

Epilepsies de l'enfant et plasticité cérébrale

Rapport Hcéres

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

Section des Unités de recherche

Evaluation report

Research unit

Pediatric Epilepsies and Brain plasticity

University Paris 5



April 2009



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Le Président
de l'AERES

Jean-François Dhainaut

Section des unités
de recherche

Le Directeur

Pierre Glorieux

April 2009



Evaluation report)

The research unit :

Name of the research unit : Pediatric epilepsies and brain plasticity

Requested label : UMR INSERM

N° in case of renewal : 663

Head of the research unit : Mrs Catherine CHIRON

University or school :

University Paris 5

Other institutions and research organization:

INSERM

Date of the visit :

February 2, 2009



Members of the visiting committee

Chairman of the committee :

M. Renzo GUERRINI, Children's Hospital A. Meyer, University of Florence, Italy

Other committee members :

M. Patrick BERQUIN, Hôpital Nord CHU Amiens

M. Lopes DA SILVA, University of Amsterdam

M. Eric BELLISSANT, Université Rennes 1

Ms. Marie VIDALHET, Hôpital Pitié-Salpêtrière, Paris

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

M. Jacques MOTTE, CNU representative

Observers

AERES scientific representative:

Ms. Jocelyne CABOCHE

University or school representative:

M. Bruno VARET, University Paris 5

Research organization representative :

Ms. Catherine LABBE-JULIE, INSERM



Evaluation report

1 • Short presentation of the research unit

- Number of lab members : 28 including
 - 12 researchers with teaching duties
 - 2 full time researchers
 - 1 postdoctoral fellow
 - 9 PhD students, 5 with a fellowship and 3 receiving medical salaries
 - 4 engineers, technicians and administrative assistants
- Number of HDR : 4, 2 of them being PhD student advisor
- Number of students who have obtained their PhD during the past 4 years : 1 (in 5 years)
- Number of “publishing” lab members : 14 out of 14

2 • Preparation and execution of the visit

The members of the visiting committee received the unit report several weeks before the visit. On Monday February 2nd, members of the visiting committee and the AERES representative met at around 9.30 at the Amphithéâtre of the Robert Debré building at the Necker Hospital in Paris. From 10 to 10.30 am, committee members and the AERES representative met with closed doors to unfold the planned day program.

From 10.30 am to 13.00, the unit Director, Team 1 and Team 2 leaders illustrated the structure of the unit, the main scientific achievements since its establishment in 2004 and the planning for research activities in the period 2010-2013. Subsequently, the visiting committee split in two parts : the President and some members met with technicians and administrative assistants, while the remaining members met with PhD students and post-doctoral fellows. Finally, all members of the committee and the AERES representative met with the vice-President of Paris 5 University and with INSERM representatives. A door-closed meeting, where members of the committee discussed and provided the analytic scores of the Qualitative assessment sheet, concluded the day. The current report has been drafted by the committee president and circulated amongst all members before being submitted in its final form.

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

This research unit represents the only aggregation of researchers and facilities that is focusing its activity on Epilepsy and brain development in France. Only a few other teams exist in Europe, and in the rest of the world, with a similar target of research. The problem of childhood epilepsy and brain development, or brain plasticity, goes even beyond the magnitude of the clinical problem that epilepsy represents in the pediatric age and opens research perspectives in the area of developmental neuropsychology, representation of cortical function, recovery after lesion, significance of electrophysiological patterns through age, response to drugs. Since its start in 2004 the unit has remarkably increased the number of research and technical staff that participates in research activities. The unit has produced a steady flow of



solid research at the international level yielding important contributions to the field of pediatric epilepsy. Part of the scientific production is internationally recognised as outstanding research leading to significant advances in the field. The unit has established sound international and national collaboration with both clinical and basic science teams. An analysis of the scientific output well demonstrates it.

Considering productivity, relevance, feasibility and training, we consider that it is a very good Research Unit. Bringing together nosology, clinical genetics, brain imaging/neuropsychology, neurophysiology and pharmacology with the general goal of advancing knowledge of “Pediatric Epilepsies and Brain plasticity” is an excellent strategy. The presented plans for the future are in line with the previous research areas and are highly promising.

The unit director provides as examples of the results achieved in the past 4 years a number of publications, which can be gathered within 4 main topics:

- 1- Nosology/Clinical Genetics - phenotypes of new age-related epilepsy syndromes, neuropsychological aspects of pediatric epilepsies, and the description of epileptic syndromes with a genetic origin.
- 2- Brain Imaging/Neuropsychology - memory functions following surgery for temporal lobe epilepsy in children; the development of white matter tracts during the first months of life revealed using diffusion-tensor imaging and tractography.
- 3- Neurophysiology - the description of cortical rapid oscillations and early motor activity in premature human neonates.
- 4- Pharmacology - extensive studies of Stiripentol, and the development of novel methodologies in clinical pharmacology in children.

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

Team 1 :

The main topic of Group 1 concerns paediatric epilepsy and the consequences of epilepsy on brain development and cognitive functions. The ability to use imaging tools (fMRI), electrophysiological studies both in animals and humans, genetics and clinical research on large cohort of patients recruited among a large French network as well as numerous international collaborations provides excellence and a unique basis for comprehensive research.

The scientific profile of this team may be characterized on the basis of how the team publications are distributed among different journals.

The strengths of this team are the interactions between highly qualified clinicians and geneticists, neuro-imaging, neurophysiology with a multimodal approach. Members of the team have a large recruitment of rare patients and an excellent clinical characterisation of these patients. They identified new mutations, thanks to these cohorts of patients (in collaboration with the Neurogenetic Units) and added an important value to the knowledge of epilepsy. They developed a very original research on neuropsychology in children, considering the consequences of epilepsy and of drugs on the neurological development. The contribution of neuro-imaging (Neurospin) brought very original data. In the publications, they have, for each sub-theme high impact factor publications with a good valorisation of their research (high IF > 7.5). They also have a steady production in good journals ($5.5 < IF \leq 6.5$).

Considering these abilities to produce original papers and considering also the relatively small number of researchers, didactic publications and more clinically oriented papers should be a matter for self reflection in order to concentrate as much time and energy as possible to a policy of publishing more in journals of high or top impact (as they demonstrated that there are fully able to do so).

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 :

A large part of the research developed by this team also concerns the field of paediatric epilepsy and most of studies implicate members of the first group. The scientific profile of team 2 can therefore be characterized according to the same perspective, although most papers have been published in journals with low IF. The small number of papers in journals of high impact should be a matter for self reflection.

Furthermore the unit should adopt a policy of publishing more in journals of high or top impact and less in journals with $IF \leq 2.5$.

Members of the unit are regularly invited as speakers to the main international Epilepsy meetings in Europe and the United States. The main areas in which their contribution is often required are epilepsy in small babies, antiepileptic drug trials in children, brain maturation and epilepsy.

The presented projects have ambitious targets but appear to be well balanced in relation to available resources and expertise. This realistic standpoint has been made possible through the team's ability to establish fruitful collaborations with local and geographically remote teams rather than by resources made available by the INSERM or the University.

It is recommended that this team pursues its research goals, possibly focussing the scientific output towards journals with a higher impact factor and re-examining the benefits of having one comprehensive team rather than two.

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

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

Human resources in the unit cover rather homogeneously many of the clinical and research areas upon which the study of pediatric epilepsy is based. As specified below, it is highly recommended that the unit be allocated a sounder contribution by an increased number of tenuring research personnel, in the administrative, technical and research domains. The scientific strategy is sound, as anticipated above. The approach to pediatric epilepsy and brain development is comprehensive and is regularly based on improved nosology as the first step, followed by attempts at understanding the pathophysiology and mechanisms of disease as the possible basis for improved diagnosis and rationale treatment strategies. What might seem unfocused to first glance is in fact a sound logical research itinerary.

PhD students are research active and have traditionally been involved in publications. Laboratory members and technical staff have expressed an excellent level of integration and appear to be highly motivated. There is a good integration of the administrative and technical personnel to research activities, with an appropriate understanding of the translational value of ongoing research activities.



6 • Recommendations and advice

– Strong points :

Comprehensive approach to a relevant health and research problem represented by childhood epilepsy and brain plasticity, by an experienced team. The scientific activity of the team is a resource for patients and for the other teams involved in the same and associated domains worldwide. The members of the unit are doing a high level research on etiology, genetics, functional studies and rationale treatment strategies in childhood epilepsy. They brought a very original contribution to the subjects with a multi-modal ambitious but very efficient approach.

They are highly recognized at the international level, and are leaders in pharmacology and in the field of correlations between neuropsychology (development) in epilepsy and innovative neuro-imaging. Links with other leading research teams in France and internationally have enhanced the value of the unit contribution and have contributed to establish valid links with more fundamental research which are based on relevant working hypotheses.

The main researchers have high level CV's, in some cases even outstanding and of the highest level within the clinical field of pediatric neurology and clinical epilepsy. This can be put in evidence by examining the citation records of the senior researchers as available in Web of Science.

– Weak points :

The visiting committee was not entirely convinced on the usefulness of having organized the unit structure into two teams. The remark that this was due to the “individualization of the Pharmacology approach” does not appear to be a sufficient motivation at the present time. It would perhaps be preferable to choose clearly for a multidisciplinary and transversal structure that includes all groups focused on specific sub-themes, but all dedicated to the general theme “Pediatric Epilepsies and Brain Plasticity”.

– Recommendations :

The question about why it was not possible to develop a “small structure of experimental epileptology” (electrophysiology) to stimulate “translational projects” remains open. It appears that this objective was abandoned “momentarily”, opting to realize this area of research outside the Unit, namely within the framework of a collaboration with the INMED Marseille. This choice has had a positive effect and resulted in some important publications on rapid cortical oscillations, the so called “delta-brushes” and early motor activity of premature human neonates, as well as some evidence on the mechanisms of action of Stiripentol. A point for speculation is whether it would have been possible to achieve similar results within a local “small electrophysiological structure”. It might be more effective to keep, and further develop this kind of collaboration, rather than starting at a small scale electrophysiological Lab.

The visiting committee strongly recommends that this unit be reinforced by adequate funding and personnel resources. In particular: a) The methodology related to Brain Imaging would be better exploited by providing a strong technical input to the unit. The active participation of more than one researcher with advanced training in the modern techniques of Brain Imaging and Neuropsychology at the senior level, that might provide the link to the groups of CEA (SHFJ and Neurospin). b) There is only one full time researcher in the unit and an additional researcher at 40%. Increasing the amount of full time researchers to at least 2 would greatly increase the strength of the unit. c) There is no administrative personnel with tenure positions.

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 20 avril 2009

DRED 09/n° 179

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-S 663 Epilepsies de l'enfant et plasticité cérébrale** » rattachée à mon établissement.

L'Université a pris bonne note des remarques du comité de visite et veillera, en partenariat avec l'INSERM, à ce que les recommandations faites soient suivies d'effet.

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

Le Président de l'Université


Axel Kahn



UMR 663

Epilepsies de l'enfant
et plasticité cérébrale

General observations on the Report from visiting committee UMR 663

We are very grateful to the visiting committee for his helpful recommendations and advice that we will seriously consider. In addition, we would like to make two punctual remarks.

The first remark regards one appreciation concerning Team 2: "*most papers have been published in journals with low IF*". Considering the fact that Team 2 was created in November 2006 and comprised 8 publishing researchers (corresponding to 2.75 equivalent full time), 12 papers were published in 2 year time (2007-2008), 9 of which had an IF > 3.5. Median IF of Team 2 during this 2 year period was 3.5, whereas median IF of the journals in the areas of Pharmacology & Pharmacy and Pediatrics (the two ISI Subject Categories concerned) are 2.1 and 1.3 respectively (aggregate IF 2.8 and 1.8).

The second remark concerns what is presented as the only weak point: "*having organized the unit structure into two teams*". We were submitted to an administrative constraint [Team 2 had been created as an Equipe d'Accueil (EA) Universitaire within our UMR in 2006]. Indeed the idea was certainly not to "*individualize the Pharmacology approach*" since "the two unit teams are strongly interconnected, at the scientific level as well as for staff and contracts" (see Bilan Directeur and Bilan Equipe 2, 01BCU). We are therefore grateful to the visiting committee for supporting our point of view to include all the unit activities within the general theme "Pediatric Epilepsies and Brain Plasticity", this should help us overcome the administrative obstacle.

Dr Catherine CHIRON
Directeur UMR 663