; **4)** 3 PhD, plus 2 MD and 3 HDR theses instead of "only 2 PhD".

(2) Specific answers

Our clinical project and focus. The reviewer wrote: *"The last project is on the treatment of sleep*

disorders with preclinical and clinical trials, …The rationale of the proposed projects is weak …." and *"The proposed expansion towards sleep disorders does not seem focused and … A second major threat is by dispersion the team may lose the leadership in the field of histamine and sleep-wake."*

The clear basic-clinical continuum in our team has been highly recommended and appreciated by INSERM so far. Our long lasting leading reputation in preclinical field is well illustrated, in the past, by identification of Modafinil (the only clinically-suitable wake-promoting compound now being used worldwide, Lin et al., PNAS, 1996) and, recently, by identification of H3-receptors as new brain target for sleep disorders and Tiprolisant (H3-receptor inverse agonist, Clinical phase III trial, Lin et al.,2008) *"leading to the next generation of wake-promoting drugs"* as the reviewer stated.

Because **somnolence** is a symptom caused by a histamine deficiency and encountered in narcolepsy sleep apnea and Parkinson's disease, our preclinical studies on somnolence associated with these pathologies seem to be perfectly on focus and tightly linked to our hypothesis on histamine.

Our new developments and leadership. The reviewer wrote: *"The major weakness and threat might come from the new development including the metabolism in humans and sleep in drosophila…."*

Without new and original developments by the next generation of experts, we may lose our leadership in this rapidly growing and very competitive field. Judged repeatedly adequate and optimal to our team's expertise, the projects on metabolism and drosophila have been approved and validated by INSERM recruitment commissions.

Whereas further evaluation will be required to confirm, as any project, the adequacy of our strategy, our extension to include an invertebrate model and human studies is clearly an asset. It is now hard to envisage the development of a research field without the benefit of multidisciplinary approaches making the best use of invertebrate and mammalian experimental systems combined with human studies. Our recent recruitments provide these needed new approaches. It is only by combining drosophila, mouse and human models that He et al (Science, 2009) were able to demonstrate a major mechanism determining sleep length, a study that Dr. Tafti defended with a highly supportive editorial. Our lab has now set up for such cutting edge strategy.

3.7 – Team 07 (P.H. Luppi)

We would like to thank the committee for his work. Overall, we are in agreement with the present report and therefore have a limited number of comments.

First, it is mentioned in the report that *"no international collaboration is listed"*. We indeed only provided a detailed list of our collaborations during the oral report. We have been collaborating with several laboratories in Europe, Japan and USA. Most notably, we recently did collaborate and publish with Prs Eric Kandel (NY, USA), Thomas Kilduff (San Diego, USA), Pierre Maquet (Liege, Belgium) and Masatomo Mori (Maebashi, Japan). Further, funding have been obtained for new collaborations with Sergio Tufik (Sao Paulo, Brazil) and Yoshihiro Urade (Osaka, Japan). We will apply for additional funding for these projects and for a new project initiated in collaboration with Isabelle Arnulf (Paris) this year.

We agree that our ambitious project on paradoxical sleep-related gene expression needs to be published quickly. Therefore, we will submit this work to a high profile journal in the following months.

We are also eager as recommended to introduce as soon as possible transfection methods and optogenetic approach to manipulate populations of neurons responsible for paradoxical sleep genesis and function. To this aim, we recently submitted two grant proposals, one in the frame of the Federative Neuroscience Institute of Lyon (IFNL) in association with teams 2 and 14 of the Neuroscience Centre and another one to the CNRS (PEPS grant) to initiate the development of these promising molecular approaches. Further, we just did set up a collaboration with Yoshiriro Urade (Japan) to develop innovative fRNAi vectors targeting vesicular GABA (vGAT) and glutamate (vGLUT2) transporters to further determine the respective contribution of glutamatergic or GABAergic neurons in PS generation. An Italian post-doc has been recruited for this project.

Finally, it is worth mentioning that since the visit of the committee, two additional articles were published with members of the team as first authors (G. Malleret, J. Neuroscience and L. Leger, J. Chemical Neuroanat). We will also recruit in October 2010 a technical staff (IE2, University of Lyon) to replace a retiring engineer, thus keeping the number of support staff to five.

3.8 – Team 08 (T. Nazir / A. Reboul)

We would like to thank the visiting committee for the positive feedback on our team and research project. Below some clarifications on the queries raised in the report:

(1) *" The conceptual clarity of the proposal could perhaps be increased – especially when it comes to the relationship between situatedness, syntax, and recursivity"*: We intend to test the possibility that (situated) motor and language systems share abstract processes of the linguistic capacity in the form of a motor syntax.

(2) *"Also, the neuroscience aspects of planned research on the "logical dimension of language", and generally in the domain of hypotheses 2 and 3, could have been outlined more clearly "*: The existence of non-situated representations brings with it the possibility of deception (such representations are produced in the absence of what they represent, so there is no immediate means of verification). A defense mechanism is the detection of logical inconsistency, which rests on the (transparent) logical structure of language (Hyp. 2) and on mechanisms for logical reasoning allowing the detection of contradiction (Hyp. 3). However, language allows speakers not to commit themselves to what they communicate through a variety of means for implicit communication, thus avoiding penalty for transmitting false information (Hyp. 2).

(3) *"they should use input from electrophysiologists (Team 1) to reinforce the EEG part"*: We have a common ANR grant with Team 1 and our technical support (A. Cheylus) was trained by O. Bertrand.

3.9 – Team 09 (D. Pelisson)

No specific comment on the report.

3.10 – Team 10 (P. Ryvlin / L. Bezin)

A minor remark concerns a mistake in the spelling of each of the two team leaders name (Rivlin and Bezzin instead of Ryvlin and Bezin). A more serious concern is the lack of any mention of the genetic aspect of our project, eventhough clinical geneticists (P Edery, D Sanlaville, G Lesca) account for about 1/3 of our researchers and publications.

Two issues were raised regarding our publication track record: 1) "*its **unbalance** between the clinical and basic research groups"*, 2) "*its **emphasis on clinical epilepsy matters** rather than on the preliminary work in our emerging research topics"*. In our view, the unbalance primarily reflects the very high publication track record of the clinical group which can hardly be matched in basic science. Indeed, the 6 senior clinicians (representing less than 2 full time equivalent researcher) have published **229** in the last 4 years, including **18** publications with an Impact Factor > 10, one in the top 0,1% and 8 in the top 1%. Many of these top publications were indeed clinically oriented, reflecting an optimal capitalization on our clinical activity and expertise, rather than an ineffective dispersion in irrelevant clinical topics. Finally, our emerging team gathers researchers from various fields who will primarily start to closely work together within the Team on recently launched topics, and cannot be expected to have already largely published in these fields.

A mention was made of a *"**multitude** of problems inherent in clinical trials"* or *"minor methodological problems or concerns about **a number of** the projects"*, without specifying any of these problems, except the issue of patient recruitment. The lack of more specific comments does not allow us to

address this issue. Nevertheless, we would like to stress, as mentionned in the AERES report, that most of our clinical studies have been recently granted mostly through very competitive national grant proposals such as “PHRC” and “appel d’offre INSERM DHOS translationnel”. Our clinical trials were thus scrutinized and validated by experts in the fields, as well as by the AFSSAPS and ethical committees. We thus **strongly disagree** with the conclusion that our clinical research studies face a “multitude” of problems, including patients recruitment, since the already ongoing projects have not faced any such issues.

A mention was made of *“some-risk taking, given our single hypotheses”*, while it was further noted that another risk was *the presence of too many projects*. Beyond the contradiction of these two comments, we wish to stress that clinical studies are required to explicitely delineate primary single hypothesis, objective, and endpoint. Fulfilling these methodological requirements, rather than representing a risk, best guarantee high impact clinical studies, even when the primary hypothesis eventually proved wrong. In terms of the number of projects, our team has clearly indicated that it will focus on only two very specific research axis, each of which has a clinical, genetic, and experimental integrated counterpart. We thus fail to understand the criticism regarding a too large number of studies.

Finally, it was encouraged that *our experimental group collaborate with experts in apnea studies in animals*. As suggested, we have recently developed a collaboration with Christian Gestreau’s team in Marseille (UMR CNRS 6231), specialized in respiratory neurophysiology. Furthermore, our group is actively participating to the french experimental task force recently set up by the French League Against Epilepsy to tackle the mechanisms of SUDEP in experimental models of epilepsy.

3.11 – Team 11 (M. Saoud)

We appreciate that the Committee recognized the relevance of our research in Schizophrenia with original and fruitful approaches on TMS treatment and PET investigation. Nevertheless, we would like to provide some precisions on the remarks raised by the Committee.

(1) About doubts on our main hypotheses

Dopaminergic hyper reactivity in schizophrenia did not convince the committee. However, dopaminergic hyperreactivity in schizophrenia is widely admitted with more than 400 papers on schizophrenia hyperdopaminergy, (source Pubmed 2010) attesting the hyper reactivity hypothesis.

A peripheral measure of dopaminergic reactivity to stress, such as plasmatic homovanilic acid (pHVA) could be **relevant for central implication**. Several studies have suggested pHVA as reliable to assess central dopaminergic function (Kopin et al. 1988; Maas et al. 1988; Pickar et al. 1990; Lambert et al. 1993; Stroe et al. 1997) including central dopaminergic reactivity to stress (Breier et al., 1993, Adler et al., 2000; Marcelis et al., 2004).

Moreover, the dopaminergic-hyper-reactivity to stress has been **directly confirmed by central PET studies** by our team (see our report and foot-note[1]) and others (Mizrahi, 2010; Soliman et al. 2008).

According to committee’s comment, current **rTMS protocols** developed to target general symptoms in schizophrenia failed to demonstrate any significant improvement. However, specific rTMS protocols targeting individual subcomponents of the syndrome such as auditory hallucinations (AH) do yield a real therapeutic impact as indicated by **78 papers in the field** (source Pubmed 2010), **including 4 positive meta-analyses**[2,3,4,5]. Moreover, our complementary, however preliminary, results on

[1] **Brunelin J, d’Amato T**, van Os J, Costes N, **Suaud Chagny MF, Saoud M.** Increased left striatal dopamine transmission in unaffected siblings of schizophrenia patients in response to acute metabolic stress. **Psychiatry Research - Neuroimaging, 2010,** 181(2):130-135**.**

[2] Tranulis C, Sepehry AA, Galinowski A, Stip E. Should we treat auditory hallucinations with repetitive transcranial magnetic stimulation? A metaanalysis. Can J Psychiatry. 2008 Sep;53(9):577-86.

[3] Aleman A, Sommer IE, Kahn RS .Efficacy of slow repetitive transcranial magnetic stimulation in the treatment of resistant auditory hallucinations in schizophrenia: a meta-analysis J Clin Psychiatry. 2007 Mar;68(3):416-21.

[4] Freitas C, Fregni F, Pascual-Leone A. Meta-analysis of the effects of repetitive transcranial magnetic stimulation (rTMS) on negative and positive symptoms in schizophrenia. Schizophr Res. 2009 Mar;108(1-3):11-24.

schizophrenia refractory symptoms using external neurostimulation are still very encouraging. Thus, we are very confident in this approach and we are the coordinator of a collaborative project including 4 European teams submitted to ANR.

Concerning susceptibility genes: Many identified candidate susceptibility genes for schizophrenia, including genes involved in the regulation of dopaminergic transmission, are likely to play roles in the pathophysiology of the illness. It is clear, however, that the etiologic contribution of these genes is not only via their own functions but also through interactions with other genes and environmental factors. The negative findings obtained when schizophrenia is used as phenotype highlight the need to consider alternative approaches using intermediate (or endo-) phenotypes in the domains of cognition, neurophysiology, or neuroanatomy as we suggested in our report.

These so-called intermediary phenotypes (because they are between the predisposing genes and the disease phenotype) might be closer to alterations in gene function than the diagnostic category of schizophrenia and related disorders and, for this reason, could be useful targets for molecular genetic studies. Some of these intermediary phenotypes could be diagnostically relevant; for example, the intermediary phenotype of cognitive impairment could have high specificity for the diagnostic category of schizophrenia.

Markers in prodrome subjects will not necessarily be transferable to the general schizophrenia population. However, from a dimensional perspective, individuals possessing the same genotype could express milder forms of the clinical disorder along a spectrum of related traits[6].

(2) About remarks on our resources/expertise

- **The access to patients from a university health care center is not a limiting step**. Indeed, our department has developed a unit dedicated to psychiatric disease detection and prevention, located on the campus of Lyon1 University (30 000 students). According to epidemiology data, about 3% could be considered as at-risk to mental state. Moreover, our team has translated a specific scale for prodromal state, now on line on Lyon University website. Since October 2009, we have already recruited 14 prodromal subjects included in the GABA study (see our report). For all these reasons we are confident in prodromal subject recruitment.

- **We have sufficient resources and personnel to run long-term follow up projects**. The largest Lyon department of psychiatry is headed by J Daléry and T d'Amato, two members of the team: catchment's population of 700,000 - 300 health professionals. Our clinical department gathers health care units for inpatients and outpatients and includes the Lyon schizophrenia expert center (CRESOP, a member of the Fondamental network).

- **Our integration in FondaMental network is recent and projects are currently under discussion**.

- About our weak points

  - We agree with the assertion of a lack of expertise which concerns specifically **neuroimaging data processing**. However, the Centre organization will strongly help us in this field. Moreover, J. Brunelin, the youngest permanent researcher of the team, is being to get this specific training. For example, he is our main investigator in a collaborative project which is in progress with F. Padberg's group in Munich. (Klinik für Psychiatrie und Psychotherapie, Universität München)
  - Our lack of expertise in statistics concerns specifically **statistics applied to epidemiology** and to multicenter clinical trials. Despite this lack, our own expertise in statistics needed for other projects is beyond doubt as attested by our publications in international scientific peer-reviewed journals (Schizophrenia Research, British Journal of Psychiatry, Biological Psychiatry…) and by specific diplomas obtained by different members of our team (M. Saoud: 2 post-graduate diplomas in statistics, J. Brunelin: "Clinical Research Coordinator" diploma)

[5] Slotema CW, Blom JD, Hoek HW, Sommer IE. Should we expand the toolbox of psychiatric treatment methods to include Repetitive Transcranial Magnetic Stimulation (rTMS)? a meta-analysis of the efficacy of rTMS in psychiatric disorders. J Clin Psychiatry. 2010 Mar 9.

[6] Pantelis C, Yücel M, Bora E, Fornito A, Testa R, Brewer WJ, Velakoulis D, Wood SJ. Neurobiological markers of illness onset in psychosis and schizophrenia: The search for a moving target. Neuropsychol Rev. 2009 Sep;19(3):385-98.

- Our impact factors are relatively low in the general Neuroscience area, but our productivity must be considered in the context of our speciality, i.e. psychiatry. Since 2005, we have **15 published papers with IF > 4**, among them 4 in collaboration with other groups.
- **We have dropped out the animal studies due to low critical mass and logistic support**, but this allows us to re-assign, in 2009, an Inserm permanent researcher (DR2) to our clinical research project.
- Finally, we did not think that data collection procedures and detail account of protocols were expected in a report whose scope seemed to us more general.

In conclusion, and as acknowledged by the Committee, we strongly believe that the scientific and methodological environment (rTMS, neuroimaging, neurogenetics) provided by the Lyon Neurocience Center could be a very good opportunity for both the Center and our team to reach a cutting edge quality in clinical research in psychiatry, particularly in the treatment of schizophrenia by innovative tools.

3.12 – Team 12 (H. Thai-Van)

We thank the committee for its valuable comments and suggestions. Although committee members have acknowledged the importance of our research, they have also raised concerns that we are willing to address.

(1) Key points: scientific leadership, strategy and future expansion of the team

Our group includes **ENT or neurology clinicians, physiologists, along with signal processing specialists**, and is located **in a University Hospital** with access to patients. As such, it is internationally known for its distinctive capability in **experimental and clinical audiology**, as demonstrated by our record of peer-reviewed journal publications (n=70) and invited conferences (n=40). This will bring a **unique know-how** to the future Centre. Our expertise may have been overlooked by the committee, which did not include any expert in ENT research. Yet the committee has highlighted our well-established reputation for our work on top-down auditory mechanisms (mediated by the efferent system) and auditory plasticity in cochlear implant subjects. It must be emphasized that our current projects are directly in line with what we have accomplished so far.

Impact and general scientific relevance of our projects. Our most recent work on the asymmetry and plasticity of the medial efferent system (MES) has triggered additional work by other well-known groups corroborating our key results: that is, the crucial role of the MES for auditory perception (de Boer and Thornton, 2008) and of subcortical auditory processing for reading acquisition (Banai et al., 2009). Furthermore, the outcomes of our future research can also impact other areas of neuroscience, covering rTMS, learning disorders and cross-modality issues.

We do therefore have a well-articulated and clear vision for the future, reflecting not only our tradition of timely and high impact research related to deafness, cochlear implant and tinnitus, but also our commitment to develop novel and translational projects.

Connection of the group with the hearing science community and the leader's strategy: *"… apparent lack of connection with other strong and relevant French and international teams of auditory scientists. A consequence of this apparent isolation is the disconnected and speculative nature of the research proposals …"* We think that these comments went somewhat too far. In regard to our main cochlear implant project, our collaborator Pr David Ostry from McGill University has already shown that adult cochlear implantees have a strong reliance on somatosensory representation for speech production (Nasir & Ostry, 2008 Nat Neurosci.). At the national level, collaborations have been set up with internationally recognized auditory scientists (e.g., Pr Christine Petit, Institut Pasteur, Paris; Pr Paul Avan, Clermont-Ferrand University). In these collaborative projects, we will bring our **unique expertise** in the area of auditory deprivation-induced plasticity (Thai-Van et al., Brain 2002, Brain 2003). Again, the relevance of our MES research proposals has been documented by recent research pointing out the crucial role of the MES in perceptual learning.

"This team needs an opportunity to spell out clearly where they are going and how they are going to get there". We have planned to focus our future research on the **two topics** that are core to our international visibility: that is (1) plasticity in deaf subjects induced both by auditory deprivation and rehabilitation, and, (2) role of the MES in auditory perception.

This goal will be achieved using **the methods we have already developed** for assessing activation of the auditory pathway in cochlear implantees (e.g., Guiraud et al., J Neuroscience 2007), for assessing control of cochlear activity by the efferent system (e.g., Veuillet et al., Brain 2007), and for assessing the corticofugal modulation of that activity (Perrot et al., Cereb Cortex 2006). Our work will also greatly benefit from **direct access to large cohorts of patients** with auditory disorders. Last but not least, we would like to point out that our **unique partnership with cochlear implant and hearing aids industry** is a strong asset for conducting research in the field of auditory rehabilitation.

"The leadership should ensure that the team will increase its national and international visibility and expand over the next years". As stated in the experts' review, our group **has just been reshaped in the last couple of years**. Nonetheless, we can already confirm that one Assistant Professor, with expertise in the fields of electrophysiology and neurodevelopment, will join us before the end of 2010. Besides, collaborations have already been set up with other teams of the future centre, who share our interest in sensory processing assessment (e.g., team 1) with complementary expertise. **Increasing human potential in the group will thus be done by expanding the group size, together with appropriate collaborations.**

We have just made clear that our strategy for the future will fit the committee's recommendations. Below are our answers to the questions related to our core research projects.

(2) Specific answers related to our core research projects

"However, it isn't clear that the basic premise of the CI research is sound. The results of tilting children who are CI users (stimulating several systems) would be difficult to interpret". Young cochlear implantees provide a unique model for investigating mutual interactions between auditory maturation and speech related somatosensory learning. A question of central interest is how congenitally deaf children develop somatosensory representations of speech sounds after getting a cochlear implant (CI). While we first planned to change the orientation of the childrens' bodies and study how they would compensate for the changing gravitational load on the jaw, we realized that this would result in a poorly controlled mechanical perturbation on the speech articulators. Our project has therefore evolved and we are now heading towards the measurement of somatosensory sensitivity. Our work hypothesis is that sensitivity to tactile stimulation on the speech articulators will increase with CI use, as children start to learn to speak. We are currently developing a solenoid device that is capable to apply small skin stretches and compressions at varying degrees.

"In the efferent work, it isn't clear how asymmetry is judged, what its significance might be, or what to do about it". In humans, activation of the medial efferent system (MES) by contralateral noise is known for more than two decades to reduce the gain of cochlear amplification and, subsequently, to decrease otoacoustic emissions (OAE) amplitude (Collet et al., 1990). We have, in addition, conducted pioneer research showing that this suppression effect is normally lateralized toward the right ear in right-handers (e.g., Philibert et al., 1998; Khalfa et al., 2000, 2001; Morand-Villeneuve et al., 2005; Veuillet et al., 2001, 2007). Here, our working hypothesis is that MES asymmetry, as a reflection of the asymmetric top-down control of cochlear activity, is also related to hemispheric lateralization known to play a decisive role in speech processing.

"The idea that cortico-cochlear control is involved in reading acquisition is complex and appears not to have been well thought through". Most researchers in our community now agree that abnormal phonological representations are likely to be involved in reading disability. Normal phonological representations rely on adequate representation of sounds in the central auditory pathway. Reciprocally, poor reading is thought to be associated with physiological deficits along the auditory pathway. Consistent with this view, we found, first, that dyslexic children present a reverse lateralization pattern of their MES and, second, that intensive audiovisual training in these children not only improves categorical perception of phonemes but also normalizes MES lateralization pattern (Veuillet et al., 2007, Brain). Our plan is now to further investigate the relationship between subcortical

sensory function and reading ability. For this, we will assess the impact of MES lateralization on reading acquisition in poor readers and their age-matched peers.

"rTMS as a way of studying efferent processes is of interest, but its relationship to tinnitus is not known nor spelt out in the proposal. Also, in questions, the ability to use rTMS on auditory cortex had not been fully considered". The relationship with tinnitus relies on the following rationale: with previous research showing, in tinnitus patients, pathological neuronal activity both at the peripheral and subcortical levels, rTMS may have a therapeutic effect by interfering and normalizing tinnitus-related neuronal hyperactivity. This would be mediated at least partly through modulation of corticofugal auditory pathway and MES. The ability to use rTMS on auditory cortex is a rather innovative topic of research which is currently under assessment in our laboratory.

3.13 – Team 13 (B. Tillmann)

We thank the committee for their positive feedback on our team. The indicated weaknesses are 1) *the small team size*, and 2) *no apparent links with the Audiology team (team 12)*.

(1) In line with the committee's recommendations, our team's recruitment efforts for a 4th PI are reflected in a) two candidates who have been applying this year for permanent research positions to join our team, and b) currently beginning local actions to open a University position (MCF) also attached to our team. The candidates' research projects integrate directly into our team's research, with competences covering cognitive neurosciences, cognitive psychology and auditory psychophysics. While one candidate has now been recruited at her home university (Montréal), the second candidate has just completed his oral presentation at the CNRS.

(2) While sharing the interest to study "top-down" modulation of auditory processing, the two teams focus on different mechanisms and processing levels: while the Audiology team investigates the connections between the cochlea and higher neural centers, our team investigates cognitive processes and related cortical correlates (beyond auditory cortex). Despite these distinct research interests, we have developed some links over the past years: a) our team has produced the Audio CD "Fonds sonores" leading to a common publication with the Audiology team (Hoen et al., 2007); b) one of us has worked with a PhD student of the Audiology team on auditory brainstem responses (Akhoun et al., 2008); c) we have tested music processing in patients with cochlear implants thanks to the patient access of the Audiology team; our findings are encouraging for the development of training programs for cochlear implant patients, which can be tested thanks to patient access and cochlear implant expertise of the Audiology team. Finally, the project "Neurocampus" (tied to the Center of Neurosciences) includes lab spaces dedicated to auditory research (i.e., sound-proofed testing boxes) that are shared by both teams, thus stimulating further exchanges.

3.14 – Team 14 (L. Zimmer)

(1) General comments

The main objective of our laboratory is **to improve the efficiency and the delay of action of antidepressant**. This project is supported by mechanistic and integrated approaches assessing the cellular changes induced by these pharmacological agents. The most significant feature of this project is to use several types of in-vivo brain exploration methods which are not often put together in **neuropsychopharmacology** (molecular and cellular PET imaging, neurochemistry, electrophysiology, animal behavior …).

We appreciate that the Committee highlighted the relevance of our scientific goal based on **the rare association of two disciplines: neuropharmacology and PET neuroimaging**. Due to the multidisciplinarity of our domain, we understand the difficulty to gather all the relevant expertise in one Committee member (indeed, one of our potential reviewers was not present during the oral defense).

It should also be noted that our team was created in 2007 by the CNRS (section 30) and the Lyon 1 University, with an evaluation by AERES in 2008. The encouraging recommendations of different AERES experts (**grade "A"**) were carefully taken into account for our team project (cf http://www.aeres-evaluation.fr/IMG/pdf/HVSDV_Lyon1_FRE3006.pdf). This new dynamics lead to the **recent strengthening of our team by recruitments of high-level researchers in 2008 and 2009** (1 CR1 INSERM, 1 CR1 CNRS, 1 PU, 1 MCU).

We acknowledge that several points concerning our strategy could be improved thanks to the present evaluation (i.e., interactions between researchers with complementary expertises,). However, we would like to provide some precisions on several remarks raised by the Committee.

(2) Team and scientific production

- *"More than 80 papers but no major publication even if they contributed to a few ones in high IF journals as collaborators in the middle of the multiple names (Nat Neurosci, JCO, Neuron)"*.

We published at least 8 papers with an IF> 5 with members of the lab as the first or last author and we have an important number of citations in Pharmacology and in Molecular Imaging. Among them, G. Lucas is listed as the first (and corresponding) author in a 2007 Neuron paper (IF: 14.9), and also as the first author (co-first) in a 2006 Nature Neurosci article (IF: 15.5). G. Lucas and M. El Yacoubi are co-authors in a 2010 PlosBiol paper, M. El Yacoubi being affiliated to Lyon University (IF: 13.5).

These publications clearly illustrate not only the potential but indeed the reality of fruitful collaborations between the different teams of the group, as well as the complementarity of their respective thematics and expertise.

Indeed, a precise bibliometric analysis, such as the one issued to the attention of the INSERM CSS members, demonstrates that our team has one of the highest records among the 14 teams of the Lyon Neuroscience Center project with mean IF=4.9 and mean IC=11.6 per paper.

(3) Scientific strategies

"*The work on the rat prefrontal cortex concerns classical coupling between pharmacology and electrophysiology that does not seem to raise cutting edge questions (though the commission recognized that deep brain stimulation in patients may be promising)".*

The committee agrees that deep brain stimulation in patients appears to be promising and, consequently, we are convinced that our project to study its fundamental ins and outs raises cutting edge questions.

- "Relevance of the "Rouen" mouse model of depression is questioned. The model lacks detailed characterization, particularly at the genetic level".

Our group developed the first mouse model of depression in the world based on selective breeding strategy. Besides, there is only one anxious mouse model based on selective breeding that has been developed in Germany (Prof. Landgraf). We agree with the Committee that a characterization of the model at the genetic level is important. Indeed, we have planned for the year 2010 a CGH array characterization at the ProfileXpert Genomics platform in Lyon. These experiments were not conducted before as the relevance of the data will be dramatically increased now (generation thirty) that the mice are inbred. Besides, a genetic study using QTL mapping is also an ongoing project in collaboration with the Centre National de Génotypage. We have crossbred the two lines of mice helpless H/Rouen and nonhelpless NH/Rouen in order to obtain a segregating population (paper submitted to Biological Psychiatry) and the tails of mice will be used for QTL mapping. These results will help us to discover some genes implicated in this pathology and thus new targets for innovative antidepressants.

It could be noticed that a Nobel Prize laureate, Prof. Paul Greengard, found important to test his hypothesis concerning the role of p11 with our mouse model of depression (Science, 2006; El Yacoubi and Vaugeois co-authors) and the results obtained with our mouse model of depression were a cornerstone for this paper.

- "Neuro-anatomical techniques: pathway tracing; evaluation of the expression of plasticity associated marker proteins and hippocampal neurogenesis. Connection to PET and imaging are difficult to see."

Indeed, our recent publication in Neurobiol of Aging, 2009 (IF: 5.5) illustrates that such connection between neuroanatomical approaches (Berod) and PET neuroimaging approaches (Zimmer) is already being developed.

- "In vivo electrophysiology : (....) the Committee wondered about the attractiveness of exploration of neuronal activities and synaptic plasticity in the proposed general context of the new team".

Considering that in vivo electrophysiology constitutes one of the main foci of G. Lucas's expertise (recruited in 2009), it is therefore clear that this technique does not simply permit to "collaborate" in works published recently in high IF journals (Neuron), but actually to bring both strong impulse and leadership for the achievement of such projects.

- "Heterogeneity between a solid technical knowledge in methods linked to neuronal dynamics, particularly in innovative PET tracers and animal models, and some standard descriptive basic methods". Actually, all those methods (in-vivo neuropsychopharmacology, electrophysiology, and PET imaging) can be considered as "descriptive". Nevertheless, we believe that their combination could provide a more comprehensive understanding of the mechanisms of drug action.

- "More hypotheses than strong results characterize the team".

Our group has issued more than 80 international publications, including high IF ones. Our hypotheses were therefore supported by strong results (although our objective is still to improve our IF).