Centre de psychiatrie et neurosciences

Rapport Hcéres

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

Department for the evaluation of research units

AERES report on unit:

Centre de Psychiatrie et de Neurosciences

CPN

Under the supervision of the following institutions

and research bodies:

Université Paris-Descartes

Institut national de la santé et de la recherche médicale

January 2013

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

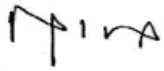
Research Units Department

President of AERES

Didier Houssin

Research Units Department

Department Head



Pierre Glaudes

The president of AERES "signs[...], the evaluation reports, [...]countersigned for each evaluation department by the relevant head of department (Article 9, paragraph 3, of french decree n°2006-1334 dated 3 november 2006, revised).

Grading

Once the visits for the 2012-2013 evaluation campaign had been completed, the chairpersons of the expert committees, who met per disciplinary group, proceeded to attribute a score to the research units in their group (and, when necessary, for these units' in-house teams).
This score (A+, A, B, C) concerned each of the six criteria defined by the AERES.
NN (not-scored) attached to a criteria indicate that this one was not applicable to the particular case of this research unit or this team.

Criterion 1 - C1 : Scientific outputs and quality ;
Criterion 2 - C2 : Academic reputation and appeal ;
Criterion 3 - C3 : Interactions with the social, economic and cultural environment ;
Criterion 4 - C4 : Organisation and life of the institution (or of the team) ;
Criterion 5 - C5 : Involvement in training through research ;
Criterion 6 - C6 : Strategy and five-year plan.

With respect to this score, the research unit concerned by this report and, its in-house teams received the following grades:

- Grading table of the unit: Centre de Psychiatrie et de Neurosciences

C1	C2	C3	C4	C5	C6
A	A	B	NN	A+	NN

- Grading table of the team: Cellular and Molecular Pharmacology of Brain Receptors

C1	C2	C3	C4	C5	C6
A	B	B	NN	A	A

- Grading table of the team: Neurobiology of physiological and pathological aging

C1	C2	C3	C4	C5	C6
A	A	B	NN	A+	A

- Grading table of the team: Clinical and genetic analysis of addictive and psychiatric disorders

C1	C2	C3	C4	C5	C6
A	A	B	NN	A	A

- Grading table of the team: Pathophysiology of Psychiatric Diseases

C1	C2	C3	C4	C5	C6
A	A+	A	NN	A+	A

- Grading table of the team: Manual dexterity in health and disease

C1	C2	C3	C4	C5	C6
B	B	B	NN	A	A

- Grading table of the team: Stroke, Prognosis and Imaging INSERM U894

C1	C2	C3	C4	C5	C6
A+	A+	A+	NN	A	A+

- Grading table of the team: Memory and Cognition

C1	C2	C3	C4	C5	C6
A	A	A	NN	A	A+

- Grading table of the team: Pain, Neuroinflammation and stress

C1	C2	C3	C4	C5	C6
A	A	B	NN	A	A

Evaluation report

Unit name:	Centre de Psychiatrie et de Neurosciences
Unit acronym:	CPN
Label requested:	UMR INSERM – Paris Descartes University
Present no.:	UMR 894
Name of Director (2012-2013):	Mr. Jacques EPELBAUM
Name of Project Leader (2014-2015):	Mr. Jacques EPELBAUM

Expert committee members

Chair:

Mr. Jean-François DEMONET, University of Lausanne, Switzerland

Experts:

Ms. Nora ABROUS, INSERM Bordeaux, (representative of CSS INSERM)

Mr. Thierry BOUGEROL, CNRS Grenoble, (representative of CNU)

Mr. Francis CHAOULOFF, INSERM, Bordeaux

Ms. Benedicte DARGENT, CNRS, Marseille

Ms. Kim DO-CUENOD, University of Lausanne, Switzerland

Mr. John GIGG, University Manchester, UK

Mr. Lorenz HIRT, University of Lausanne, Switzerland

Mr. Rainer SPANAGEL, University of Heidelberg, Germany

Scientific delegate representing the AERES:

Mr. Laurent GROC

Representative(s) of the unit's supervising institutions and bodies:

Mr. Stephano MARULLO, Université Paris Descartes

Mr. Etienne HIRSCH, INSERM

1 • Introduction

History and geographical location of the unit

The first research group was set up at Hopital Sainte-Anne (Paris) in 1971. The present Centre for Psychiatry and Neuroscience (CPN) was created in January 2008 (administrative label UMR_S 894 INSERM/Université Paris-Descartes). From 2010 it involved 8 teams (following the recommendations of previous AERES evaluation / authority decisions in 2009) that in the present proposal have been reconfigured after some teams decided to leave the CPN while others are new incomers ; however, although some of their PIs partook in teams of the former version of the CPN, some "new" teams have been set up in the present proposal after some PIs have been redistributed in a different way, with new team leaders.

Management team

Director Mr. Jacques EPELBAUM; managing committee ; the director is assisted by 3 deputy directors and by an administrative director, with whom a meeting is held fortnightly. An executive committee composed of the above listed members and the team leaders get together monthly. Sessions of other committees dedicated to "hygiene and security", data processing, continuing education are regularly organized.

The administrative director assisted by an administrative staff, is in charge of the management of diverse dimensions of the CPN such as human resources, communication, financial management of grants, funding and regulatory issues relating to conference travels/stays of researchers.

AERES nomenclature

SVE1- LS5

Unit workforce

Unit workforce	Number as at 30/06/2012	Number as at 01/01/2014	2014-2018 Number of project producers
N1: Permanent professors and similar positions	25	25	22*
N2: Permanent researchers from Institutions and similar positions	23	23	23*
N3: Other permanent staff (without research duties)	28	29	3
N4: Other professors (Emeritus Professor, on-contract Professor, etc.)	10	10	10*
N5: Other researchers from Institutions (Emeritus Research Director, Postdoctoral students, visitors, etc.)	43	48	32*
N6: Other contractual staff (without research duties)	5	5	
TOTAL N1 to N6	**134**	**140**	**90***

Percentage of producers	**64.29 %**

* These numbers are to be taken with caution as the information was not always available in the dossier or the various data the committee was presented / given.

Unit workforce	Number as at 30/06/2012	Number as at 01/01/2014
Doctoral students	55	
Theses defended	69*	
Postdoctoral students having spent at least 12 months in the unit*	33*	
Number of Research Supervisor Qualifications (HDR) taken		
Qualified research supervisors (with an HDR) or similar positions	45	

* These numbers are to be taken with caution as the different sources of information the committee was given (or asked to be given) resulted in discrepant results.

2 • Assessment of the unit

Strengths and opportunities

The CPN is located at Sainte-Anne Hospital (SAH) which is the main hospital site in Paris for Psychiatry; the Hospital plays also an important role in Neurology especially for strokes and ageing brain diseases; about 33000 patients are seen a year. A number of Psychiatrists and Neurologists at Sainte-Anne Hospital are members of one or the other of the research teams of the CPN. In addition to patient recruitment opportunities, one of the major strenghts of CPN is the existence of important cohorts and biobanks that have been set up and maintained over years thanks to the CPN and its technical teams. Some of the applicant teams are renown research groups in diverse domains of clinical, cognitive and behavioral Neuroscience and Psychiatry, be it in the basic neuroscience or in the clinical type of research. In addition, the CPN has acquired and developed a number of platforms, that:

(i) involve excellent facilities for clinical research (Clinical Research Centre, MRI equipment partly dedicated to research), for pharmacological and neurophysiological experimentations in animal models (including rare ones), as well as for cellular and molecular imaging

(ii) are available to the CPN teams and upon agreement to external teams.

The CPN benefits from an impressive amount of research grants from many funding sources either institutional or private, at both national and international levels. It has also strong support from INSERM and Paris Descartes University (in terms of positions and internal funding) so that collaborations within the CPN and with external laboratories are facilitated (e.g. Axe Thematique Prioritaire of Paris Descartes).

Weaknesses and threats

The main weakness of the CPN project as such is a lack of internal coherence that can be seen at two levels of granularity of the structure; the CPN may suffer from a lack of global coherence as it involves traditionally split apart domains (e.g. stroke versus Psychiatry), with too numerous teams that do not necessarily colloborate with or complement each other; at a lower level of granularity, the team level, especially so for some of the largest ones, it may be that these groups, sometimes formed very recently, are too heterogeneous as they address too distant topics or aim at science projects that are not focused enough in consideration of the low number of PIs and staff involved.

Aside from these somewhat classical weakness features (that are encountered in many large laboratories), a special problem consists in the retirement of the current Director who will terminate his Directorship by the end of 2015. Under the auspices of INSERM and Université Paris-Descartes, a search committee has recently and actively conducted interviews of potential candidates after a shortlisting process; one of them has been identified as a potential successor and the contract is being negotiated currently.

Another feature of the current dossier is its complexity of its analysis that is a consequence of:

(i) the many reconfigurations that have been performed across otherwise long established research groups or sub-groups; apart from experts of the contemporary history of neuroscience in Paris it is a quasi impossible challenge to assess the precise rationale of these changes; it is especially difficult for a panel of external, foreign experts.

(ii) the dossier as such has proved difficult to read and explore for the Committee members with missing parts, passages left in preliminary stage, new members of a team about whom the committee was informed during the site visit, various values of parameters such as the number of doctorates students, post-docs and so on.

Finally, the CPN suffers from having its teams to work in poorly maintained buildings and premises. The Committee has been impressed to see that some parts of the buildings of the CPN were in so bad a condition that it raises safety issues for the staff working in these premises.

Recommendations

CPN is a major player in the field of Psychiatry and in some fields of Neuroscience in Paris and at National level. Overall the teams that are involved in the project in its current state are somewhat heterogeneous not only in terms of science objectives or methods but also in terms of inner coherence and relevance. The CPN project is likely to benefit from a reapparaisal of its team structure and team leadership. In addition, a major challenge is the transition from the current Director and the foreseen one involving shift in drive and overall management.

3 • Detailed assessments

Assessment of scientific quality and outputs

The overall evaluation of such a large and heterogeneous structure as CPN is of limited relevance. The bibliometric analysis conducted by the (expert) service of INSERM is explicit about this heterogeneity as it states that the range of IF of the journals goes from 0.085 to 53.484 (New England Journal of Medicine). 18 articles, 8 letters and 3 review papers were published in "prestigious" journals (Lancet, Lancet Neurology, JAMA, Nat. Genetics, New England Journal of Medicine, Nat. Reviews Drug Discovery, Science). However, it is only in two cases that CPN members were in leading position in the author list of these papers (Lancet Neurology). The bibliometric output of the CPN is likely to be impaired by a number of publications in French-speaking journals in the Psychiatry domain (e.g. Annales Medico-Psychologiques). One should emphasize however that the scientific evaluation of a group has not to be based only on this type of analysis and that the content of the reported research and its implication in terms of novelty and relevance to the science domain it addresses should be the main criteria of evaluation. In addition, publishing in French-speaking journals has a certain role in the medical milieu in terms of continuing education, or these papers may stand also as the very first publications for young MDs.

Overall the productivity of the CPN is deemed very good and involve important and frequent contributions to sub-domains such as stroke, genetics, or epidemiology of psychiatric disorders. Also revealing is the mapping of collaborations established via their publications by the actual leaders in the CPN. It might be useful for the current and future leaders of the CPN to take a look to this map (from the bibliometry service of INSERM).

Assessment of the unit's academic reputation and appeal

Sainte-Anne is a prominent site for Psychiatry and some components of Neurology in Paris and in a broader sense. Research teams address various topics and altogether represent a somewhat unique ensemble of expertises in as diverse themes as (i) clinical and genetic epidemiology of addictions, schizophrenia and other developmental pathologies, as well as bipolar and obsessive-compulsive diseases, together with animal models and basic neuroscience and genetic research for some of these conditions, (ii) epidemiology, brain imaging and clinical research in stroke, (iii) retrograde and personal memory impairments in pathological ageing and in schizophrenia, (iv) synaptic transmission mechanisms and their implications in age-related pathologies especially Alzheimer's disease, (v) molecular approach to serotoninergic transmission and its links on depression symptoms and treatment. The number of scientists, neurologists and psychiatrists that CPN brings together constitute an impressive potential for generating new research lines, teaching students in these various domains and supervising young researchers.

Assessment of the unit's interaction with the social, economic and cultural environment

Good contacts exist between the CPN members and patient associations and media to foster communication to the general public.

Assessment of the unit's organisation and life:

CPN is a large ensemble of teams which are heterogeneous and which have been re-shaped at various points of the CPN history. Complex relationships and potential conflicts of interest are likely to persist in spite of the cautious way teams have been administred and re-organized throughout the past few years. Members of the committee interviewed the assembly of the CPN researchers in the absence of their group leaders and gathered that the current project was openly and largely discussed by the researchers and the CPN leaders. However, some Committee members also got further separate individual comments according to which some of researchers/staff members regret a lack of democratic debate on certain issues or decisions.

Assessment of the unit's involvement in training through research

The team members are involved at various levels in a number of Master and PhD programs; the CPN is central to several of these teaching programs that it contributed to create and develop. The teaching role of the CPN is prominent in the domain of the neurobiology of behavioral disorders and age-related modification of brain functions.

Assessment of the five-year plan and strategy

The current Director will retire by the end of 2015 and a new Director has to be nominated and to take over the responsibility of the existing CPN since then. A candidate has been selected after a search-committee has explored potential candidates on an international basis, has short-listed and has interviewed several high-level scientists. Over the evaluation session, the Committee of experts had the opportunity to interact with this potential candidate via a conference call.

The proposed structure of the CPN for the next five-years period involves 8 teams that address the following main topics in terms of both basic science and clinical research, addiction, ageing-related neurodegeneration, depression, schizophrenia, stroke; this structure is meant to promote translational processes from experimental and animal-based research to the research in well-defined patient cohorts and the reverse, and to facilitate – already existing - interactions across on-site teams and with external partners. The CPN will soon benefit from a new building in which the main laboratories will be hosted, including a Clinical Research Centre that will enhance the potential of translational research. This potential is reinforced by the existing cohorts related to the major clinical CPN topics such as schizophrenia, at-risk relatives, addictions, eating disorders, and the same holds true for various tissue biobanks.

Across the above-listed main topics, the respective contributions of basic science and clinical research is far from being always well- balanced. In addition, both the proposed structure and the global science strategy will have to be re-assessed according to the views of the future Director and his/her specific strategical plans.

4 • Team-by-team analysis

Team 1 : Cellular and Molecular Pharmacology of Brain Receptors

Name of team leader: Ms. Michèle DARMON

Workforce

Team workforce	Number as at 30/06/2012	Number as at 01/01/2014	2014-2018 Number of project producers
N1: Permanent professors and similar positions	1	2	2
N2: Permanent EPST or EPIC researchers and similar positions	3	5	5
N3: Other permanent staff (without research duties)	1	1	
N4: Other professors (PREM, ECC, etc.)			
N5: Other EPST or EPIC researchers (DREM, Postdoctoral students, visitors, etc.)			
N6: Other contractual staff (without research duties)			
TOTAL N1 to N6	**5**	**8**	**7**

Team workforce	Number as at 30/06/2012	Number as at 01/01/2014
Doctoral students	1	
Theses defended	7	
Postdoctoral students having spent at least 12 months in the unit		
Number of Research Supervisor Qualifications (HDR) taken		
Qualified research supervisors (with an HDR) or similar positions	4	3

• Detailed assessments

Assessment of scientific quality and outputs

A selection of the main features in the summary of the bibliometric analysis provided by the dedicated service of INSERM is as follows: number of PIs, 6; number of publications, 31; percent within-team collaboration, 10; total number of citations, 360; number of publications with top1+10% citations, 3; number of publications with IF top 10%, 8; number of 1st or last author, 4. The structure of this team for the next contract period will consist in the merging of two teams that have already undergone collaborations (albeit none has yielded enough material to generate any publication). Thus, the first team, led by Dr Michèle DARMON (referred to below Team 1) will integrate part of a second team (referred to below as Team 2). Accordingly, comments on the past research activity of this new team will mostly focus on the activity of Team 1 (see above Tables), as compared to the second team. Team 1 was composed of 3 permanent scientists (before being joined by a Maitre de Conférences in 2012) that focused mostly on the identification of the mechanisms allowing appropriate trafficking of serotonergic receptors (e.g. 5-HT1A, 5-HT1B). One of these mechanisms, i.e. the recruitment of Yif1B for the correct trafficking of 5-HT1A autoreceptors, has set the basis for the best two publications of the team (J Neurosci). The tools used by this team are those usually found in molecular pharmacology and cell biology research. In total, Team 1 contributed to 12 original publications from 2007 to 2012, 8 of which bear 10 > IFs > 5. The scientific quality of this first team can be considered as being good but not exceptional. Confirmingly, members of Team 1 are not often invited to international conferences. Team 2 focused mainly through pharmacological means on the histaminergic system, such an analysis being led from the molecular step to whole body investigations. The leader of Team 2 and two Maitres de Conférences joining Team 1, contributed to 14 publications, only one of which bearing 10 > IFs > 5. Team 2 should thus be considered as "above average" although it should be mentioned that good specialty (i.e. pharmacology) journals, such as J Pharmacol Exp Ther (where the team often publishes its findings), do not rank high but are still highly considered in the field. Moreover, The team leader of Team 2 bears an international audience, as illustrated by an invited review in Trends Pharmacol Sci.

Assessment of the Team's academic reputation and appeal

Both teams are able to achieve academic collaborations. These range from local (including within the Unit to which they belong) to national (Team 2) or international (Team 1) levels. The leader of Team 1, but not that of Team 2, organised one symposium. This symposium was part of an international meeting focusing on serotoninergic systems. The leader of Team 1 is invited to give oral lectures on several occasions only. For the other PI, such invitations are rare. Except from her past 4-year participation to the INSERM Neuroscience commission, the team leader was involved neither in editorial commitees nor in congress/meeting boards. This is also true for the other PI. None of the two teams are involved in the organisation of meetings/symposia on their respective subjects of interest. Except from one Maître de Conférences who joined the team, none of the two teams attracted permanent scientists. It should be noted however that this statement should be considered with caution given that Team 2 has now decided to be part of Team 1, indicating that the latter team may bear attractiveness.

Assessment of the Team's interaction with the social, economic and cultural environment

Both teams have proved their abilities to raise funds through collaborations with pharmaceutical companies or through successful candidacy for local/regional grant programs. Moreover, the group leader, beside her team leader position, also coordinates the imaging platform of the Institute. With regard to that aspect of the group leader activity, it is noteworthy that she was able to raise funds to acquire a STED microscope. Lastly, the leader of former Team 2, in collaboration with former colleagues or past collaborators, has published several patents.

Assessment of the Team's organisation and life

There are mainly 6 projects, each one being under the responsibility of at least one PI (see below). There is no information regarding the decision process and internal/external communication means. This is also true for the reasons why the leader of former Team 2 working mainly on histaminergic systems, has decided to integrate Team 1 working on serotonergic systems. Undoubtedly, the team maximal performance will be reached only if an appropriate equilibrium between these two scientists will be reached. The means provided to gather such an equilibrium are not documented. It should be noted here that the team, composed of 7 full or half-time scientists (5.5 ETP), bears a weak technical assistance (1 engineer only).

Assessment of the Team's involvement in training through research

The team was composed of 2 PhD students during the past contract and from what I understood one of these is still performing his PhD. For the former Team 2, 6 PhD students went successfully to the end. However, it is noteworthy that among these students, 3 of them, who ended respectively their PhDs in an one-year interval, were put under the responsibility of one permanent scientist. Beyond this aspect, it is also noteworthy that this team has access to several university training programs, allowing a constant renewal of Master students.

Assessment of the five-year plan and strategy

The team will focus on 6 projects, 4 of which are derived from Team 1 and the 2 others being relevant to the former activity Team 2. As concerns the first 4 projects, these mainly involve receptor trafficking mechanisms in serotoninergic neurons and in serotoninoceptive neurons. Thus, based on their most important discovery, i.e. the identification of Yif1B as a crucial partner for the appropriate targetting of 5-HT1A autoreceptors, the team wishes to further characterise the role of this protein. This includes the characterisation of Yif1B knock-out mice, including at the behavioural level. The main concerns here are related to the possibility that Yif1B regulates the targetting of different receptors for other transmitters than 5-HT, thereby raising the question of the relevance of the results to the specific study of 5-HT receptor trafficking, and the relationships of the latter with depression or antidepressant efficacy. The second concern relates to the behavioural outcomes of Yif1B mutation. It is briefly stated that behavioural studies will include evaluation of anxiety and depression scores. Committee's experts would like to know how depression scores will be assessed given the intense debate related to the real existence of depression in laboratory rodents. Beyond this main topic, studies related to 5-HT1B and 5-HT3 receptors will be given further development. Although the 5-HT1B receptor-related project was clear to committee's experts, that regarding the 5-HT3 receptor was not. The main reason for that lack of clarity mainly stems from the fact that priority has been given to past results at the expense of a clearcut project description. This holds true for another project where it is intended to study the hypothesis that the delayed efficacy of antidepressants is linked to the internalisation of 5-HT1A autoreceptors. The project aims to associate pharmacological treaments with "co-expression of some genes". It is not clear what these words meant and which genes were to be targetted. It is also mentioned that the integration of an electrophysiologist from former Team 2 will allow an investigation of "the properties of the 5-HT1A response in serotonergic neurons". Again, this lacks clarity as the electrophysiological properties of these receptors, with/without antidepressants, are known since a long time. Besides these projects, collaborative projects that started during the last years will be continued. Among these, the quest for the mechanisms leading to male infertility in Yif1B-knock out mice is noteworthy.

The two projects that originate from the activity of former Team 2 concern histamine neurotransmission and further characterisation of the orphan GPR88 receptor. Beyond the fact that these projects are not really detailed, it is noteworthy that the histamine project is referred to as being "nearly completed". What next then? This again raises the question of the effective contribution of former Team 2 to the projects of Team 1, especially when one considers that 2 over the 3 scientists on these "Team 2" projects are part time scientists. Maybe one should propose to these scientists to fully focus on Team 1 projects, these being reinforced by additional forces. The document already raises this need but there is no indication as to the time needed to begin this process.

Conclusion

- Strengths and opportunities:

The committee appreciated the strengths of the team: Number of PIs (n=7), among which 4 full-time scientists, good publication rate, including through fruitful collaborations, ability to raise funds for functionning, links with several universities allowing recruitment of Master and PhD students.

- Weaknesses and threats:

Several points have appeared as potential weaknesses: too many projects, some of which are not efficiently described; uknown ability of the members of the second team to invest fully in the projects of the first team; the need, given the number of PIs, to raise in a qualitative manner the publication level; the limited technical assistance that PIs and students may rely on; the leader of the team has not a widespread international audience, limiting thereby the possibility to extend fundraising; the link with the other teams of the Institute is not straightforward.

- Recommendations:

This team has a good level and has the staff and scientific potential to reach an excellent level. Among the means needed for, the Committee recommends a reduction of the number of projects and a clarification of the forces engaged in each of these projects. Furthermore, the team leader should work in order to get a much larger international audience.

Team 2 : Neurobiology of physiological and pathological aging

Name of team leader: Mr. Patrick DUTAR

Workforce

Team workforce	Number as at 30/06/2012	Number as at 01/01/2014	2014-2018 Number of project producers
N1: Permanent professors and similar positions			
N2: Permanent EPST or EPIC researchers and similar positions	7	7	7
N3: Other permanent staff (without research duties)	1	1	
N4: Other professors (PREM, ECC, etc.)			
N5: Other EPST or EPIC researchers (DREM, Postdoctoral students, visitors, etc.)	10	1	1
N6: Other contractual staff (without research duties)			
TOTAL N1 to N6	**18**	**9**	**8**

Team workforce	Number as at 30/06/2012	Number as at 01/01/2014
Doctoral students	2	
Theses defended	6	
Postdoctoral students having spent at least 12 months in the unit	9	
Number of Research Supervisor Qualifications (HDR) taken		
Qualified research supervisors (with an HDR) or similar positions	7	

• Detailed assessments

Assessment of scientific quality and outputs

A selection of the main features in the summary of the bibliometric analysis provided by the dedicated service of INSERM is as follows: number of PIs, 6.6; number of publications, 65; percent within-team collaboration, 22; total number of citations, 694; number of publications with top1+10% citations, 14; number of publications with IF top 10%, 12; number of 1st or last author, 2. Following the recommendations of the scientific advising board of CPN, the team led formerly by Dutar recently merged with a part of Epelbaum's team. This new team under the coordination of Patrick Dutar, includes 1 DRE, 4 DR2 and 2 CR1.

During the last 4 years, the scientific production of the two teams was very efficient, 22 and 63 ACL publications respectively. The overall quality is good to very good, with several first and last author publications in the Journal of Neurosciences, Neurobiology of Aging, Aging Cell. The two teams successfully characterized IouC/jall rats as a model of healthy aging. Most importantly, they have made several and significant contributions in identifying several targets to improve cognitive aging impairements. In addition, they have participated to clinical studies on age-associated cognitive impairement in collaboration with Hôpital Broca (PHRC) and they recently investigated the role of the vesicular glutamate transporters as early markers of Alzheimer desease (AD) through an international ANR grant (ANR-MALZ).

Assessment of the Team's academic reputation and appeal

In the past period, the two teams had a very good ability to raise several funding grants. Three major grants (ANR Somaldolf (PI); ANR MALZ (co-PI, PD), FP7 grant (PI) are currently running until 2014 and 2015 respectively. The PI and head of the unit has a good international visibility (member of the executive FENS committee). He is involved in distinct advisory and foundation committees at the international and national levels. During the past years, several members were regularly invited as speakers in international and national meetings. Members are also involved in meeting organization and in editorial activities. A large network of collaborations is active both at the national and international levels.

Assessment of the Team's interaction with the social, economic and cultural environment

A sub-team produced two international patents, in 2011 and 2008 respectively. An investigator is very active in societal communication on aging and several members of the team regularly participate in « semaine du cerveau ».

Assessment of the Team's organization and life

Nothing specific to mention.

Assessment of the Team's involvement in training through research

Several team's members regularly contribute to Master teaching. One team member is in charge of the Master « Biologie du Vieillissement » (Paris Descartes-Paris Diderot) and is responsible of a Master teaching unit in Neuroendocrinology (Paris-Sud, UMPC, Paris Descartes and Paris Diderot). He is also a member of the directory of the Ph. D. program GC2ID.

The two teams hosted 9 postdoctoral fellows and 7 predoctoral students during the previous years. This may be conjonctural, but only one postdoc and one PhD student are actually present.

Assessment of the five-year plan and strategy

The overall aim of the team is to reinforce the axis of pathological aging for the next 5 years. The project, in continuation with the achieved work, is organized into 4 axes :

Axe 1: Age-dependent effects in the tripartite glutamatergic synapse

Axe 2 : Cellular impact of pathophysiological pathways in AD

Axe 3 : Somatostatin interneurons a preferential target of aging pathophysiology

Axe 4 : BioMarkers and functional Markers in AD

The team uses a combination of molecular, cellular, electrophysiological and cognitive approaches to tackle basic questions in the field of physiology and physiopathology of aging. The overall project is ambitious and has a strong rationale basis. The proposed studies are extremely complementary, and the team has all the necessary expertise. On the basis of previous achievements the committee is confident that the team has the expertise, leadership, and motivation to successfully carry out the proposed experiments in five years time, although they might need more support, especially in post-doc and students recruitments. A challenging aspect of the proposed studies consists in deciphering causal mechanism(s) and this is strongly encouraged by the committee.

Conclusion

- Strengths and opportunities:

The committee evaluates positively the new organization chart of the team. The complementary expertise of the 7 tenure researchers constitutes a very strong scientific power. The potential of synergy is very high. The two teams have already successfully worked together in the past and such a dynamic interaction will continue. The committee notices a good integration of the translational and basic research projects.

- Weaknesses and threats:

The ratio between permanent researchers and post-doc and PhD students is extremely low.

- Recommendations:

The overall proposed project is dense. Given complementary expertise in the team, the committee wishes that a major effort is undertaken to design projects able to produce high impact papers. It is also suggested nurturing dynamic interactions between the team's members to avoid a potential scattering of the projects. An increase in research funding (ANR, European grants, Foundations, or through collaborative projects) will allow PhD student and foreigner post-docs to be attracted and will secure technical support(s).

Team 3 : Clinical and genetic analysis of addictive and psychiatric disorders

Name of team leader: Mr. Philip GORWOOD

Workforce

Team workforce	Number as at 30/06/2012	Number as at 01/01/2014	2014-2018 Number of project producers
N1: Permanent professors and similar positions	9	9	9
N2: Permanent EPST or EPIC researchers and similar positions	5	5	6
N3: Other permanent staff (without research duties)	3	3	
N4: Other professors (PREM, ECC, etc.)	3	3	3
N5: Other EPST or EPIC researchers (DREM, Postdoctoral students, visitors, etc.)	17	17	16
N6: Other contractual staff (without research duties)			
TOTAL N1 to N6	**37**	**37**	**34**

Team workforce	Number as at 30/06/2012	Number as at 01/01/2014
Doctoral students	19	
Theses defended	16	
Postdoctoral students having spent at least 12 months in the unit	12	
Number of Research Supervisor Qualifications (HDR) taken		
Qualified research supervisors (with an HDR) or similar positions	13	

• Detailed assessments

Assessment of scientific quality and outputs

A selection of the main features in the summary of the bibliometric analysis provided by the dedicated service of INSERM is as follows: number of PIs, 16.6; number of publications, 301; percent within-team collaboration, 35; total number of citations, 2131; number of publications with top1+10% citations, 46; number of publications with IF top 10%, 73; number of 1st or last author, 43. To note the number of publications includes already 94 publications from the newly formed team. Although this is an impressive number of publications the break down by researchers involved (ETP 16,6) shows a less striking publication productivity. In terms of quality the IFm of 3.66 also shows an average level with few scientific highlights including 1 x Am J Psychiatry, 1 x Mol Psychiatry, 1 x Hum Mol Genet and 2 x Neuropsychopharmacology over 6 years. There are other high ranking papers listed (like PNAS) but only with a minor contribution from one of the team members.

Assessment of the Team's academic reputation and appeal

The team is very successful in attracting money on all levels. Not only on a national level with numerous grants the team has and is still involved in several FP6/7 EU grants and a team member is currently coordinating two FP7 programs (e.g. NANODIAMED). Very impressive! They have also attracted 3.2 M€ from the pharmaceutical industry. Beside this outstanding funding situation the team leader acts as Editor in Chief of European Psychiatry and several team members are listed in the editorial boards in journals in the categories of Psychiatry & Neurosciences.

Assessment of the Team's interaction with the social, economic and cultural environment

The only highlight which is mentioned is that a new team member is a principal organiser of the Brain Awareness week for Ile de France. Given the lack of information no score is provided.

Assessment of the Team's organisation and life

Nothing specific to mention.

Assessment of the Team's involvement in training through research

The team has trained 19 PhD students and 28 master students in the past years. Several team members are listed for their active involvement in several training activites in neurosciences.

Assessment of the five-year plan and strategy

A new very large team (with 4 new PIs) has now been formed with 30.8 ETP. It will thus be a challenge for the group leader to manage such a large team. As the wish of all team members and of the newly appointed director one should give this team project a chance. All new team members seem to be very enthusiatic to contribute to translational studies in annorexia nervosa, alcohol dependence and several other psychiatric disorders. However, the project would benefit to be better presented, streamlined and more focused on 3-4 major aims. As it stands now it contains several highlights such as world-wide unique clinical samples (e.g. 300 Trios in AN and 800 alcohol dependent patients with longitudinal suicidal assessment), very interesting tools for studying ghrelin in reward processing, but the very heterogenous project description calls for better formulated major goals and hypotheses. Would this project be coordinated with those of the foreseen new CPN director, the team goals and working hypotheses will surely gain great potential and will represent a strength of the CPN in the field of translational Psychiatry.

Conclusion

- Strengths and opportunities:

The strengths of the team are: world-wide unique patient samples, especially in anorexia nervosa and alcohol dependence; great access to new patient recruitment; great potential for translational psychiatry.

- Weaknesses and threats:

The weaknesses are: team size too big to get managed in an efficient way; having large samples requires millions of € for getting them on the chip or sequencing; this is a great problem despite the fact that the group has excellent funding; the overall project is diverse and heterogenous.

- Recommendations:

Together with the newly appointed director and its overall view of the CPN project a more stringent formulation of the team goals will further strengthen its great potential.

Team 4 : Pathophysiology of Psychiatric Diseases

Name of team leader: Ms. Therese JAY & Ms. Marie-Odile KREBS

Workforce

Team workforce	Number as at 30/06/2012	Number as at 01/01/2014	2014-2018 Number of project producers
N1: Permanent professors and similar positions	2	2	2
N2: Permanent EPST or EPIC researchers and similar positions	2	2	2
N3: Other permanent staff (without research duties)	11	11	
N4: Other professors (PREM, ECC, etc.)	3	3	3
N5: Other EPST or EPIC researchers (DREM, Postdoctoral students, visitors, etc.)	3	3	2
N6: Other contractual staff (without research duties)	3	3	
TOTAL N1 to N6	**24**	**24**	**9**

Team workforce	Number as at 30/06/2012	Number as at 01/01/2014
Doctoral students	14	
Theses defended	10	
Postdoctoral students having spent at least 12 months in the unit	8	
Number of Research Supervisor Qualifications (HDR) taken	4	
Qualified research supervisors (with an HDR) or similar positions	7	7

• Detailed assessments

Assessment of scientific quality and outputs

A selection of the main features in the summary of the bibliometric analysis provided by the dedicated service of INSERM is as follows: number of PIs, 9.6; number of publications, 197; percent within-team collaboration, 32; total number of citations, 1573; number of publications with top1+10% citations, 36; number of publications with IF top 10%, 70; number of 1st or last author, 34. The team has achieved very good results in the past few years. The main results were :

- Identification of de novo point mutations in schizophrenic disorders : the team found that sporadic cases of schizophrenia have more de novo point mutations in genes, among which some have been implicated in autism. They also publish the first full-exome in schizophrenia, in collaboration with a team in Montreal, that confirmed the higher prevalence of de novo mutation in sporadic cases of schizophrenia in new genes, some of which being involved in neurodevelopment or immune processes.

- Identification of markers of deviant neurodevelopment in schizophrenia : the main results are that neurological soft signs are associated with poorer response to therapeutics, abnormal oculomotor control, volumetric alterations in the cortico-thalamo-cerebellar network and modified cortical gyrification suggesting that such soft signs are endogenotypic markers of a developmental form of psychosis.

- Identification of cannabis consumption as a risk factor for psychosis and its role in prodromal patients : sensitivity to psychotomimetic effects of cannabis is associated with earlier age of exposure and more family history of psychosis and characterized by earlier age at onset and more resistance to treatment. They show, in a large population of students, that experiencing strong psychotic-like effects of cannabis such as referential ideas or hallucinations could identify individuals sensitive to psychotomimetic effects of cannabis. In rats, using a full cannabinoid agonist, they show that chronic exposure during adolescence leads to long-term deleterious effects on cognitive processes. These impairments were associated with changes in hippocampal-prefrontal synaptic plasticity and alteration in the dendritic morphology of pyramidal neurons in the prefrontal cortex. The main result is that repeated exposure to cannabinoids or excessive activation of CB1 receptors during adolescence can significantly alter the level of prefrontal plasticity necessary for proper cognitive function.

Validation of an animal model for psychosis onset (MAME 17 model) : adult rats exposed to the DNA-methylating agent methylazoxymethanol (MAM) on embryonic day 17 show a pattern of neurobiological deficits that model some of the neuropathological and behavioral changes observed in schizophrenia. They were the first group to show that this model has predictive validity by showing that antipsychotics can reverse abnormal behaviours displayed by MAM rats.

Study of intracellular signaling cascades critically involved in the disruptive effects of stress and identification of potential molecular targets : the group investigated the effects of exposure to stress on prefrontal networks plasticity in rats, and demonstrated a fundamental role of the prefrontal cortex in the maladaptive responses to stress. They also show that intracellular signaling cascades are critically involved in the disruptive effects of stress and that prefrontal tissue responds differently after stress than hippocampal and amygdala tissue. They proposed that this modulation of downstream mechanisms and neuroplasticity circuits could be used for new therapeutic strategies.

These results lead to a substantial number of publications with 36 in top 10 journals (among them : Nature genetics, Lancet neurology, Schizophrenia bulletin, Trends in Molecular Medicine) with only 9,6 full time equivalents of searchers. Approximatively two thirds of these publications are exclusively from the team (32% in collaboration). These data could be considered as an outstanding achievement for this small and recent team.

Assessment of the Team's academic reputation and appeal

The academic reputation and attractivity of this team appears to be very good. The team succeded in raising grants for their researches with a rather high level of fundings (4 Millions €) (especially 5 ANR, 1 ERANET-Neuron). They obtained the coordination of an International consortium (Era-Net Neuron: Canada-Spain-Germany) in a very competitive field and collaborate to the international consortium IMI NewMeds (with the coordination of the WP « development of a circuit-based analysis of drug discovery »). They have organized numerous scientific meeting (« Transition » ; "Encephale" ; International COST B30 meeting « Regeneration and Plasticity ») and several symposium in international psychiatric meetings. The reputation of the institute and the team have permitted the recruitment of 2 foreign PhDs, 7 foreign Post docs (UCLA, USA ; Mexico ; Germany ; Spain) and 4 invited professors from New Zealand, Bel Horizonte, Brasil, McGIll Ca, Stanford, USA.

They have several international collaborations in Europe and North America as well as in France (Active participation to Neuroimaging networks (ATP « Imagerie », Platform Ibiza « Imagerie petit animal ») and Neurospin in human and animal). One team leader coordinates the National collaborative Network « Groupe de Recherche in Psychiatry (GDR – Aviesan CNRS- Inserm) » with the objective to create a collaborative space for research and methodological reflection on priority themes of Psychiatry and to develop a shared scientific strategy between 15 resarchs teams involved. The other team leader is involved in the Editorial board of Frontiers in Neuroscience.

Assessment of the Team's interaction with the social, economic and cultural environment

Interaction with social environment is quite good. The team leaders have establish a long term collaboration with industrial partners (pharmaceuticals companies, Eyebrain). They have had several invitations to professional meetings and interviews by decision makers (including french government). The professors of psychiatry members of this team are considered as opinion leaders for psychiatry by decision makers, media and other professionals. As such they made numerous contributions to media (french or foreign newspapers) or communications in the community and have durable collaboration with patients advocacy groups. One of the group leaders also organized an exhibition on cannabis at Cité de la Science La Villette. The team obtained 2 patents (Transdifferentiation of macrophages into Neuronal-like-Cells as a potential model for treatment prediction in schizophrenia (in progress) and prediction, use, information storage and corresponding material (AD10999), 2010.

Assessment of the Team's organisation and life

Nothing specific to mention.

Assessment of the Team's involvement in training through research

Several members of the team are deeply involved in training for medical students (teachers at the Faculty of Medicine). In the field of training through research they have the responsibility of the coordination of teaching courses in Neuropsychopharmacology (Master 2 University Paris Descartes). They also coordinate an educational training for medical and non medical staff of the Ste-Anne hospital (« Initiation in Clinical Research in Neurosciences ») to improve the translational vocation of CPN-Ste Anne center that is an important initiative to boost clinical research and implication of nursing staffs. During the period 2007 to 2011 they welcome 24 Master students (1st and 2d year) among them 12 achieved PhDs during this time. They also recruited 10 post-docs researchers. As a whole these activities could be rated as very good.

Assessment of the five-year plan and strategy

The team plans to set a new organization based on 3 research sub-groups :

Critical periods in the pathophysiology of psychiatric disorders. This group will continue to work on the characterization of developmental deviations in schizophrenia and autism (collaboration within the AUSZ-EUCan consortium) with, as a first objective, a systematic multimodal characterization of a large sample of patients, genetic screening for CNV, detailed phenotyping and brain morphology in patients carrying de novo mutation, and development of a new animal model with developmental abnormalities of white matter. The second objective of this group is to study the interaction between gene and environment in young patients at high risk for psychosis. They will continue an ongoing prospective study that combines clinical, cognitive, brain imaging and biological data with a one year follow up (ICAAR PHRC study) to assess the predictive value of developmental markers, including neurological and morphological signs, cognitive deficit and brain anatomy, and the reactivity to stress and/or to psychotomimetic effects of cannabis. They will also examine the efficacy of Cognitive Behavioral Therapy focusing on individual stress management compared to an usual 'support' therapy in a randomized single-blind controlled prospective 12 month longitudinal design.

Emotional dysfunctions and the dynamics of frontal limbic networks. This theme is organized on 3 topics. They firstly plan to study regulation of frontal limbic network both at a cellular level and at brain level in collaboration with Neurospin. They will study modulation of prefrontolimbic network in pathological conditions. For this they will explore the neurocognitive characteristics of high risk patients, focusing on memory, emotion and the correlation of stress response with cognitive dysfunction. Secondly they will use optogenetic strategies to target hippocampal and prefrontal interactions in rats and to explore the role of Hippocampal/Prefrontal pathway in mediating hippocampal and prefrontal interactions. Finally, they will study the effect of deep brain stimulation of nucleus accumbens on an animal model of depression to investigate the behavioral effects of stimulation, cortical changes and neuroendocrine changes in stimulated rats.

Pharmacology of cognition and innovative therapeutics. As part of a european consortium (the team is in charge of the WP of the European Union consortium IMI-Newmeds, dedicated to the development of a circuit-based analysis of drug discovery), they will investigate neuronal elements responsible for the altered prefrontal activity and disruption of cortical oscillations induced in pharmacological and genetic animal models of schizophrenia. Using the ketamine model, they will conduct comparative studies in controls and high risk patients in order to understand the cognitive features (with focus on uncertainty monitoring) of psychosis and their neural basis in a dynamic and diachronic way. They want also to assess the cognitive profile of "nonpsychotropic" drugs with psychotropic properties (drugs currently developed in oncology and haematology targeting signalling pathways common to all cells, including neurons such as PI3K/AKT/mTOR inhibitors and tyrosine kinase inhibitors). Their last objective is to implement Individually-tailored treatment strategies by studying the link between executive functions and impairment in everyday life using virtual reality protocol or BCI technics.

Conclusion

- Strengths and opportunities:

This multidisciplinary translational research team has a very good opportunity to access large clinical population in Ste-Anne hospital and then to link fondamental research to clinic. The international visibility is excellent with many collaborations (European projects, many collaborations with foreign groups as well as French ones).

- Weaknesses and threats:

The committee must point out some heterogeneity between the domains of research within the team. The coherence between the 3 axes of the project is difficult to assess. In the second group, the project on DBS appears to be artificially linked to the other objectives focused on the effect of stress on frontal/limbic networks and the study of neurocognitive characteristics of high risk patients. Mostly, the third group seems to have few connections with the other groups within the team, especially for the studies of new pharmaceutical compounds. This last theme and the methodology ought to be independently developed as such. The interactions with other teams in CPN appear good but, surprisingly there seems to be few connections with teams having expertise in addiction for genetic approaches.

Another pitfall could be the competition with other well-known team in Psychiatry in the Paris area (e.g. Mondor). Both institutes are devoted to translational research in psychiatry including genetic studies of psychosis and long term follow up of large cohorts of patients. But the objectives seem to be more complementary than competitive : at risk subjects, schizophrenics, alcohol addicts and eating disorders patients on one side for CPN, mostly bipolar, schizophrenic and Asperger patients on the other side for Creteil. The major overlap is about construction by both teams of large cohorts of patients, constitution of biobanks and maybe for the new domain of DBS. However, the huge challenges for the future of psychiatric research in France may justify 2 institutes of psychiatric research in Paris area.

- Recommendations:

This team should adapt its overall strategy to the context of the existing opportunities both within the CPN (in consideration of the foreseeable changes induced by the future new direction of the CPN) and outside, especially in the Paris area and abroad, based on the important links the team has developed in the past with several groups in France and in Europe.

Team 5 : Manual dexterity in health and disease

Name of team leader: Mr. Marc MAIER

Workforce

Team workforce	Number as at 30/06/2012	Number as at 01/01/2014	2014-2018 Number of project producers
N1: Permanent professors and similar positions	2	2	2
N2: Permanent EPST or EPIC researchers and similar positions	1	1	1
N3: Other permanent staff (without research duties)	1	1	1
N4: Other professors (PREM, ECC, etc.)	1	1	1
N5: Other EPST or EPIC researchers (DREM, Postdoctoral students, visitors, etc.)	3	2	2
N6: Other contractual staff (without research duties)			
TOTAL N1 to N6	**8**	**7**	**7**

Team workforce	Number as at 30/06/2012	Number as at 01/01/2014
Doctoral students	5	
Theses defended –		
Postdoctoral students having spent at least 12 months in the unit		
Number of Research Supervisor Qualifications (HDR) taken	2	
Qualified research supervisors (with an HDR) or similar positions	2	2

• Detailed assessments

Assessment of scientific quality and outputs

A selection of the main features in the summary of the bibliometric analysis provided by the dedicated service of INSERM is as follows: number of PIs, 1.3; number of publications, 27; percent within-team collaboration, 22; total number of citations, 133; number of publications with top1+10% citations, 2; number of publications with IF top 10%, 5; number of 1st or last author, 2. The team would be a new recruit to the currently proposed project of the CPN. It has undergone some substantial changes from the previous combination of a group headed by the team leader and another group at UMR 8194, with the latter group leader deciding not to move to CPN. However, many of the personnel present in 2012 are still within the team moving to CPN, which will hopefully allow for good continuity. A major strength of the team is the interdisciplinary approaches by the different team members within a common field of interest. The team research breaks down into two major related themes: (1) recovery of manual dexterity in disease; and (2) Neurorobotics and brain-machine interfaces for arm/hand control. These themes are within fields that are evolving fast, with much attention globally on recovery of function (particularly with TMS) and replacement of limbs with/without BMI. In terms of overall output, the number of papers published per year over the assessment period by the team has risen steadily, with papers appearing in some good to very good international journals. The focus on publication has been resolutely outward looking. The team is relatively small, with a low level of external funding, and has two early career PIs with only a small number of post-docs and PhD students; however, the impression is that ouputs are increasing in both frequency and quality and this should facilitate further funding.

Theme 1 has mostly investigated the normal control of dexterity with more recent work including a focus on disruption of motor output associated with either motor system disruption or stroke. Output has been in good to very good journals (2 papers in J. Neuroscience; 1 paper in J. Physiol.). The association of the team leader with a group in London working with the macaque motor system has resulted in papers in two very good journals; however, the last of these was in 2009. It is not clear whether this collaboration will continue; if not, this is a shame as continued access to primate spiking data would help to increase the impact of team outputs. Related to this, the team have identified the current lack of a permanent physiologist as a weakness and the committee would agree.

Theme 2 has clearly developed well, with substantial improvements in both mechanics (with industrial partnership) and control software (e.g., inclusion of feedback error control via cerebellar-like monitoring of actual vs planned movements). The group will collaborate with a group at INT, Marseille, who will provide spiking data from monkey motor cortex. Whether the long-term goal is to implant BMIs into trained monkeys that will use the robotic interface is not clear. The output from Theme 2 in robotics journals has been in journals with mid to low IF, the same for neuroscience-related journals and average IF for general life sciences (PLoS ONE). This is reflected in the low mean IF and number of actual citations. However, this theme has attracted some recent funding.

Assessment of the Team's academic reputation and appeal

There are some good signs that the team take part in and help organise international academic events. The group leader has been invited to speak regularly at meetings and research institutes both nationally and internationally. He has also contributed to a recent FENS-Hertie school on primate hand function. A team member served on the organization committee for two international symposia and has won prizes for poster presentation and best innovation at international/national events. Another team member was invited to speak at a philosophical conference and this resulted in further colaboration. All of the team also take part in the FENS and Society for Neuroscience meetings. The team leader also has an ongoing visiting Professorship at UCL, UK as his principal international connection. However, as noted above, this has produced no output since 2009. Indeed, the committee is a little surprised that the team leader does not have a more substantial international reputation and presence. There is no indication of any Journal editorships or membership of grant awarding committees, etc. When looking at the current and past sources of funding the track record has been very reliant on national rather than international sources. This is perhaps natural for the more junior PIs who are yet to build a reputation, but one would expect the group leader to be part of more substantial international networks, ideally based on EU funding.

Assessment of the Team's interaction with the social, economic and cultural environment

The team have an important and clearly productive relationship with their industrial partner in Poitiers. The technical developments through this link were awarded a patent in 2012. Another patent was awarded in 2009. This is an important link and potential source of research support and economic impact. It will also serve as a foundation for the further development of the group.

Assessment of the Team's organisation and life

The scientific objectives of the team are very clear. There is a clear link between the different research themes (Topics 1 and 2) and each team partner has an obvious role within the overall structure. As such, this should facilitate further collaborations and developments within the group. As the team will be a new part of CNP it is perhaps a little early to assess the contribution of members to the management of the centre and the allocation of space.

Assessment of the Team's involvement in training through research

The team has successfully trained Master and PhD students over the last years.

Assessment of the five-year plan and strategy

Firstly, it was disappointing that the document presented was apparently incomplete. The team's plan is to further develop their current strategy whilst initiating collaborations with other members of CPN (most notably with teams having expertise in stroke and psychiatric disorders). This is a good strategy, as it will potentially open more avenues for funding streams. The bringing together of expertise from these different Teams makes good sense and should produce a synergistic effect. However, it is clear that the avenues identified (motoric aspects of stroke and schizophrenia) are relatively new (which can of course be seen as a good thing as competition for funding will be minimal); however, pilot data and, ideally, publications would be required first by a funder in order to be confident. The incorporation of comtemporary techniques such as TMS (via future links locally) and DTI (an exisiting technique within this Team) will further enhance the multidisciplinary aspects fo the research. One aspect that may be quite challenging is to separate executive from motor (dis)function in normal and schizophrenic patients as the distinction between these is becoming more blurred. Also, these are major subcortical motor regions that would be inaccessible to TMS. As presented, the five-year plan is a set of ideas for collaborative and other work; it would have been useful to see a time-line for implementation and specific prediced targets within the five year period where success could be measured together with an idea of what the shape of the Team would ideally look like at the end (but all the plans were in this format). Collaborations beyond CPN were targeted but how/where international links would be sought, funded and managed was not clear. One would hope that the collaboration with London group would continue (to supply spiking, LFP, EMG, etc.) and that a more explicit strategy for BMI development could be made with extension towards animal models. The identified funding streams were principally from national sources, so some elaboration of strategy for potential international funding (e.g., EU networks) would have been good to see. The SWOT analysis was very honest and the committee agrees with the major points. The Team needs to become larger, attract more funding and publish in higher impact Journals. The identified 'opportunities' from CPN incorporation should open up avenues to address these 'weaknesses'.

Conclusion

- Strengths and opportunities:

The team has a major theme running through all the approaches. The team encompasses different complemetary techniques and approaches. Staff in the team have been working together productively for some time, yet PIs are still mostly early career scientists with an experienced team leader. This bodes well for the future. Outputs have been modest so far, but the rate of output is increasing and the quality of Journals publishing the work is improving. National funding has been won for the robotics/BMI work. The proposed move to CPN has clear mutual benefits for the Team and other CPN Teams. This represents an excellent opportuity to broaden the approaches to scientific and medical issues and strengthens.

- Weaknesses and threats:

In order to get the required funding this has the 'risk' of requiring pilot data (and, ideally, publications) at the point of application to funding agencies. There is a clear benefit of incorporating TMS as a technique but there is no track record for this in the Team. Some form of appointment in this area would be beneficial. As in most research-intensive Universities and Institutes, the impact of administration has to be minimised in order to allow academics in research teams opportunity to develop grant applications and produce high-quality output.

- Recommendations:

The team should concentrate on the operationalization of the proposed experimental paradigms in the context of potential applications offered by the CPN so that such its projects could materialize in terms of translational research outputs and publications in high visibility journals.

Team 6 : Stroke, Prognosis and Imaging INSERM U894

Name of team leader: Mr. Jean-Louis MAS

Workforce

Team workforce	Number as at 30/06/2012	Number as at 01/01/2014	2014-2018 Number of project producers
N1: Permanent professors and similar positions	4	4	1
N2: Permanent EPST or EPIC researchers and similar positions	1	1	1
N3: Other permanent staff (without research duties)	7	7	
N4: Other professors (PREM, ECC, etc.)			
N5: Other EPST or EPIC researchers (DREM, Postdoctoral students, visitors, etc.)	3	3	3
N6: Other contractual staff (without research duties)	2	2	
TOTAL N1 to N6	**17**	**17**	**5**

Team workforce	Number as at 30/06/2012	Number as at 01/01/2014
Doctoral students	3	
Theses defended	2	
Postdoctoral students having spent at least 12 months in the unit	3	
Number of Research Supervisor Qualifications (HDR) taken		
Qualified research supervisors (with an HDR) or similar positions	6	

• Detailed assessments

Assessment of scientific quality and outputs

A selection of the main features in the summary of the bibliometric analysis provided by the dedicated service of INSERM is as follows: number of PIs, 6.7; number of publications, 227; percent within-team collaboration, 30; total number of citations, 3442; number of publications with top1+10% citations, 57; number of publications with IF top 10%, 90; number of 1st or last author, 43. The Stroke Prognosis and Imaging team is performing outstanding clinical research with an impressive publication record over the past five years, with a total of 155 papers including 21 papers in journals with an impact factor higher than 10 (such as the Lancet, Lancet Neurology, JAMA, Brain, Circulation; 38 papers in journals with an IF from 5 to 10; 59 papers with an IF from 2 to 5). Publications from this team, for instance on the use of stenting in carotid artery stenosis, influence the decision making in daily clinical practice in the field (endarterectomy prefered for patients above age 70). The team is conducting large clinical trials which are not funded by the pharmaceutical industry but supported by public funding, a very remarkable achievement.

Assessment of the Team's academic reputation and appeal

The Stroke Prognosis and Imaging team is organizing or taking part in numerous international clinical trails. It is collaborating with numerous French, European and North American research teams and has projects in collaboration with industry. The team leader has hosted the European Stroke Conference in Nice in 2008 as conference chairman and is board member of the European Stroke Conference, of the European Stroke Organisation and of the World Stroke Organisation. He is member of scientific boards in European countries (France, UK, Spain). The team has held 201 invited lectures. The team leader is assistant editor of Stroke and 2 other specialised journals and editorial board member of numerous journals. Surprisingly, despite its outstanding research and publication record, the team has not hosted any post-doctoral fellows.

Assessment of the Team's interaction with the social, economic and cultural environment

The team has taken part in TV and radio broadcasts. It has published numerous educational articles for general practitionners. Lectures were open for the general public. The team has provided an expert report on cerebrovascular diseases to the French Government, Department of Health ("Plan AVC"). It has also chaired the guidelines committee of the European Stroke Organisation (the team leader being Chair of the guidelines committee). The team has ongoing partnerships with industry . There is no mention of filing for patents.

Assessment of the Team's organisation and life

The team is organised into two research areas (Stroke prevention and Prediction of the response to treatment in acute ischemic stroke), each lead by one or two PIs. Most team members take part in both. There are regular thematic and team meetings.

Assessment of the Team's involvement in training through research

The team is involved in teaching and training of masters and PhD students. Two masters M1 students and 4 masters M2 students were trained in the last 4-year period as well as 5 PhD students. Two of the PhD students have completed their PhD within the 4 year period.

Assessment of the five-year plan and strategy

In the new five-year plan, the team is continuing along its two main areas of research, stroke prevention and prognosis and response to treatment in acute stroke. It is adding two new areas of research on functional recovery after stroke and on cognitive impairment in stroke in collaboration with new teams joining the Centre (Memory and Cognition team; upper limb control team).

Axis 1, entitled stroke prevention, deals with:

Carotid atherosclerosis (a. reevaluation of stenting vs surgery; b. imaging plaque instability using MRI and PET), 2 Patent foramen ovale (a. secondary prevention, randomised multicentric CLOSE trial; b. stroke mechanisms in PFO-associated stroke: the ROPE trial, establishing the causal relation of PFO in stroke patients with PFO; c. genetic predisposition for PFO, using the large cohort of patients enrolels in the CLOSE trial).

Transient ischemic attack (a. refining the diagnosis of TIA, using mulitmodal MRI; b. should low risk TIA patients be hospitalised or dealt with by GPs: a pragmatic comparative trial).

Coronary artery disease and stroke (a. database evaluation to assess the coronary artery disease risk in stroke patients. B. Search for biomarkers).

Intracranial aneurysms (a. evaluation of intracranial aneurysms using MRI flow patterns at 3T; B. long term evolution after endovascular treatment (EVT, coiling). C. Aspirin in EVT.

Sickle cell disease : defining the optimal therapeutic strategy in adults.

The projects outlined in this axis are promising and solid. The team is extending its previous successful projects, as well as exploring new aspects, such as the management adult sickle cell disease patients, teaming up with experts in the field.

Axis 2, acute ischemic stroke, response to treatment (a. DWI reversal after rTPA; b. early neurological deterioration; c. predicting early and late responders to rTPA). The projects in this axis are feasible and should yield results. Project c involves a newly aquired TCD equipment.

Axis 3, Functional recovery after stroke: a. effect of chronic fluoxetine treatment on the corticospinal system; b. effect of combining rTMS and virtual reality in post-stroke motor recovery. These projects will study functional recovery after stroke, an important and very timely topic, using transcranial magnetic stimulation, a potent tool to study brain function, as well as a virtual reality approach to enhance recovery.

Axis 4. Stroke and cognitive impairment (a. understanding the role of the neurovascular unit in vascular cognitive impairment VCI and Cerebral Amyloid Angiopathy versus Alzheimers Disease; b. ImaBio3 study). In this project, the team will study amyloid deposition in stroke patients including an in vivo detection using PET, linking stroke, Alzheimer's disease and cerebral amyloid angiopathy.

Conclusion

- Strengths and opportunities:

Outstanding clinical research team, conducting large clinical trials sponsored by public funds, with access to a large patient cohort (large stroke center), with an impressive publication record, very well represented in international specialised societies, with numerous participations in European scientific boards. The arrival of two new teams opens new possibilities for research. The planned renovation of new building in proximity with large surfaces dedicated to research is an addtionnal strength.

- Weaknesses and threats:

As pointed out in previous evaluations, a stronger connection with preclinical research would be an additional strength and is recommended. A connection with the excellent preclinical team from GIP Cyceron in Caen is planned. An in-house experimental stroke lab would be even better to promote interactions between bench and bed side and thereby trigger innovating ideas and projects. Surprisingly, there are few post-docs in this highly productive team with top-ranking publications. Availability of post-doc positions would be advisable to attract foreign clinicians or scientists and promote the visibility of the team.

- Recommendations:

The committee is impressed by the quality of this team. The possibility to attract an experimental stroke lab should be explored although it may be very difficult to attract well integrated stroke research teams such as the ones in Caen and Nice. However, it may be feasible to closely interact/attract some in University Paris Descartes. Creating positions for post-docs, and perhaps also for additional PhD students, should allow to attract excellent clinical scientists from abroad and further improve the visibility of the team and facilitate scientific interactions with other institutions.

Team 7 : Memory and Cognition

Name of team leader: Ms. Pascale PIOLINO

Workforce

Team workforce	Number as at 30/06/2012	Number as at 01/01/2014	2014-2018 Number of project producers
N1: Permanent professors and similar positions	3	3	3
N2: Permanent EPST or EPIC researchers and similar positions			
N3: Other permanent staff (without research duties)	3	3	
N4: Other professors (PREM, ECC, etc.)	3	3	3
N5: Other EPST or EPIC researchers (DREM, Postdoctoral students, visitors, etc.)	7	7	7
N6: Other contractual staff (without research duties)			
TOTAL N1 to N6	**16**	**16**	**13**

Team workforce	Number as at 30/06/2012	Number as at 01/01/2014
Doctoral students	7	
Theses defended	4	
Postdoctoral students having spent at least 12 months in the unit	4	
Number of Research Supervisor Qualifications (HDR) taken	-	
Qualified research supervisors (with an HDR) or similar positions	4	

• Detailed assessments

Assessment of scientific quality and outputs

A selection of the main features in the summary of the bibliometric analysis provided by the dedicated service of INSERM is as follows: number of PIs, 6.1; number of publications, 77; percent within-team collaboration, 12; total number of citations, 595; number of publications with top1+10% citations, 10; number of publications with IF top 10%, 17; number of 1st or last author, 11. The research addresses major issues in mental / brain diseases affecting the human memory and other cognitive functions such as ageing-related pathologies (Alzheimer's disease and associated disorders) and more recently the strategy of research has evolved to developmental topics such as those related to autobiographical memory and self disorders in schizophrenia, a re-orientation or an extent of research strategy that accounts for the integration of the team in the CPN (whereas in the past contracts the team was located in Boulogne and had long established collaborations with other groups specialized in studies of the clinical neuroscience of dementias and Alzheimer's disease such as INSERM Laboratory in Caen).

This team is especially innovative and productive in the domain owing to the activity of the team leader; she has developed a research line on autobiographical memory that had both theoretical and clinical implications since her memory test (TemPAU) is now a daily used test in the memory clinics. Other members of the team develop research in the diverse topics of psychology or neuropsychology that seem both less coherent with the team main topic (e.g. spatial cognition, mechanisms of learning, embodied cognition) and with a productivity less visible. Overall, considering the fact that cognitive neuroscience and neuropsychology is a specialized sub-domain that does not yield the same audience as some areas of the biology literature, the scientific productivity is deemed good with about 77 publications from 2007, half of them involving the team leader as main author; the IF ranges from 1.22 to 9.46 (co-authorship in Brain). The rate of co-publications across this small team members is relatively low.

Assessment of the Team's academic reputation and appeal

The team has a good potential to attract young researchers (4 postdocs) and students.

Assessment of the Team's interaction with the social, economic and cultural environment

The team leader has a clear visibility in the media and was invited to present her work and to address the general audience about recent advances on memory and related brain diseases. The team leader received a number of awards and prizes.

Assessment of the Team's organisation and life

The students seem well supervised and co-authored publications. The team leader has a prevalent role. The fact that diverse projects are conducted by other members and that they do not seem to cross collaborate much may be a concern.

Assessment of the Team's involvement in training through research

The team has successfully trained PhD (7). PIs are Professors or Associate Professors and are by essence involved intensively in teaching.

Assessment of the five-year plan and strategy

The project is original as it has a broad scope, with life span perspective and trans-disciplinary approach (from concepts of experimental Psychology to brain imaging, transcranial magnetic stimulation – TMS -and virtual reality). It has also practical implications with interesting perspectives of applying new information technologies (virtual reality environment to induce artificial travelling conditions) to innovative memory testing and remediation (impact of transcranial magnetic stimulation). An important issue in the context of the CPN is whether the team will manage to interact optimally with other teams that represents partners to apply their scientific programs (with regards to the project on memory of the self in patients with schizophrenia) and the stroke team, owing to the arrival of a PI who will develop a new topic in the strokes team, focusing on dementias, especially related to the relationships between neurodegeneration and vascular insult in the elderly.

Conclusion

- Strengths and opportunities:

The team has a vast experience ranging from experimental Psychology to brain imaging. It presents a renewed program of research with innovative concepts and proposals for using new technologies and intervention methods such as virtual reality and TMS to alleviate cognitive disorders in a large spectrum of brain/mind disorders (schizophrenia, strioke, ageing). The re-localization of the team or of a part of the team in the CPN will provide very good opportunities to interact with other on-site teams addressing clinical neuroscience topics (psychiatric disorders, stroke) and to exploit technical facilities at Ste Anne such as the MRI equipment and the Clinical Research Centre.

- Weaknesses and threats:

The team will face the challenge of working on both Boulogne (teaching) and the CPN (research). The will have to install their equipment and create clinical research procedures at Ste Anne to set up new programs. Most importantly the team will have to find the ways of collaboration in the clinical domain with the local teams dealing with the patient populations they aim to study / treat. The team is small and has no full-time (INSERM or CNRS) researcher. Owing to the limited time PIs could spend in research, they should concentrate on well-focused objectives rather than exploring the (though seducing) multiple perspectives and potential developments of research they presented.

- Recommendations:

The arrival of this team is a plus for the CPN new project. The team leader and the CPN PIs and Director should facilitate the integration of the team at Ste Anne and the development of its very interesting and innovative programs. The team should make any possible effort to reinforce the visibility of its publications, including those in which the team leader is not the main investigator or promoter.

Team 8 : Pain, Neuroinflammation and stress

Name of team leader: Mr. Michel POHL & Mr Luis VILLANUEVA

Workforce

Team workforce	Number as at 30/06/2012	Number as at 01/01/2014	2014-2018 Number of project producers
N1: Permanent professors and similar positions	4	3	2
N2: Permanent EPST or EPIC researchers and similar positions	4	2	2
N3: Other permanent staff (without research duties)	2	2	
N4: Other professors (PREM, ECC, etc.)			
N5: Other EPST or EPIC researchers (DREM, Postdoctoral students, visitors, etc.)			
N6: Other contractual staff (without research duties)			
TOTAL N1 to N6	**10**	**7**	**4**

Team workforce	Number as at 30/06/2012	Number as at 01/01/2014
Doctoral students	5	
Theses defended	4	
Postdoctoral students having spent at least 12 months in the unit	4	
Number of Research Supervisor Qualifications (HDR) taken		
Qualified research supervisors (with an HDR) or similar positions	5	4

• Detailed assessments

Assessment of scientific quality and outputs

A selection of the main features in the summary of the bibliometric analysis provided by the dedicated service of INSERM is as follows: number of PIs, 5.8; number of publications, 31; percent within-team collaboration, 32; total number of citations, 265; number of publications with top1+10% citations, 5; number of publications with IF top 10%, 8; number of 1st or last author, 7. The team (2DR2, 2 MCU, 2 ITA) is formed by the merger of 2 pre-existing teams : 1) Pathological pain : neuroinflammation, tissue plasticity and new therapeutic targets (Dr Pohl) 2) Pain stress & autonomic regulation (Dr Villanueva). The group 1: The project aims to better understand the role of immune-related molecules (cytokines & chemokines) on neurone-glial interaction (at a spinal level) in a model of extracephalic pain (chronic constriction injury of the sciatic nerve : SN-CCI) or a model cephalic pain (lesion of the trigeminal nerve). The results obtained revealed that different pathophysiological mechanisms contribute to the development of cephalic versus extracephalic neuropathic pain. The group 2: The project focus on the control of pain by central structrures (thalamus,Cortex) in a model of extracephalic (spinal LTP) or cephalic (lesion of the trigeminal nerve) pain. It is shown that LTP-mediated mechanical hyperalgesia can be antagonized when stimulating the endogenous antinociceptive hypothalamic system (PVN stimulation or spinal oxytocin administration). In the context of cephalic pain, a top down influences onto interoceptive nociceptive inputs onto the trigeminal nerve is highlighted with BDNF as a central pronociceptive modulator of pain. The scientific quality of each group is deemed good although the number of papers is low, but with sometimes in highly visible journals (3x Journal of Neuroscience).

Assessment of the Team's academic reputation and appeal

Each PI has proved his ability to attrack student, postdoc, to raise funds, to established international collaboration (several projects with latine america). Each PI has been invited to several international meetings and organized several symposia and workshop. (even meetings). They participate to International Editorial Boards as Member (Archives of Oral Biology; Faculty F-1000, Anesthesiology & Pain Management), as Section Editor (European Journal of Pain) as Councilor (SFETD Executive Committee); Vice-Chair.

Assessment of the Team's interaction with the social, economic and cultural environment

Members of the team coordinates the program " Formation Inserm" on pain. In addition, the team has several contracts with industrial partners.

Assessment of the Team's organisation and life

Nothing specific to mention particulalrly given the size of the team (2 DR,1PU-PH, 2MCU, 2 technicians IR, 1PHD, 1M2).

Assessment of the Team's involvement in training through research

For Dr POHL's group, 4 students (3 HDR) ended successfully their PHD. For VILLUANEAVA's group (2 HDR plus a MCU-PH arrival in 2010) one went successfully to the end and one is beginning. Both PI have a teaching activity (IFSBM, Paris-Sud, Master, UPMC, ENS Ulm, ….). Both have organized symposia, participated to juries (PhD, HDR), to committees (AERES..). Three members of the team have teaching activity (1PU-PH & 1 MCU-PH 120 h/y, 1MC 192/years).

Assessment of the five-year plan and strategy

The project seeks to study at a cellular level the pathological plastic process associated with pain (JAK/STAT3 signal pathway, eNVU) and at a network level, the cognitive processing of pain signals by central structures (cortex, hypothalamus…). Even if the impact of stress will be scrutinized, the project wil benefit of being better intgrate into the CPN scope. The project appears too large considering the work force in the team.

Conclusion

- Strengths and opportunities:

The strengths of the team are: complementary expertise of the two PIs both in conceptual and technical terms; good publication rate (several JN) although not in generalist high rank journals (>10); ability to raise funds (865 kE); contact with pharmaceutical firms (133kE) (this should be however increased); international collaboration (USA, latine America); links with several universities (plus erasmus program) allowing recruitment of Master and PhD students.

- Weaknesses and threats:

The weaknesses of the team are: too many projects, a prioritization is required; the two "merging" teams never worked together; the written project lacks of identifying clearly the synergies between the two previous "teams" and the additive value of this fusion; the project is not presented in an holistic manner. As it is, each PI continues independently his own research and the interaction between the 2 groups is unclear. During their talk, the interaction between the two groups was however explicit. Scare internal collaboration, the team is isolated within the centre (no input in psychiatric research). And finally, there is a lack of clinical interaction.

- Recommendations:

The committee makes the following comments: the project appears too large considering the work force in the team; the team could hire more people at the postdoctoral level to alleviate this issue. The visibility and rate of publications could also be improved. The link to psychiatry disorders is unclear at this stage and could constitute a real additional strength for the future.

5 • Conduct of the visit

Visit dates:

Start: Monday 28th january 2013, at 9AM

End: Tuesday 29th january 2013, at 5PM

Visit site(s): CPN premises at Ste Anne Hospital, Paris

Institution: INSERM & Hopital Ste Anne

Address : 2 ter Rue d'Alesia, Paris 14eme

Conduct or programme of visit:

January 28, 2013

09h00-09h30	Committee member meeting
09h30-10h00	General presentation by the director
10h00-11h00	Team GORWOOD
11h00-11h40	Team JAY/KREBS
11h40-12h00	Coffee break
12h00-12h40	Team MAS
12h40-13h10	Team MAIER
13h10-14h30	Lunch (on site)
14h30-15h00	Team PIOLINO
15h00-15h40	Team DUTAR
15h40 16h10	Team DARMON
16h10-16h50	Team POHL/VILLANUEVA
16h50-17h10	Coffee break
17h10-18h00	Discussion with lab members and close door debriefing

January 29, 2013

09h00-09h30	Discussion with current director (Mr. Jacques EPELBAUM)
09h30-10h00	Phone-conference with potential «future » director
10h00-11h00	Platform presentations
11h00-11h30	Coffee break
11h30-12h00	Parallel discussions -Students/Postdocs -ITAs (technical personal) -Researchers
12h00-14h00	Lunch/meeting with official representatives (INSERM, Université Paris Descartes)
14h00-17h00	Closed door meeting – final report
17h00	End of the visit

Specific points to be mentioned: (unexpected events, etc.)

The visioconference with Pr LICINIO (Canberra, Australia) could not be performed because of technical problems in Canberra and was replaced by a telephone interview in which several members of the Committee (not only the Chairman) had the opportunity to talk to him.

6 • Statistics by field: SVE on 10/06/2013

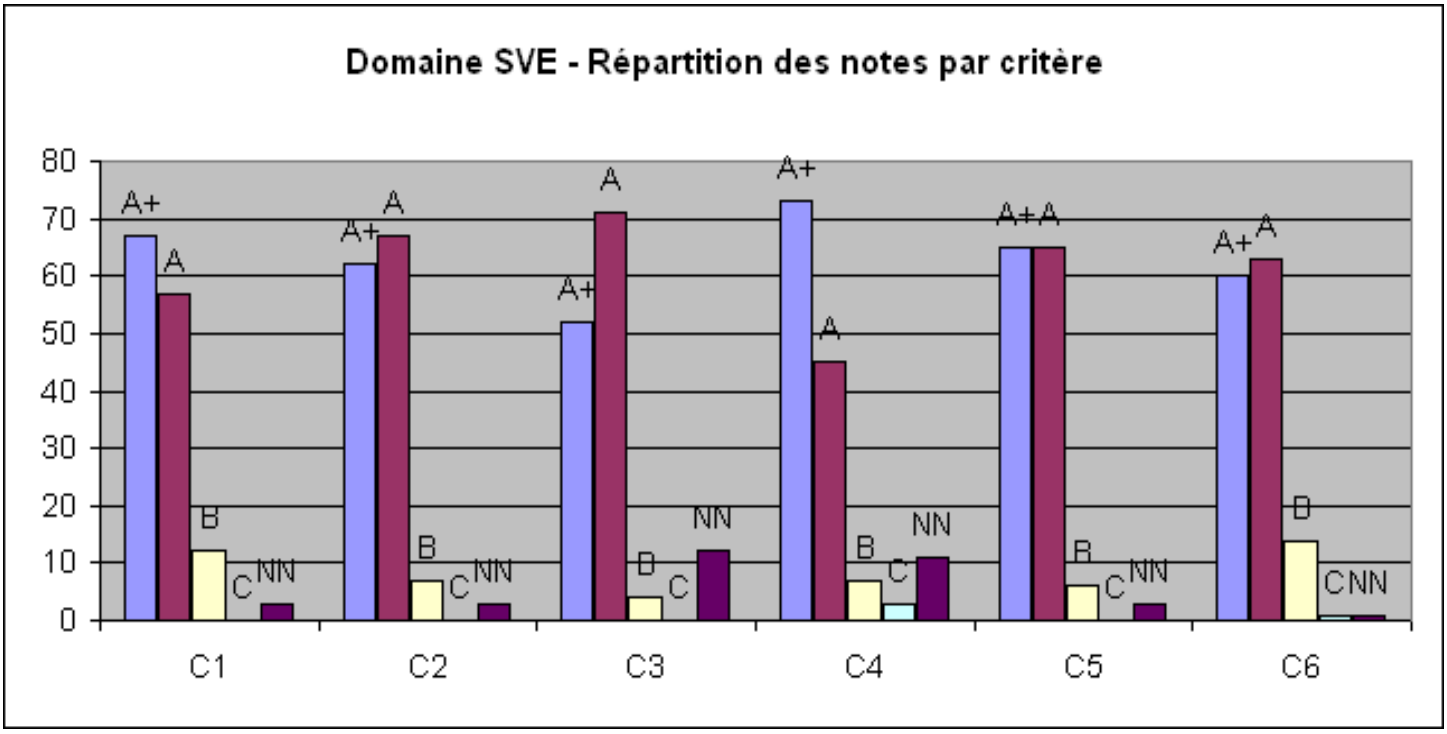
Grades

Critères	C1 Qualité scientifique et production	C2 Rayonnement et attractivité académiques	C3 Relations avec l'environnement social, économique et culturel	C4 Organisation et vie de l'entité	C5 Implication dans la formation par la recherche	C6 Stratégie et projet à cinq ans
A+	67	62	52	73	65	60
A	57	67	71	45	65	63
B	12	7	4	7	6	14
C	0	0	0	3	0	1
Non Noté	3	3	12	11	3	1

Percentages

Critères	C1 Qualité scientifique et production	C2 Rayonnement et attractivité académiques	C3 Relations avec l'environnement social, économique et culturel	C4 Organisation et vie de l'entité	C5 Implication dans la formation par la recherche	C6 Stratégie et projet à cinq ans
A+	48%	45%	37%	53%	47%	43%
A	41%	48%	51%	32%	47%	45%
B	9%	5%	3%	5%	4%	10%
C	0%	0%	0%	2%	0%	1%
Non Noté	2%	2%	9%	8%	2%	1%

Histogram



7 • Supervising bodies' general comments

UNIVERSITÉ PARIS DESCARTES

Vice Président du Conseil Scientifique

Paris le 23.04.2013

Vos ref : S2PUR140006467 – Centre de Psychiatrie et Neurosciences – 0751721N

Monsieur Pierre GLAUDES
Directeur de la section des unités de recherche
Agence d'Evaluation de la Recherche et de l'Enseignement Supérieur
20, rue Vivienne
75002 PARIS

Monsieur le Directeur

Je vous adresse mes remerciements pour la qualité du rapport d'évaluation fourni à l'issue de la visite du comité d'expertise concernant l'unité « Centre de Psychiatrie et Neurosciences »

Vous trouverez ci-joint les réponses du Directeur du Centre, Jacques EPELBAUM.
La restructuration de ce centre, qui va s'accompagner d'un changement de direction et d'un projet immobilier d'envergure permettant une amélioration significative tant qualitative que quantitative de ses capacités d'accueil est une priorité de l'Université et de l'INSERM pour le prochain contrat. Nous attendons de ces changements un impact très positif sur la visibilité du centre au niveau international dans la discipline.

Je vous prie d'agréer, Monsieur le Directeur, l'expression de ma considération distinguée.

Le Vice Président du Conseil Scientifique

Stefano Marullo, DM, DesSci

Université Paris Descartes, Vice-présidence du conseil scientifique, 12 rue de l'école de médecine, 75170 PARIS cedex 06
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Comments on AERES report on unit :
Centre de Psychiatrie et Neurosciences
Université Paris Descartes Inserm

1. Introduction

Management team.
The executive committee is composed of the managing committee (the Director assisted by 3 Deputy Directors and by an administrative Director), the team leaders and one elected representative of researchers, technicians and students, respectively.

Unit Workforce
According to the files provided to the Committee and a careful reexamination by each team (see team-by-team analysis), numbers as at 01/01/2014 are N3 29, N5 : 48 for a total of 140. Numbers of 2014-2018 project producers are N1 22, N3 3 N5 32 for a total of 90 and the percentage of producers is 64,29%.

2. Assessment of the unit

Strengths and opportunities.
We acknowledge the Committee's positive assessment regarding our patient recruitment capacity and large cohorts, as well as regarding the setting up and maintaining over the years of biobanks and, in the last five years, of common technological platforms. This encourages the CPN to continue in this direction for the next quinquennial period.

Weaknesses and threats
The committee sees the specificity of the CPN on traditionally split apart domains (e.g. stroke versus Psychiatry) as a main weakness. However, we believe that Psychiatry and Neurology have been separated for too long and that the whole history of neuroscience in the last ten years reflects the merging of the brain/mind concepts.
We would like to emphasize that the brain/mind merging has been effective for years and is gaining further momentum at the CPN. For instance, fMRI studies on memory and language have been completed, and some already published, involving psychiatry teams (Krebs team notably) in collaboration with psychology teams (Piolino team notably). With Piolino team joining the CPN, and TMS being installed as a new platform at the moment, more brain/mind merging type of studies have already started or are in the planning stage presently, involving not only healthy subjects but also early Alzheimer's and MCI patients in collaboration with the nearby Broca hospital. It is important to note in this respect that the CPN is by definition dedicated to translational research in brain disorders, and as such is not supposed to carry out large sale pure cognitive neuroscience programmes. Regarding the "split apart domains", note that apart from the integration of Piolino's team, the new Professorship of Neurology dedicated to behavioural neurology, to be filled from 1st October 2013 (appointee: Dr Marie Sarazin) was created specifically to fill this gap, and the research programmes already identified by the new Professor will deal with both vascular and degenerative brain diseases with psychiatric components such as vascular cognitive impairment, fronto-temporal dementia and Alzheimer's disease. The CPN is therefore fully aware of this gap, has worked towards filling it and is determined to continue along this line. For instance, the proposed integration of the Maier team would also bridge motor control across psychiatry and stroke (both programmes already effective).

Concerning, team diversity in term of structure and ambition, we believe that each team should have the entire liberty of organization within its constituency. We also believe that to perform translational research, a certain size is needed with people from different backgrounds (full time clinician, clinicians involved in research, researches involved in clinical protocols, full-time researchers, and technical an clinical staff). This may explain the size of some of the teams.

Concerning the retirement of the current Director, we concur with the Committee that a potential successor has been identified and the contract is still being negociated.

Complexity of the centre analysis
We completely agree with the committee concerning the complexity of the AERES dossier and the necessity of an historical perspective to really assess the trajectory of a living structure such as the CPN[1]. This complexity is not to be confused with a lack of ambitious scientific horizon. The challenge to create some conceptual and practical links between neuroscience and psychiatry is not the less to mention.
We also completely agree with CPN suffering from having its teams to work in poorly maintained buildings and premises. This unfortunate situation is due to the anticipation of the CPN move in an entirely refurbished building on the hospital premises in 2015 (12 M€ project). In the meantime, safety issues are taken very seriously by Inserm regional administration with a budget of 280k€/year and neither the local « Comité d'Hygiène, de Sécurité et des Conditions de Travail » (CHSCT) nor the one from « Ministère de l'Enseignement Supérieur et de la Recherche » did detect any specific biological hazard, so far.

3. Detailed assessments

Assessment of scientific quality and outputs
We acknowledge the Committee's opinion that the overall evaluation of such a large and heterogeneous structure as CPN is of limited relevance. The bibliometric analysis conducted by the (expert) service of INSERM is explicit and was made available to current and future leaders of the CPN as well as to members of our external scientific advisory board who help us for strategic decisions.

Assessment of the unit's academic reputation and appeal
We thank the Committee for stating that : « The number of scientists, neurologists and psychiatrists that CPN brings together constitute an impressive potential for generating new research lines, teaching students in these various[2] domains and supervising young researchers ».

Assessment of the unit's interaction with the social, economic and cultural environment
We concur with the committee in assessing our good contacts with the social, economic and cultural environment which still can be improved.

Assessment of the unit's organisation and life
We thank the Committee for their insight into the complex relationships and potential conflicts of interest which are likely to persist in a large ensemble such as the CPN. To quote Winston Churchill « It has been said that democracy is the worst form of government except all the others that have been tried ». Nevertheless, some decisions have to be made alone by the person in charge.

Assessment of the unit's involvement in training through research
We thank the Committee for the positive evaluation.

Assessment of the five-year plan and strategy
The timing of the AERES evaluation was not optimal for the CPN. One year later would have been more appropriate since the new Director would have been in post and would have presented his five-year plan and strategy.

[1] For instance, one research group joined the center early november and was not even mentioned in the files. Information about this group were provided on site during the visit. Several documents were provided to the committee on the days of the visit concerning the number of students and postdoctoral fellows and récent bibiliographical data to help them in their task of retrieval from AERES files.

[2] clinical and genetic epidemiology of addictions, schizophrenia and other developmental pathologies, as well as bipolar and obsessive-compulsive diseases, together with animal models and basic neuroscience and genetic research for some of these conditions, (ii) epidemiology, brain imaging and clinical research in stroke, (iii) retrograde and personal memory impairments in pathological ageing and in schizophrenia, (iv) synaptic transmission mechanisms and their implications in age-related pathologies especially Alzheimer's disease, (v) molecular approach to serotoninergic transmission and its links on depression symptoms and treatment

4. Team-by-team analysis

Team 1. Cellular and Molecular Pharmacology of Brain Receptors
Name of team leader: Ms. Michèle DARMON

Factual response:
The number of theses defended during the previous period is 7 if we cumulate those defended in the two preexisting teams, and not 1 as it is written in the table.

Comments of Team 1: Cellular and Molecular Pharmacology of Brain Receptors
Name of team leader: Ms. Michèle DARMON
We appreciate the AERES evaluation of our recently created team as having a "good level and the staff and scientific potential to reach an excellent level". The gathering of all members of the team in the same place has occurred only in October 2012 and explains the high number of existing projects, resulting from the recent fusion of the 2 preexisting teams. We believe that the scientific complementation between the members of the team will help to reach an excellent scientific level in order to complete all these projects. We agree with the AERES committee on the necessary reduction of the number of projects, that we hope to achieve after the ongoing programs have reached the publication level (1 to 2 years). We are confident that we will extend our fundraising during the next years, especially after the recent financing by the PRES in 2013 of our project TRAFICSTERIL (120 k€) selected by an international committee (30% success rate). We agree that our technical assistance is now limited, but it will increase with this recent grant, and we are confident that in the next years, with other grants, we will also extend our technical staff. Concerning our integration in the Center, the team has already some internal collaboration with other CPN teams: team 2 and team 3, but is also currently developing other collaborative projects.

Team 2. Neurobiology of physiological and pathological aging
Name of team leader: Mr. Patrick DUTAR

Factual response:
On the tables p. 13, the number for N2 is 7 in the three columns; N3 is 1 in the first two columns and for N5, 1 post doctoral fellow will be present in 2014 in the team. Therefore total numbers in the three columns are 18, 9 and 8, respectively.
Two doctoral students were present at 30/06/2012, 6 theses defended during the previous period, 9 postdoctoral students spent at least 12 months in the team, 3 HDRs were taken (CV, VT, JMB and a fourth JP is pending) which makes 7 qualified supervisors in the new team.

Comments of Team 2 Neurobiology of physiological and pathological aging
Name of team leader: Mr. Patrick DUTAR
We thank the AERES committee for positively evaluating our team.
We acknowledge their main concern on the present low number of PhD students and post-docs in 2013 which is due to the reorganization of the team. During the last 5 years, 10 post-Doctoral fellows, 10 PhD and 16 M2 students worked in our laboratory. Two students finished their thesis or contracts end of 2012-early 2013 and the new ones are not yet hired. We are currently applying for a PhD grant (Bourse Cifre) for one student and a Paris Descartes University contract for another student. The latter, as part of a European contract, is an Erasmus PhD student who arrived in October 2012 and was not mentioned in the AERES files. A third M2 student is currently debating whether she will stay in the laboratory for a PhD thesis beginning next September. Finally, we have recently applied for three grants (France-Alzheimer, LECMA and ANR-PRTS) to increase the number of post-docs to a figure more adapted to the size of our team.

Team 3. Clinical and genetic analysis of addictive and psychiatric disorders
Name of team leader: Mr. Philip GORWOOD

Factual response:
Regarding the first table p16, one engineer (PZ) is a project producer and the total number is 34.
Regarding the second table, the documents (S2-1-3-Results.xls) from Gorwood, Lanfumey & Hamon teams' combined a total of 13 defended thesis between 2007-2012, and an additionnal number of 3 Pharmacology

thesis. To date, there are also 9 PhD students. For the HDR, 3 have been defended (Mongeau R, Purper-Ouakil D & Ramoz N).

Comments of Team 3 Clinical and genetic analysis of addictive and psychiatric disorders
Name of team leader: Mr. Philip GORWOOD
Assessment of scientific quality and outputs
We acknowledge the assessment of the number of publications as "impressive". Concerning the breakdown by researchers involved, 30 additional articles were published in late 2012 and provided to the Committee among which 3 Molecular Psychiatry and 1 Neuropsychopharmacology.

Weaknesses and threats: *The weaknesses are: team size too big to get managed in an efficient way; having large samples requires millions of € for getting them on the chip or sequencing; this is a great problem despite the fact that the group has excellent funding; the overall project is diverse and heterogenous.*

We acknowledge the fact that out team is a large one, but this organization was proposed following the previous advices that we received from the AERES four years ago and, especially facilitating bridges between basic and clinical sciences. As this organization is a proposition, already approved by our external Scientific Advisory Board but not yet fully active, it is not a surprise that we appear a bit too diverse and heterogeneous. The assessment that we were expecting was more on the rational of our potential. As the different teams, now gathered as Team 3, already had some collaborative works, and were all in favor of this new organization, we think that this guarantees a smooth and efficient organization.The team size is indeed a challenge. However, the efficient way to manage is in the hands of the different group leaders within the team. Each one manages 4 to 8 persons. Thus we think that the challenge will turn out a success.

To succeed in the next step of analyses on the screening of large cohorts, three approaches are conducted in parallel, (1) participation to large national & international consortiums, like GCAN for GWAS of AN patients, (2) be supported by national & international programs to access genotyping or sequencing facilities like CNS & CNG, and (3) be funded by academic and private grants to subcontract work of GWAS, Exome, Epigenomics. It is difficult to congratulate us for the importance of obtained grants on the one hand, and to criticize that even more ambitious researches would be possible if larger grants were to be obtained. A good example is our prospective cohort of 800 patients with alcohol dependence for which we collected a huge amount of clinical, phenotypical and biological material of high quality (for 400K€). The present funding is not compatible with a GWAS study on this sample. But when this databank will be completed, the obtention of other grants will largely be facilitated by its description.

Recommendations: *Together with the newly appointed director and its overall view of the CPN, a more stringent formulation of the team goals will further strengthen its great potential.*
Discussing with the future head of the CPN will focus the team goals and increase their probability of success. The present candidate as a director has a large expertise in genetics of psychiatric disorder, mainly mood disorders including obesity with specific interest in leptin and ghrelin, so we will received him in a really open-minded state, ready to follow his suggestions.

Team4. Pathophysiology of Psychiatric Diseases
Name of team leader: Ms. Therese JAY & Ms. Marie-Odile KREBS

Factual response:
Please take note of the following corrections of the factual errors (in bold) that should be added in the table at the bottom of page 19.
Eight postdoctoral students have spent at least 12 months in the team at 30/06/2012. **Four** Research Supervisor Qualifications (HDR) have been taken from 2007.
Seven qualified supervisors (with an HDR) or similar positions will be present at **01/01/2014** (second column)

Comments of Team 4 Pathophysiology of Psychiatric Diseases
Name of team leader: Ms. Therese JAY & Ms. Marie-Odile KREBS
We are very grateful of the overall very positive appreciation of our team and would like to clarify some points that have been pointed as weaknesses and threats.
Some 'heterogeneity' has been perceived between the domains of research within the team. This is not our perception. The team's project has been organized in three topics or axis, in which the expertise of the PIs are shared (all PIs are involved in at least two topics) and both animal and human models are combined. This is

indeed an overall strategy of our team to cross examine animal models and human with schizophrenia, anxiety and depression by translating issues from bed to bench and from bench to bed. In the second topic, the DBS project will bridge the gap between our current and previous studies of the dysfunctional response to stress at the cellular, regional and system levels and the understanding of resistant depression in human. Specifically, the DBS project in animals, will gain insight in the mechanisms and dynamics of 'therapeutic' neuromodulation of limbic networks in two rat strains showing a different sensitivity to stress. Incidentally, we could have moved the DBS therapy project to the third topic 'Innovative therapeutics', further indicating the interconnections between the 'topics' or 'axis' of the team's project. In the same line, the third topic is in direct continuity with the two previous ones, including the project of characterizing the cognitive and psychopathological effects of new compounds, which takes its origin in the expertise of the PIs. If some specific approaches might lead to the development of an independent team in the future, we believe that they still require some maturation. Nevertheless, as suggested, we will keep this in mind in our future projects to avoid heterogeneity.
Regarding the apparent lack of connections with the team working in addiction for genetic approaches, it must be stressed that we are actually not studying addiction: in our projects, cannabis is studied as an environmental factor disrupting development and maturation and precipitating psychosis. In addition, there are actually ongoing collaborations in the genetics of schizophrenia (papers into revision related to a previous ANR project).
We agree that other nearby excellent research groups are working in Psychiatry and connections do exist. For instance, joint participation to collaborative studies or networks including those addressing DBS topics (e.g. STHYM, STOC) where methodology and theoretical background are discussed and shared). In addition, our team is participating to the ENP (Ecole de Neurosciences de Paris) or to the INC (Institut des Neurosciences et de la Cognition) in Paris Descartes. The existence of large independent collections of patients and blood samples can be useful for possible replication studies. Nevertheless, as pointed in the comment, our objectives are more complementary than competitive with those nearby teams: for instance the assessments of patients in our cohort are enriched in neurodevelopmental assessments (clinical, cognitive, brain imaging etc) in line with our specific scientific programs.
As underlined, (this comment goes probably beyond the team 4), it is obvious that the tremendous challenge and needs of research in Psychiatry justify two or even more centers devoted to research in Psychiatry within the 'Ile-de-France' and scientific interactions will have to be developed. Regarding our team, as recommended**,** our overall strategy will be to further adapt to the existing local opportunities both within the CPN, with the foreseeable changes induced by the future director of the CPN, and beyond (Paris area and abroad).
We would like to thank the AERES committee for their positive evaluation of the team. Their useful suggestions will be taken into account.

Team 5. Manual dexterity in health and disease
Name of team leader: Mr. Marc MAIER

Factual response:
Please update Table 'Team workforce' p.24 as such:
Number as at 01/01/2014 N5 other EPST or EPIC researchers: 2 instead of 3 and Total: 7 instead of 8
2014-2018 Number of project producer N3 other permanent staff (without research duties): 1and N5 other EPST or EPIC researchers: 2 instead of 3.

Comments of Team 5 Manual dexterity in health and disease
Name of team leader: Mr. Marc MAIER
We fully agree with the committee's conclusion p. 27.

1) *Strength*: we appreciate that the committee considers the proposed move to the CPN as having "clear mutual benefits for the team and other CPN teams" and that this move represents "an excellent opportunity to broaden the approaches (of the team) to scientific and medical issues".
2) *Weaknesses*: we are also aware that the team requires strengthening in the domain of human physiology (TMS etc). We are actively seeking an appointment, either via Inserm or the University.
3) *Recommendations*: we fully agree that our effort should aim at "potential applications offered by the CPN" in order to boost "translational research outputs and publications in high visibility journals". This indeed is our goal.

Team 6. Stroke, Prognosis and Imaging INSERM U894
Name of team leader: Mr. Jean-Louis MAS

Factual response: nothing to add

Comments of Team 6 Stroke, Prognosis and Imaging INSERM U894
Name of team leader: Mr. Jean-Louis MAS
l Strengths and opportunities*:*
Outstanding clinical research team, conducting large clinical trials sponsored by public funds, with access to a large patient cohort (large stroke center), with an impressive publication record, very well represented in international specialised societies, with numerous participations in European scientific boards. The arrival of two new teams opens new possibilities for research. The planned renovation of new building in proximity with large surfaces dedicated to research is an addtionnal strength.

Response: We thank the Committee for the very positive comments.

l Weaknesses and threats:
As pointed out in previous evaluations, a stronger connection with preclinical research would be an additional strength and is recommended. A connection with the excellent preclinical team from GIP Cyceron in Caen is planned. An in-house experimental stroke lab would be even better to promote interactions between bench and bed side and thereby trigger innovating ideas and projects.

Response: As clearly stated in the AERES application, we are fully aware of the necessary stronger connection with preclinical stroke research. This was already a major recommendation at the previous AERES evaluation, and had been raised by the first SAB in 2006 and reiterated by the second SAB in late 2011. As explained, it was our judgment that in order to interact efficiently with a preclinical team, the latter needed to be on site, particularly given the very busy schedule of the clinical academics in the Dept of Neurology precluding frequent external meetings. This view was seconded by both the Neuroscience ITMO and Paris Descartes University, and in consultation with them we advertised for a potential position in early 2011 and had many applications. The idea was that if a good candidate could be identified, this person would be appointed as post-doctoral scientist or MCU (senior lecturer) and would at least initially work in close collaboration with the Vivien group in Caen. Several candidates were shortlisted and invited to give seminars at the CPN, but eventually none of the good ones was interested in the job. We then turned to both the Vivien team and the Experimental Stroke grroup at the Paris Descartes Faculty of Pharmacy asking them to try and identify a young post-doctoral scientist who might be interested but again in vain. In the meantime we were successful in attracting in the Mas Team the group of Jean Rossier, Alan Urban and Gabriel Montaldo, who have expertise in in vivo neuroscience experiments, neurovascular coupling and in vivo vascular and neuronal imaging, and who were interested in developing pre-clinical stroke research. This group integrated our team on 1st November 2012, after submission of the AERES application, and their methods were briefly presented during the AERES site visit. We have already designed two projects involving clinically-relevant projects in rodents, and have organised the training of the Rossier group into the various rodent stroke models through JC Baron group in Cambridge which has the necessary expertise. We expect to start the actual stroke studies in September 2013. Our hope is that by having on site the infrastructure and platform to do such studies, we will in due course attract on site an experienced young preclinical stroke scientist to integrate the Team. In parallel, we will work towards developing collaborations with the Paris Descartes Faculty of Pharmacy group for specific types of projects.

Surprisingly, there are few post-docs in this highly productive team with top-ranking publications. Availability of post-doc positions would be advisable to attract foreign clinicians or scientists and promote the visibility of the team.

Response: We agree with the Committee that it would be nice to have more post-doctoral scientists working in the Team, however post-doctoral positions are not customary in the clinical area since clinicians hold clinical positions as a rule immediately after completing their training. Having foreign post-docs with inadequate hold of the French language would preclude any clinical type of research involving patient/family contacts. However, we expect that via the just created "*Departement Hospitalo-Universitaire*" (DHU) with Lariboisière Hospital Dept of Neurology, which must involve the set up of an European Master in Stroke Reserarch (presently in the planning stage) there will be opportunities for attracting foreign neurologists to spend time in the Team. The other major opportunity in this respect is the development of preclinical stroke research within the Team (see point above) which being in the basic sciences should be ideal for attracting young post-docs. As a matter of fact, we have already been contacted by numerous potential candidates. We are also determined to attract more PhD students in both the clinical and soon the preclinical fields, and have had good success recently with the funding of Master and PhD students by private foundations.

l Recommendations:
The committee is impressed by the quality of this team. The possibility to attract an experimental stroke lab should be explored although it may be very difficult to attract well integrated stroke research teams such as the ones in Caen and Nice. However, it may be feasible to closely interact/attract some in University Paris Descartes. Creating positions for post-docs, and perhaps also for additional PhD students, should allow to attract excellent clinical scientists from abroad and further improve the visibility of the team and facilitate scientific interactions with other institutions.

Response: We agree with both points and are working hard towards achieving them, as detailed above.

Team 7. Memory and Cognition

Name of team leader: Ms. Pascale PIOLINO

Factual response:
First, we would like to correct some aspects of the workforce Table. We are 6 permanent members (3 PR, 3 MC) with 50% of their time devoted to research, but two of us have a discharge of 75% of teaching; in the other permanent staff (1 IE, 1 TE, 1 adm), the engineer is primarily involved in our present and future research program since he is in charge of our virtual reality technical development and as such a co-author of several articles and partner of research grants, many of them directly connected with the CPN (e.g., "Chaire junior Paris Descartes" VR-TMS, PlaniR and DIM 2012 projects). Lastly, in the 2007-2012 period, one of us took her HDR.

Comments of Team 7 Memory and Cognition
Name of team leader: Ms. Pascale PIOLINO
We acknowledge the Committee's positive assessment regarding the interest of our research program and future integration in the CPN.
Regarding the specific comments of the committee about the five-year plan and strategy, we would firstly like to address their issue about the large spectrum of our studies. We concentrate our efforts on novel assessments of memory phenomenon in daily life to develop new and more sensible strategies of cognitive assessments and therapeutics (e.g., via virtual reality, and studying memory processes in a more ecological context). In fact, the investigation of episodic/autobiographical memory (i.e., memory that is self-relevant) is of major interest considering the fundamental theoretical and clinical challenges for cognitive neuroscience and clinical domains. Due to its complexity, this kind of memory is inextricably linked to several other cognitive processes such as spatial cognition, sensorimotor processing, emotional and motivational processes that are at the core of learning abilities. These aspects are potentially new targets of clinical studies in early detection and remediation of neurological and psychiatric diseases. Therefore, we think that developments of projects on spatial cognition, learning factors, emotion, and embodiment are strictly relevant with the main topic of our team (self-memory and self-related cognitive processes). Some developments are new, but they benefit from previous solid backgrounds in the team, and the recruitment of two new assistant professors. Moreover, these fields of research are at the core of the interests of teams of CPN (e.g., Jay/Krebs; Mas including Sarazin's group, Maier). We have already initiated new projects on these specific topics within the CPN. We have therefore already experienced the strict clinical procedure to carry out clinical studies in the CPN (CPP Nemauvi, Transmen, RV-TMS). This already validates the interaction of all the team members in the CPN and their interactions within the team. We will benefit in 2015 from the new CPN building in which our team could be hosted in complete. Thus all the members could be present on site. Moreover, the presence of the RV-TMS platform in the Clinical Research Centre will greatly enhance the potential of translational research involving all the team. Of note, we think that the second location of the team at the Institute of Psychology should be viewed as strength instead of a weakness. Indeed, the team and therefore the CPN will benefit to a large pool of students potentially interested by participating in our studies. In conclusion, we are greatly interested to improve our collaborations within the CPN, and we think that these collaborations will contribute to improve the visibility of our publications and the team national and international attractivity.

Team 8. Pain, Neuroinflammation and stress

Name of team leader: Mr. Michel POHL & Mr Luis VILLANUEVA

Factual response: No comments

Comments of Team 8. Pain, Neuroinflammation and stress
Name of team leader: Mr. Michel POHL & Mr Luis VILLANUEVA
We thank the visiting Committee for their comments and recommendations. Below is our point-by-point response to the points raised:

1. Assessment of scientific quality and outputs
The number of papers published during the last years by the Villanueva team is still low simply because after returning to Paris, he had to wait another 2 years to get his devices back from his former laboratory based in Clermont-Ferrand. Thereafter, the group was able to set up their new laboratory at the Salpétrière site. However, we effectively restarted our research activities in September 2008 only, with 2 permanent members (LV and L Bourgeais) and 2 short-term fellows gained from international collaborations. Later in 2010, two other permanent members (CD Arreto; C Robert) joined the team. Nevertheless, in spite of our recent creation, the small size of our team and our moving from the Salpétrière to the Center of Psychiatry and Neurosciences (CPN), during we have been able to produce 3 original full papers in the last 4 years, all in highly visible journals including Pain (2009), J Neuroscience (2010) and J Pain (2012). Having acquired now a stable and powerful configuration, the rate and visibility of publications of the team should considerably improved in the near future.
Moreover, we would like to stress that Michel Pohl's team has joined the CPN only a few months ago, in November 2012. Despite his recent arrival, thanks to a quick functional integration of the team in the CPN, a first collaborative program, based on our common expertise in inflammatory markers and pathways is being launched with the Mas team, focusing on inflammatory biomarkers identification associated with cerebrovascular aneurysms. This project will be managed in our group by a clinician applying for an Inserm « *Poste d'accueil* ».

2. Assessment of the 5 years plan & strategy/Weakness and threats/Recommendations
Both groups of our new team started to work on the design of the new project when still at the Salpetrière site. We decided to not start working together until arriving to the CPN, since the Villanueva group had to finish creating their team (see point 1) and starting quickly the scientific production necessary for supporting our new project.
However, we agree that, considering the low number of full-time researchers, our project is probably too ambitious and oversized. In full agreement with the Committee's advice, we propose to reduce our research lines and prioritize a smaller project, on the basis of two main aims: i) developing multidisciplinary studies of pain mechanisms associated with neuropsychiatric comorbidities, and ii) cellular/molecular studies of neurovascular mechanisms implicated in pain and stroke. Both aims are in complete agreement with the general objectives of the CPN.

As stated in the Committee's report, the interaction of both groups within our team was clearer during the oral presentation, as compared to our written project. Unfortunately, several Committee members did not receive the text of our project before the site visit. We will thus continue our fusion process progressively, as illustrated by two main examples:

A project termed "Central network dysfunction as neural substrates of headache disorders" involving both components of our team was recently submitted as a grant to the ANR. This project aims to identify, in rodent models, the main Central Nervous System networks and endogenous maladaptive mechanisms that are involved in the pathophysiology of migraine and trigeminal autonomic cephalalgias. We will evaluate how the functional anatomy, pathophysiology and pharmacology of hypothalamic and corticofugal networks in headache-relevant paradigms, may alter the excitability of the trigeminovascular system in rat models of headache. Our previous (J Neurosci 2010) article and ongoing studies provide a set of promising central maladaptive mechanisms as contributors/biomarkers of headache modulation/triggers that will be simultaneously used for detailed, cell-specific functional analyses. Given that glial, inflammatory markers and neurovascular units are markedly affected during headaches, consequences on activation of glial and vascular endothelial cells transduction pathways and their impact on production and release of various signaling molecules involved in the crosstalk between these different cell categories will also be studied. This project will be driven by all our team members, including a co-supervised PhD student (Pia Vayssière) and part of the funding will be devoted to a post-doctoral position.

We are also aware of the necessity to hire post-doctoral fellows. For this purpose, we obtained recently a strong support from the Scientific Committee of the Faculties of Dentistry of Paris 5-7 Universities. In the context of the fusion of these UFR, this Committee supports our application for a post-doctoral position funded by Paris 7, starting in 2014. We have chosen a candidate that has both clinical (DDS) and scientific (PhD in Neurosciences) experience for working on a common project of the team as a whole. We will set up a new rodent model useful for combined behavioral and electrophysiological studies of the interaction of pain/stress/biological rhythms.

Our team is neither isolated within the Center nor without psychiatric input. As shown below, in addition to the common project with the Mas team, this issue is being surely, progressively and successfully resolved by establishing internal collaborations within the CPN, on the basis of complementary skills.
Accordingly, we already started in 2011 a strong and fruitful internal collaboration with the Jay/Krebs team. We investigated in rat models the role of acute stress on top-down, paraventricular hypothalamic regulation of trigeminovascular processing mechanisms involved in headache pain. We demonstrated that acute stress elicits maladaptive mechanisms via a reduction of $GABA_A$-inhibition impinging on parvocellular PVN neurons, probably via down-regulation of KCC2 transporter. Importantly, such homeostatic disturbances could constitute a more universal maladaptive mechanism involved also in other kinds of so-called dysfunctional pains, which are among the most important pain syndromes associated with psychiatric comorbidities. This work was submitted for publication to J Neuroscience and the revised version of this paper was recently resubmitted, after positive peer reviews (http://jneurosci.msubmit.net/cgi-bin/main.plex?el=A6DC5Yqe3B2nPY2F2A9d3FalwAi1H9Nf4cjOiNgwZ>).
A second collaboration with the Jay/Krebs team is supported by an internal grant from the CPN. Our main aim is to set up new tools for combined functional neuroanatomical and behavioral studies with optogenetic tools. We propose a combined research program that takes advantage of the large, complementary experience of both teams in the study of endogenous brain mechanisms of stress and pain processing in rats. Our pilot project will investigate the interaction of stress and pain on hippocampal-prefrontal cortex (PFC)-periaqueductal gray (PAG) networks.

Finally, we would like to point out that our fusion and the building of this new team provides a unique research group in the Ile-de-France region. In the future, thanks to the clinical knowledge and expertise of several members of our team (Y. Boucher is managing a PHRC, OPIODYN grant), we aim to bring together basic researchers and clinicians into combined studies devoted to research on pain and associated psychiatric comorbidities.