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

Section des Unités de recherche

Evaluation report

Research unit

Laboratory of Brain Physiology

University Paris 5



March 2009



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University Paris 5



Le Président
de l'AERES

Jean-François Dhainaut

Section des unités
de recherche

Le Directeur

Pierre Glorieux

March 2009



Evaluation report



The research unit :

Name of the research unit : Laboratory of Brain Physiology

Requested label : UMR CNRS

N° in case of renewal : UMR 8118

Head of the research unit : M. Alain MARTY

University or school :

University Paris 5

Other institutions and research organization:

CNRS

Date of the visit :

February 9, 2009



Members of the visiting committee

Chairman of the committee :

M. Arthur KONNERTH, Technical University Munich (TUM) Institute of Neuroscience, Germany

Other committee members :

M. Christoph SEGEBARTH, Institut des Neurosciences, Grenoble, France.

M. Joachim DEITMER, University of Kaiserslautern, Germany

M. Remy SCHLICHTER, Université de Strasbourg, France

M. Alan HAWKES, Swansea University, UK

CNU, CoNRS, CSS INSERM, INRA, INRIA, IRD representatives :

M. Joel de LEIRIS, CNU representative

M. Michel ROUX, CoNRS representative

Observers

AERES scientific representative:

M. Pierre-Hervé LUPPI

University or school representative:

M. Arnaud DUCRUIX, University Paris 5

M. Daniel JORE, University Paris 5

Research organization representative :

Ms Nathalie LERESCHE, CNRS



Evaluation report

1 • Short presentation of the research unit

- Number of lab members : 29 including
 - 4 researchers with teaching duties
 - 10 researchers
 - 5 postdoctoral fellows
 - 5 PhD students
 - 5 engineers, technicians and administrative assistants
- Number of HDR : 7
- Number of students who have obtained their PhD during the past 4 years : 4
- Number of lab members who have been granted a PEDR : 0
- Number of “publishing” lab members : 14 out of 14

2 • Preparation and execution of the visit

In general, the visit was well organized. The committee appreciates the effectiveness of the local organization of the visit. All activities (scientific presentations, lab visits, interactions with lab members) went smoothly and according to the schedule.

An even better organization may be achieved if the AERES would compile a summary checklist of all the procedures. This may be particularly helpful for the visiting scientists coming from foreign countries.

3 • Overall appreciation of the activity of the research unit, of its links with local, national and international partners

The research unit is one of the top institutions in its domain not only in France but also in Europe and worldwide. Its members have pioneered methodological approaches of membrane biophysics and cellular physiology (e.g. patch clamp, calcium imaging) that are nowadays in use in many laboratories. The unit has made major contributions to our understanding of cellular physiology of the mammalian central nervous system, to the basic properties of membrane ion channels, to intracellular calcium signalling, to novel mechanisms of cell-cell interactions and to the basic mechanisms of synaptic transmission. The projects that are planned for the coming years are highly innovative and very promising.



4 • Specific appreciation team by team and/or project by project

Team 1, synapses gabaergiques du cervelet :

The team is composed of four permanent researchers (one being emeritus, another leaving the unit in 2009) and one post-doc. A PhD student defended his thesis in 2008 (and is now assistant professor in Uruguay), another as started in 2007. In collaboration with teams 4 and 6, the team has demonstrated that the passive properties of the axon membrane influence synaptic integration, allowing molecular layer interneurons (MLIs) of the cerebellar cortex to have a higher temporal precision than expected by their RC properties. The team has also revisited the function of axonal GABA_A receptors, classically considered as inhibitory. On MLIs, up to postnatal day 15, they are excitatory, favouring burst firing and facilitating transmitter release, and thus may play a role in the establishment of the cerebellar wiring. A similar action was also demonstrated on parallel fibres, though with a role that goes beyond development as it was present at least until PN30. The study of presynaptic GABA_A receptors will be pursued, comparing their pharmacology with the one of postsynaptic receptors, taking advantage of the caged-GABA newly developed by Team 2. As GABA_A receptors are the target of many drugs for the treatment of a variety of pathological conditions, ranging from migraine to epilepsy, the ensuing results may help to fine tune the treatments and reduce unwanted side effects. Calcium rise induced by presynaptic GABA receptor activation will be characterized in both MLIs and parallel fibres. The team also have preliminary results suggesting the existence of "preminis", that is of miniature autoreceptor currents. Further experiments should definitely establish this new concept in synaptic transmission, which may prove particularly important during development. In conclusion, the team has pursued its studies regarding information processing in the cerebellar cortex, focusing on presynaptic GABA receptors in MLIs and parallel fibres. As the results of the past four years, the ongoing projects should significantly increase our understanding of synaptic transmission.

Another project, developed by an emeritus member of the team in collaboration with a group in Baltimore, concerns the progeny of bone marrow stem cells, more specifically the CD34+ cells. In a mouse model of Down syndrome, these cells were shown to have a drastically decreased growth rate, while seemingly keeping other aspects of their phenotype. They have also demonstrated that CD34+ cells have the capacity to myelinate neurons. This topic will be pursued with the characterization of the myelin sheath that can be formed by CD34+ cells.

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+

Team 2, Photolyse de précurseurs de neurotransmetteurs pour l'expérimentation en neurosciences :

This is a new team in the review period with two permanent researchers, one post-doc and one PhD, with the team leader recruited from outside the unit. Much of the early effort was spent in developing improved techniques/equipment for photolysis, with new laser sources and significant improvements in the efficiency of caged reagents. This has been done in an EU Framework programme, coordinated from the laboratory, involving nine academic and commercial partners.



Applications include studying glutamate receptor signalling in cerebellar Purkinje neurons, and interactions between glutamate and AMPA receptors. Planned experiments include studies of behavioural responses to in vivo stimulation: thought to be the first application of photolysis in vivo. Many current and planned experiments involve collaboration with other members of the laboratories evaluated in this exercise.

In summary, the team is very good with several strong points. It displays an added value in terms of improved techniques and equipment that will become generally available. It has partnership with industry. It contributes to graduate programs through continuing internationally available workshops that the team leader has been organising for many years.

Nevertheless, the quality and impact of scientific publications is perhaps good rather than very good. Some of the panel felt that the deployment of energy was perhaps too widespread and quality would be improved by a narrower focus.

The committee found out that it is a very good new team that should continue to be encouraged. A planned experiment using multi-electrode recordings of the spike output of cerebellar Purkinje neurons would surely benefit considerably from the work done by Team 6, also report on here.

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

Team 3, Imagerie synaptique :

This small and young team counts only one permanent researcher, and now two post-docs. Its visibility is however excellent, with two visiting professors from the University of California in the last two years, and participation in three European networks (ENI-NET, PHOTOLYSIS and VESTICODE). The team is using and/or developing new optical tools (caged compounds, holographic uncaging, voltage-sensitive fluorescence dyes) with strong interactions with teams from the neighbour unit Inserm U603. This allowed studying notably the biophysical properties of synaptic ionotropic glutamate receptors in their native environment (acute cerebellar slices) rather than in expression systems. The team has contributed to the demonstration of the possibilities opened by holographic uncaging, using a spatial light modulator, in the field of synaptic integration and neuronal physiology. Ongoing and future projects involve a combination of electrophysiology, glutamate uncaging and/or calcium imaging, to study transmission onto cerebellar granule cells, and from granule cells to stellate cells. A major advance is the development of voltage-sensitive voltage dyes combining a high $\Delta F/F$ ratio and a fast response time, combining dipicrylamine and a lipophilic carbocyanine dye. This will allow examining the voltage properties of various sub-compartments of neurons in brain slices.

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+



Team 4, imagerie calcique de neurones centraux :

This team with four permanent researchers, one engineer and three PhD students represents one of the central research groups of the unit. Since many years the researchers work in the forefront of cellular physiology in neurosciences. They are world leaders in the fields of calcium signalling in neurons as well as in synaptic physiology. The team has strong cooperations with all other teams within the unit and has an important role for the coordination of the scientific activities, for the strategic planning and the organization of the infrastructure. A particular strength of the team is that it is very innovative. Members of the team have pioneered important techniques for cellular neuroscience, like patch clamping in brain slices and calcium imaging. An important focus of their research is high-speed two-photon imaging and the establishment of powerful and original approach for in vivo analyses in genetically modified mutant mice. These developments are very promising and the group has accepted the risk of a reduced rate of publications in the last years. However, the review committee feels that the strategy of the groups and the risk taken are fully justified in view of the excellent preliminary results presented. Especially impressive was the demonstration of the newly developed two-photon technology that can be used not only for imaging, but also for targeted microdissection of very fine neuronal process, like axon or dendrites, in the living brain. Together with team 1, team 4 is internationally leading this line of research. Another important development took place in the field of molecular biology, namely the establishment of tools for the targeted neuronal transfection using viruses as well as the gene inactivation with shRNA in defined subregions of the brain by using stereotactically guided delivery of constructs in vivo.

An important new project deals with the molecular identification of presynaptic iGluR subunits and mGluR activated pathways. This project is based on published preliminary work of the group. The work is original and highly promising. The second project focuses on presynaptic calcium buffering proteins. This work represents a continuation of a line of research that was pioneered by the team. The work is aimed to addressing significant neurophysiological questions that are important for both basic research but also for a better understanding of neurological diseases. The third project deals with the identification and characterization of axonal receptors for neurotransmitters, especially NMDA receptors. Although the existence of presynaptic receptors is known for a long time, their function analysis has been strongly delayed because of the lack of effective tools. The technical developments of the team have the potential of overcoming these limitations. The preliminary results obtained by using targeted two-photon dissection are very promising and convincing. Finally, the planned new project involving in vivo two photon calcium imaging is of outstanding strategic importance not only for the team, but also for the entire unit. The team has presented excellent preliminary results. This project may become a central area of research of the team in the coming years.

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+

Team 5, Récepteurs au glutamate :

This is an atypical team composed of two emeritus researchers, pursuing two separate projects. One consists in understanding the synaptic interactions at the motoneuron-Renshaw cell synapse. Four components have been identified, two being cholinergic, the other two being glutamatergic; their influence on the pattern of RC discharge depending on the resting potential have been characterized. The project will continue with paired recordings of a motoneuron and a Renshaw cell, to determine if the communication between the two cells systematically involves a mixed glutamate/acetylcholine transmission, or can be mono-transmitter - and which consequences this will have during sustained activity. The identification of a synaptic $\alpha 7$ component will allow the characterization of these receptors in situ. In collaboration with Inserm U686, the consequence of the absence of the various forms of acetylcholine esterase on both nicotinic components will be characterized and compared to the motor phenotypes. Even if this project is on the spinal cord rather than the cerebellar cortex,



which is central to the Unit, it is close in the tackled questions and can benefit from the tools developed by other teams.

The second line of research evolved from past studies on synaptic transmission in the classical model *Aplysia californica*. Due to the increasing difficulty in getting *Aplysia*s for research, the project has been re-oriented in a molecular and phylogenetic point of view, and includes various collaborations, both national and international. Two ligand-gated chloride channels from *Aplysia californica* have been cloned and expressed and characterized in CHO cells. Their sequences have been included in a phylogenetic study of 2cys-loop receptors, which pushed back the timing of the apparition of the ancestor of this class of receptors as well as the divergence of GABA_A receptors. These studies will be extended by the cloning of similar channels from an annelid (*Capitella sp.*), while results from the phylogenetic studies will be used to better define the required motif for a glycine agonist site.

It should be noted that the team contributes quite significantly to the undergraduate and graduate neuroscience teaching, not only in Paris Descartes and Paris Diderot, but also at the ENS, Inserm School and IBRO.

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

Team 6, Méthodes statistiques pour les neurosciences :

This team composed of one permanent researcher and one post-doc is unusual in specializing in computational statistics for neurophysiological data analysis. The methods developed here use modern statistical techniques that are complex in theory and computationally heavy. A lot of time has therefore gone into developing data analysis software, for (a) spike sorting and (b) spike train analysis, documenting them and making them freely available to the research community. This is a significant achievement. This should be borne in mind when considering the publication count over the review period, which is numerically modest but good in quality. The team also provides a valuable service to other teams in the unit in assisting in data analysis, thereby improving the quality of research overall compared to other laboratories : despite the large amount of data they typically generate, physiologists tend to use primitive data analysis methods.

The software completed will be valuable in the analysis of multi-electrode recording that have begun with collaborators in France and Germany. At the same time, with the help of recently appointed postdoctoral researchers and American collaborators, it is planned to extend the methods to study the possible interactions between signals emitted by adjacent neurons, in particular trying to understand signals resulting from different odours : an interesting and difficult problem, which would have very interesting applications in many other contexts.

A second project on point-process based methods of analyzing results from calcium fluorescence experiments will have applications to many experiments within and external to the neurophysiology units based at Paris Descartes University.

As a result of these initiatives, the publication count has already started to increase and should be good over the next few years.

In summary, the team makes a good quality work in a much-needed but relatively unusual specialty within the neurophysiology community. Its well developed software made available for general use and it has useful interactions with other research teams.

Its weak point is the relatively low, but increasing current publication count. It also provides much appreciated statistical advice to PhD students but perhaps more could be done by way of formal instruction.



The committee recommends continued support and encouragement of this valuable resource. The team might also put on a regular course on “statistical analysis in physiology” that might be available to PhD students within and outside the units based at Paris Descartes.

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	A	B	C	B

5 • Appreciation of resources and of the life of the research unit

The administrative and technical support of the Unit is numerically quite limited and additional support may be soon necessary for the accomplishment of all the duties. The most serious present problem is that this very innovative Unit requires for their many methodological developments serious help from the mechanical workshop. This support is at present insufficient.

Despite these difficulties, all staff members presently employed within the unit are content with the scientific environment of their work and the trust consistently shown in them by those in charge and the researchers from the various teams of the Unit. They are happy that they are asked to contribute to the design of the research projects, included as co-authors on publications and offered various training opportunities. As a general rule, these members of staff strongly believe that the institute to which the Unit is linked (University René Descartes Paris 5) needs to be involved in the future development of the Unit; they overwhelmingly support this development. Finally, the staff members have concerns about the housing of the animals.

PhD students and post-docs

In its present configuration the laboratory features 5 PhD students and 6 post-doctoral fellows. This non permanent research staff represents an important part of the research potential of the laboratory. The PhD students, as well as the post-doctoral students, are well integrated in the laboratory and rate very positively their training. They mention the absence of any major problem on the level of their interactions with their supervisors. They have a large degree of freedom in the way they are allowed to conduct their research projects and mention that their mentors are always ready to help them. They appreciate and rate as positive points the facts that they belong to different nationalities and conduct interdisciplinary research projects. They attend progress reports and journal clubs on a regular basis and present their research work at international meetings. There is a clear publication policy in the laboratory: the student or post-doc in charge of the main part of the work is signing the research papers as a first author.

Meeting with research council and university representatives

The meeting with the representatives from the research council (CNRS) and the University (University Paris 5, René Descartes) was held at the end of the laboratory examination session. Both parties mentioned a strong support of the laboratory. The latter appears as a major element of the research policy of the CNRS in the field of molecular and cellular neuroscience. The laboratory is also a crucial element in the development of the research policy of the University Paris 5, who has indicated that the development of research activity in the



field of Neuroscience is an absolute priority of the University. The examination committee members have mentioned the existence of problems in the organization of the animal facilities and the University representatives committed themselves to resolve these problems. This point should be followed seriously by the research authorities.

6 • Recommendations and advice

- Strong points
 - Top quality of the research.
 - High international visibility.
 - Excellent performance in training young scientists.
 - Highly successful acquisition of financial support through grants.
 - High degree of innovation.
- Weak points :
 - The infrastructure, in particular the mechanical workshop situation, needs to be strengthened.
- Recommendations :
 - Improve the infrastructure.
 - Improve the interactions with the other research units of the University.

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+

Le Président
Axel KAHN

Paris, le 7 avril 2009

DRED 09/n° 148

Monsieur 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 « UMR 8118 Laboratoire de physiologie cérébrale » rattachée à mon établissement.

Ce laboratoire est un des piliers du Département de neurobiologie moléculaire et cellulaire de l'IFR des neurosciences des Saints-Pères au prestige duquel il contribue beaucoup. La discussion contractuelle avec la co-tutelle, le CNRS, étudiera les conditions dans lesquelles un renfort technique pourra être apporté à l'UMR.

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

Le Président de l'Université


Axel Kahn

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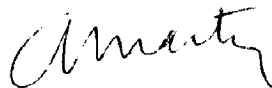
Objet: Rapport AERES sur l'UMR 8118, fond

le 1er avril 2009

Madame, Monsieur:

J'ai pris connaissance du rapport de l'AERES concernant notre unité. Je n'ai pas de remarque à exprimer sur le fond. Je remercie le Comité de Visite et l'AERES pour leur dévouement et pour leur professionnalisme.

Je vous prie de croire, Madame, Monsieur, à l'expression de ma considération distinguée.



Alain Marty