

HCERES

High Council for the Evaluation of Research
and Higher Education

Research units

HCERES report on research unit:

Cerebral Imaging and Neurological Handicaps

ICHN

Under the supervision of the following
institutions and research bodies:

Université Toulouse 3 - Paul Sabatier - UPS

Institut National de la Santé Et de la Recherche

Médicale - INSERM

Evaluation report

This report is the result of the evaluation by the experts committee, the composition of which is specified below. The assessments contained herein are the expression of an independent and collegial deliberation of the committee.

Unit name:	Imagerie Cérébrale et Handicaps Neurologiques
Unit acronym:	ICHN
Label requested:	U
Present no.:	825
Name of Director (2014-2015):	Mr Pierre CELSIS
Name of Project Leader (2016-2020):	Mr Pierre PAYOUX

Expert committee members

Chair:	Ms Fabienne COLLETTE, Université de Liège, Belgique
Experts:	Mr Damien GALANAUD, La Pitié Salpêtrière, Paris (representative of the CCS Inserm) Mr Olivier GODEFROY, Hôpital Roger Salangro, Lille Mr Olivier MUNDLER, Hôpital de la Timone, Aix-Marseille Université (representative of the CNU)

Scientific delegate representing the HCERES:

Mr Jacques NOËL
Ms Céline SOUCHAY

Representatives of the unit's supervising institutions and bodies:

Ms Armelle BARELLI, Inserm
Ms Marie-Josèphe LEROY-ZAMIA, Inserm
Jean-Michel ROQUEJOFFRE (représentative of the Doctoral School ED n° 475 MITT "Mathématiques Informatique Télécommunications de Toulouse")
Mr Alexis VALENTIN, Université Paul Sabatier
Ms Chantal ZAOUCHE (représentative of the Doctoral School ED n° 326 CLESCO "Comportement, Langage, Education, Socialisation, Cognition")

1 • Introduction

History and geographical location of the unit

The unit was open in the early 1980s, and since has been continued through the uninterrupted succession of three Inserm/Université Toulouse 3 Paul Sabatier (UPS) research units (U 230, U 455 and U 825). The unit is located at the Purpan university (Toulouse) and has a long research tradition on the main central nervous system diseases, using neurological, neuropsychological, neuropharmacological and neurosurgical investigations coupled with neuroimaging explorations and brain stimulation/rehabilitation techniques. The research programs of the unit are centered on neurological diseases and handicaps, in particular those occurring in the aging context (Alzheimer's and Parkinson's diseases, stroke and other pathologies of the aging brain). In 2011, the unit moved to a new pavillon, pavillon Baudot at the Purpan hospital, with more space available. A full-time research 3T MRI platform operated under the responsibility of the unit was installed. This unit continued to progress during the reference period on its research topics, both at a methodological and theoretical level, and can be considered as an expert in these domains. The unit was composed of three teams in the previous period. Two of them were closely interconnected, and will be grouped together in the next reference period (under the label "DEVIN") while a new "iDREAM" team will be in direct continuation of the former team 3 "Therapeutic innovations in cerebrovascular disease". The objective of team 1 "Clinical and cognitive neuroimaging" was to develop neuroimaging tools that can be used in clinical and cognitive brain research and, ultimately, in clinical practice. The aim of team 2 "Language, memory and action in neurological diseases" was to improve diagnosis and treatment of brain diseases affecting language, memory and action systems, but also to address the cognitive functioning of specific components of these systems in the normal human brain. Team 3 "Therapeutic innovations in cerebrovascular disease" project aimed at developing an experimental approach to therapeutic strategies likely to be transferable to clinical studies of advanced treatments of ischemic, hemorrhagic or traumatic brain lesions.

Management team

The unit was directed by Mr Pierre CELSIS, DR1 Inserm, also responsible of the team 1. Mr Jean-François DEMONET, DR1 Inserm, was responsible of the team 2, but left in 2011. Ms Isabelle LOUBINOX, DR2 Inserm, was responsible of the team 3. For 2016-2020, Mr Pierre PAYOUX, PUPH UPS, will be responsible of the unit, reorganised in two team (DEVIN, under the responsibility of Mr Patrice PÉLAN, CR1 Inserm, and iDREAM, under the responsibility of Ms Isabelle LOUBINOX). The layout of the unit facilitates interactions and collaborations between researchers, as can be seen in common publications. Moreover, interactions between clinicians and researchers are frequent and lead to fruitful research projects. The unit can be considered as really multidisciplinary and fostering the exchange of information between researchers of various specializations.

HCERES nomenclature

SVE: SVE1 "Biologie, Santé"; LS7 "Epidémiologie, santé publique, recherche clinique, technologies biomédicales"

Unit workforce

Unit workforce	Number as at 30/06/2014	Number as at 01/01/2016
N1: Permanent professors and similar positions	23	29
N2: Permanent researchers from Institutions and similar positions	4	2
N3: Other permanent staff (without research duties)	14	23
N4: Other professors (Emeritus Professor, on-contract Professor, etc.)		
N5: Other researchers (Emeritus Research Director, Postdoctoral students, visitors, etc.)	1	
N6: Other contractual staff (without research duties)		
TOTAL N1 to N6	42	54

Unit workforce	Number as at 30/06/2014	Number as at 01/01/2016
Doctoral students	20	
Theses defended	28	
Postdoctoral students having spent at least 12 months in the unit	1	
Number of Research Supervisor Qualifications (HDR) taken	3	
Qualified research supervisors (with an HDR) or similar positions	24	

2 • Overall assessment of the unit

Global assessment of the unit

Pluri and interdisciplinarity is a characteristic of the unit that must be emphasized: the group has long been bringing together specialists of various disciplines, in medicine, applied mathematics, signal processing and image analysis.

The main lines of the research effort are to develop imaging markers of brain macro and micro structures, of brain dysfunction and therapeutic efficiency (team 1); to better characterize brain anatomic and functional correlates of developmental language disorders and post-stroke aphasia, of pain and behavioral symptoms in Parkinson's disease, of cortical reorganization related to memory impairment in Alzheimer's disease and of language, orthographic production and writing processes in normal subjects and patients (team 2); to evaluate the impact of drug treatment, rehabilitation programs and brain direct stimulation in stroke recovery, and the feasibility and impact of combining stem cells graft and nanotechnology in post-stroke motor recovery in animal models (team 3). So, the unit elaborates and develops specific tools to improve clinical practice. The scientific production of the unit as a whole is very high with 349 original publications in peer-reviewed journals, and publications in high-level journals occur frequently (Lancet Neurology, Brain, Annals of Neurology). The unit benefits from a high-level technological platform dedicated

to research, whose the utility is reinforced by constant interactions with clinical staffs. The unit is organised in an optimal way, that favor efficient development of research programs. Importantly, the departure of the leader of the team 2 “Language, memory and action in neurological diseases” in 2011 did not impede deeply the scientific production of the team. The unit is highly involved in teaching and training, and also in diffusion of scientific information to large audiences. The three teams of the unit have proved their capacity to find the financial support to attain their scientific objectives.

Strengths and opportunities in relation to the context

The main strength of the Unit is to build on in parallel methodological developments, more particularly in brain imaging, and cognitive and clinical researchs in neuropsychology and cognitive neurosciences. In that context, the relationships established since years between the Unit and clinicians from the Neurology department of the Toulouse University Hospital offers unique opportunities for recruiting carefully selected patients for the research programs. Generally speaking, the unit is well integrated in a clinical settings and develops major thematics in the health domain. The acces to neuroimaging and electrophysiological facilities full-time dedicated to research is also an unique opportunity to the efficient realization of the neuroimaging research projects. Otherwise, the multidisciplinary nature of the research is an incontestable strong point of the unit that brings together specialists from many disciplines: clinical and cognitive neurosciences, medical imaging, as well as specialists in the methodologies and techniques that support these research lines. A wide range of competences is thus on hand within the unit to enable it to carry through the project. The multidisciplinary of the members of the team enables it to rapidly set up effective cooperation with specialists when the project requires specific knowledge or know-how. Importantly, there is large cohesion between the members of the unit, and the directors have a clear overall view of the research objectives and how to develop the unit expertise in the various domains investigated. In that context, it must be stressed the optimal and thoughtful way by which the three teams were re-organised in two for the next five-year period. The moving of the entire unit, by the mid-2011, to the new office space in the newly renovated pavillon Baudot at CHU Purpan, the opening of the 3T full-research MRI facility and the opening in 2013 of the L2 laboratory are undoubtedly key events that will increase the scientific production of the unit during the next period. Moreover, the proximity of the CERCO Unit in the same building naturally leads to increase the collaboration projects between the two labs. The unit has a great attractivity for master and PhD students. The pluridisciplinarity of the team is also evidenced by their involvement in three doctoral schools (ED n°323 GEET “Génie Électrique, Électronique, Télécommunications”, ED n°326 CLESCO “Comportement, Langage, Éducation, Socialisation, Cognition” and ED n°475 MITT “Mathématiques Informatique Télécommunications de Toulouse”). The unit trains a large number of PhD students who actively contribute to the research activity. The PhD students finalize their thesis in 3-4 years, with several scientific publications most of the time, that certify the quality of the supervision. The professional insertion of these students after their thesis is also very good. Finally, the scientific production of the unit is important, and of high quality. In that context, the experts committee must emphasize the quality of the scientific presentations during the visit.

Weaknesses and threats related to the context

The methodological and scientific developpement proposed by the unit are very ambitious by reference to the actual human resources. The departure of Mr Jean-François DEMONET could slightly impact on the scientific production of the Devin team more specifically dedicated to neuropsychological questions. However, the team is aware of this threat and will pay attention to continue the development of these questions in the context of the multimodal neuroimaging studies performed. Two related other weaknesses are (1) the weak recruitment of high-level foreign post-docs that could improve “out-of-the-lab” recruitment of talented young researchers on permanent position in the unit, and (2) the retirement in the next years of several permanent members of the team (two researchers and two research ingeneers), for which no replacements were planned. Consequently, the projects proposed by the unit for the next five years could suffer from a lack of human ressources to help for supervision, administration and coordination tasks.

Recommendations

The experts committee recommand to the directors to pursue the development of an active policy to recruit more high-level post-doc staff from other countries. More precisely, the contacts initiated with Stanford University and the Fondazione Santa Lucia at Rome must be reinforced. This will lead indirectly to increase the international visibility of the unit. It also seems essential to pursue the development of the preclinical technological platform, to optimize the use of the cyclotron platform and to update the IRM equipment. In that context, the grouping of all technological tools (humans and non-humans) on a same site will facilitate data acquisition by the unit. To keep the

high level of scientific work, it will also be necessary to ensure the continued existence of human resources (both in the scientific, technical and administrative staff). To note that the current lack of administrative staff could be compensated by a supplementary half-time secretary in 2015. Finally, the unit must pay attention to the risk of dividing its attention and resources too broadly between the various research thematics proposed in the five-years project, and to assure an optimal follow-up these research projects.

3 • Detailed assessments

Assessment of scientific quality and outputs

The unit has a sustained scientific production, well-recognized at the international level. The unit develops a research program centered on the more frequent neurological pathologies, in a clinical and cognitive perspective. This approach is based on methodological development aiming to evidence biomarkers, in order to improve diagnostic and therapeutics of various population of patients. The complementarity of the three teams (grouped into two for the next period) in their scientific approaches must be emphasized and leads to excellent work. In the last four years, around 350 articles (50 in common between DEVIN and iDREAM) were published in international high level journals covering the fields of neurology (i.e., Brain, Neurology), neuroimaging (i.e., Neuroimage, Human Brain Mapping), neuropsychology (i.e., Cortex), medicine (i.e., Lancet Neurology) or biology (i.e., Biomaterials). Around half of these articles were co-authored as first or last authors by one member of the unit. A software licensing for a program allowing the accurate measurement of cortical thickness from 3D-T1 MR images has been entrusted to Inserm - Transfert in 2010 but no license transfer has been signed to date. Team 1 participates to the multi-disciplinary research network IRON that aims at developing new pharmaceuticals for molecular imaging and diagnosis in oncology and neurology, as well as new therapeutic approaches in molecular radiotherapy.

The team is also involved in research effort to promote personalized medicine. Team 3 developed a treatment based on fluoxetine, for patients with ischemic stroke with moderate to severe motor deficits. There also exists a project of creation of an European Associated Laboratory (MultiBrain: Multimodal MRI in Brain) between team 1 and the Italian team of Mr Umberto SABATINI at the Fondazione Santa Lucia in Rome. The unit is associated to the Paul Sabatier University of Toulouse and is located on the Purpan site. The moving of the clinical department and the imaging platform on the site will reinforce the integration and interactions between the teams of the unit, and also with the others units on the same site (and more particularly the CERCO teams).

Short appreciation on this criterion

The scientific production of the unit is very good and is acknowledged by the international scientific community.

Assessment of the unit's academic reputation and appeal

As a whole, the three teams are involved in national and international research projects /clinical trials (i.e., labex IRON Innovative Radiopharmaceuticals in Oncology and Neurology, European consortium of the IMI project, european trial promoted by the Laboratoires Pierre Fabre), organised international congress (i.e., European Society of Magnetic Resonance in Medicine and Biology 2013), attended (notably as invited speakers, i.e. Chairman of the European section of the International Parkinson and Movement Disorders Society) to international events and are considered as international leaders for the recommendations for future clinical trials in pharmacological therapies for post-stroke recovery. One member of the Unit received a prize from the *Fondation pour la recherche médicale (FRM)*. National and regional academic visibility of unit members is attested by their involvement in various scientific committees, notably at the Inserm. However, the recruitment of high-level post-doc researchers can be considered as weak in regard to the scientific output of the unit.

Short appreciation on this criterion

The unit has a very good reputation and appeal, to the exception of the recruitment of post-docs and researchers from other countries.

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

The unit recruits frequently high level clinicians, coming from masters in which members of the unit are involved in, that are associated to clinical and cognitive research projects. Researchers of the unit are also strongly involved in clinical activities in hospitals located at Toulouse. Since 2010, the unit obtained around 50 research contracts for an amount of 4,651 M. euros, that is very satisfactory according to the size of the unit. Several research projects gave rise to patents or are related to translational investigation programs. For 9 years, members of the unit

participated to the “Week of Brain” popular scientific activity. On the economic side, many members of the unit also worked in collaboration with the local industry.

Short appreciation on this criterion

The interactions of the unit with its environment is of high quality.

Assessment of the unit's organisation and life

For the current contractual period, the unit has been organized in 3 research teams and a 3T MRI platform was opened. During the reference period, the unit demonstrated its capacity to ensure the promotion of internal personnel and recruitment of new personnel. The unit possess large and up-to-date brain imaging equipment (MRI platform, for which the process for ISO 9001 was undertaken, PET centre, EEG/ERP system, TMS system, Movement laboratory and L2 laboratory) that are shared and accessible to the 3 research teams. The research programs of the three teams are the continuation of the studies performed during the 2010-2014 period, and the grouping of previous team 1 and 2 in the new Devin team will help to keep coherence in the research projects following the departure of Mr Jean-François DEMONET. Each team organized monthly their meeting which are opened to everybody in the lab. Students initiated a monthly meeting in english where they present their protocols, results and meeting by oral communications. However, there exists no regular meeting of the Laboratory council, although the General Assembly of the unit was convened 5 times between april 2013 and march 2014 to discuss the research program for the forthcoming contractual period and to choose the new director of the unit who was elected last march. The members of the unit feel satisfied by the working conditions, the work atmosphere and the interactions within the team. The PhD students report a large involvement, supervision and support of their director theses.

Short appreciation on this criterion

Globally, the unit's organisation and life is very satisfactory, to the exception of the sparse laboratory council meetings.

Assessment of the unit's involvement in training through research

Two research masters and one professional master of the UPS are leaded by members of the unit, and there is, on the whole, more than 2000 hours of teaching given by members of the unit each year. The unit also contributed to post-university medical training which amounts to about 300 hours per year. In addition to their high teaching involvement in master direction and teaching, researchers and engineers of the U825 also deliver a lot of teaching at the first and second level of medical studies or at the licence level of other scientific disciplines, as well as in specific university or inter-universities diplomas. The unit has been agreed with three doctoral schools ((ED n°323 GEET “Génie Électrique, Électronique, Télécommunications”, ED n°326 CLESCO “Comportement, Langage, Éducation, Socialisation, Cognition” and ED n°475 MITT “Mathématiques, Informatique, Télécommunications de Toulouse”) that highlights pluridisciplinarity of the research. Two members of the unit are directors of 2 research master degree and one is co-director of a professional master degree. The units hosts each year around 18 doctoral students and 10 research master 2 students. 28 PhD thesis were defended during the period, with 25 associated to publications and patent. 3 HDR were also defended. The discussion with the delegates of the doctoral schools emphasized the very good supervision of PhD students, and the involvement of researchers of the unit in the life of these doctoral schools.

Short appreciation on this criterion

The unit has a high involvement in teaching and training practices, that leads to the recruitment of high quality doctoral students.

Assessment of the strategy and the five-year plan

The strategy and the five-year plan is centered on (1) the consolidation and development of an advanced platform dedicated to multimodal MRI/PET neuroimaging; (2) the recruitment of experienced post-doctoral student and development of international collaborations; (3) the improvement of opportunity and chances of success in applying to ERC programs; (4) the development of partnership with private companies; (5) the development of teaching and training programs. The thematics developed by the unit are essential in terms of public health and are of

great interest due to their translational nature. In the five year plan, the teams 1 and 2 will be grouped together (DEVIN team) and their objective will be to develop neuroimaging tools that can be used in clinical and cognitive brain research and clinical practice, in the continuity of the research work performed in the previous period. The team 3 will become the iDREAM team whose objectives will be to develop an experimental and methodological approach for therapeutic strategies likely to be transferable to clinical trials on advanced treatment of acute brain injury. Some of the projects planned for the next period are already funded and funding demands are submitted for most of the others. Grants obtained are important and are distributed between the three teams. The quality of the SWOT analyses for the two teams are realistic and corresponds to some comments from members of the experts committee, notably the lack of full-time researchers to conduct and supervise the numerous research projects as well as the limited technical staff. Members of the experts committee also noticed that the large number of planned projects could lead to a dissipation of the research effort. Generally speaking, the strength of the unit is reinforced by the long history of collaborations between the DEVIN and iDREAM teams. These collaborations will continue in the future since three large projects involving the two teams are already running for the next years.

Short appreciation on this criterion

The five years plan is ambitious and well-designed. The potential risks come from the limited number of full-time researchers and technical staff to assist the responsible of the two teams in the implementation and supervision of the various projects (both at an administrative, technical and scientific level).

4 • Team-by-team analysis

Team 1: Clinical and cognitive neuroimaging

Name of team leader: Mr Patrice PÉRAN

Workforce

Team workforce	Number as at 30/06/2014	Number as at 01/01/2016
N1: Permanent professors and similar positions	8	18
N2: Permanent EPST or EPIC researchers and similar positions	3	1
N3: Other permanent staff (without research duties)	4	8
N4: Other professors (PREM, ECC, etc.)		
N5: Other researchers (DREM, Postdoctoral students, visitors, etc.)	1	
N6: Other contractual staff (without research duties)		
TOTAL N1 to N6	16	27

Team workforce	Number as at 30/06/2014	Number as at 01/01/2016
Doctoral students	9	
Theses defended	10	
Postdoctoral students having spent at least 12 months in the unit	1	
Number of Research Supervisor Qualifications (HDR) taken	2	
Qualified research supervisors (with an HDR) or similar positions	10	

• Detailed assessments

Assessment of scientific quality and outputs

The general objective of the team 1 is to expand translational novel image based research to clinical practice by developing clinically relevant neuroimaging based methodologies. Team 1 research projects are devoted to Imaging markers of brain macrostructural and microstructural alterations and connectivity; as well as to Imaging markers of brain dysfunction and therapeutic efficiency. More particularly, team 1 developed an original and effective method for measuring cortical thickness from 3D T1 MRI, validated on large multicentre MRI databases including patients and

controls The method has been demonstrated to be sensitive enough to allow prediction of conversion of MCI patients to Alzheimer's disease within 2 years with a global accuracy of 75%. A multimodal MRI quantification method (R2* relaxometry) was developed to characterize the physiological aging of deep grey-matter nuclei in healthy people. Team one was also involved in neuro-oncologic field with important results in Multimodality imaging for radiotherapy dose-painting of high grade brain tumors of adults and children and molecular imaging (PET) with innovative radiopharmaceuticals. These research projects are detailed below.

1) Cerebral cortex morphometry:

- the cortical thickness:

Normalized index is predictive of conversion from MCI to Alzheimer 24 months before clinical disorders with a 75% global accuracy (Querbes et al. Brain, 2009).

The fingerprint of cortical thickness in normal subjects was related to the socio-cultural level, thus accrediting the idea of an anatomic fingerprint of the cognitive reserve. They also showed that the measurement of cortical thickness was pertinent in other pathologies or handicaps such as dyslexia.

- two others morphological indices from anatomical MRI:

Exploration of the local curvature of the cortical mantle (CSF/gray matter and gray matter/white matter interfaces) and the fractal dimension of these surfaces. Besides, these indices carry different information so that the combination of cortical thickness and sulcal curvature improves the prediction of conversion from MCI to AD up to 80%.

2) Mutimodal MRI:

Collaboration with an Italian team for iron brain quantification. mMRI was used, for the first time, to study the integrity of brain structures on idiopathic Parkinson's Disease (IPD) and control subjects. The findings revealed that the multimodal MRI is able to discriminate IPD patients from healthy controls with high accuracy (Péranet al., 2010).

Connectivity approach. Functional brain connectivity approaches provided new interesting advances to measure functional brain networks integrity. Dr. de Pasquale, who works in radiology department of IRCCS Santa Lucia (Rome), in collaboration with Mr Patrice PÉRAN, developed a whole-brain data-driven approach to extract cortical functional cores and examined their connectivity from a resting state fMRI experiment (de Pasquale et al, 2013). This whole-brain data- driven approach to analyze functional brain connectivity is a new tool that can be integrated in future mMRI protocol. Indeed, complementary to the MRI detection of macro and microstructural local defects, functional brain connectivity can help to reveal and better characterize also functional changes in the diseases by providing a signature of pathological changes at a larger scale and at the individual level

3) Tridimensionnal quantitative imaging and modeling of human cortical microcirculation:

Recently, Ms Sylvie LORTHOIS, Mr Pierre CELSIS and coworkers have developed a kinetic model for cerebral blood flow quantification from PET H2 15O images taking into account the problem of the permeability coefficient at the capillary level (Ms Sylvie LORTHOIS et al., J. Theor. Biol. 2014; 353: 157-169). Such an up-scaled approach will be applied in the framework of the 2014 ERC-Consolidator project BrainMicroFlow led by Ms Sylvie LORTHOIS, in collaboration with the U 825 (Mr Frédéric LAUWERS) and the Department of Biomedical Engineering, Cornell University (USA).

4) Multimodality imaging for radiotherapy dose-painting of high grade brain tumors of adults and children:

A Laprie and coworkers develop methods for analyzing different MRI modalities (MR spectroscopy, diffusion and perfusion MRI). Within the framework of the FP7 Marie Curie project SUMMER (Software for the use of MultiModal imaging in External Radiotherapy, <http://summer-project.eu/>, coordinated by the French company Aquilab), Ms Anne LAPRIE and colleagues of the Institut Claudius Regaud received 350 k€. They participated in the coordination of the Work Package 1 (Oncological Focus) and supervised MR spectroscopy post-treatment and integration.

5) Innovative Radopharmaceuticals:

- 18 FET PET brain tumours:

The amino acid O-(2-[18F]fluoroethyl)-L-tyrosine (FET) PET imaging has been proposed to improve the diagnostic accuracy of MRI for cerebral gliomas (Pauleit et al., Brain 2005) or to assess the prognostic of low-grade glioma (Floeth et al., J Nucl Med 2007). In most of the FET studies published so far, images have been acquired at a

steady state. However, preliminary data indicate that exploiting the kinetic of FET brain uptake would be much more informative, especially with regard to the differential diagnosis of high-versus low-grade tumor. During this period, Mr Pierre PAYOUX, and collaborators have implemented the routine synthesis of FET at the PET Centre of Toulouse, and conducted pilot studies on the potential ¹⁸F-FET for brain tumor assessment. To enlarge the field of clinical valorisation of FET, they have obtained the coordination of a multicentre study on low-grade glioma coordinated by Mr Pierre PAYOUX will largely rely on this kinetic approach (PHRC 2010).

- Amyloid:

The team performed the synthesis of [¹⁸F]-AV45, a derivative of stilbene. This radiopharmaceutical was more interesting in terms of yield and reproducibility: 92 syntheses have been carried out which allowed obtaining images for 230 patients. It is currently used in many institutional clinical trials and in April 2012 received approval from the FDA (Food and Drug Administration) and from the EAMA in 2013. These early successes led to clinically validate the chain to synthesize fluorinated molecules for clinical application and allowed to consider the development of innovative molecules with a kinetic and affinity optimized.

There exists a large heterogeneity of research (from parkinson disease to brain glioblastoma, from the diagnosis to the treatment) in team 1 but with a main axis which is a methodological one. Nevertheless, the team has a sustained scientific production (around 150 publications over the five years), mainly as original research papers in medical and neuroimaging journals covering their research domains (a significant number of articles being published in high level journals). The research work of the team is internationally known, that is reflected by the number of invited communications. There also exists numerous oral and written communications in international congress. This show the efficiency of the team, and the adequation of the research protocols.

Short appreciation on this criterion

All the research developed are innovative, one out of them (Multimodality imaging for radiotherapy dose-painting of high grade brain tumors of adults and children) could have soon important clinical application. The scientific production of the team 1 is very good.

Assessment of the team's academic reputation and appeal

Team 1 is one of the teams of the Labex IRON (Innovative Radiopharmaceuticals in Oncology and Neurology), a multi-disciplinary research network aiming the development of new pharmaceuticals for molecular imaging and diagnosis in oncology and neurology, as well as new therapeutic approaches in molecular radiotherapy.

One member received the prize Rose Lamarca 2013 from the "Fondation pour la Recherche Médicale (FRM)" and has been elected chairman of the european section of the International Parkinson and Movement Disorders Society (2013-2015).

Organization of the european society of "Magnetic Resonance in Medicine and Biology", 2013, congress in Toulouse (local organizing committee, Ms Isabelle BERRY, chairperson, Mr Pierre CELSIS and Mr Jean-François BONNEVILLE, members). Coordination of the French Clinical Research Infrastructure Network F-CRIN (Mr Olivier RASCOL, funding: 20M€). Organization of the "International Congress of Parkinson Disease and Movement Disorders" - Paris June 2009 (Mr Olivier RASCOL, Co-Chair).

Short appreciation on this criterion

The unit has an excellent reputation and appeal.

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

The studies developed by team 1 adress very important public health issues, and are therefore in close connexions with social environment. Some examples are presented below:

- industrial research contract between the "Institut de Recherche International Servier (IRIS)" and Inserm-Transfert SA acting for the Inserm U 825 for contractual performance of cortical thickness measurements on 3D-T1 MR images recorded in patients and controls of the ROSAS study (October 2011);

- QuantaVita SRL (Catanzaro, Italy), a member of the team is a confounded of a start-up that aims at providing engineering services to physicians, research institutes and pharmaceutical companies involved in the diagnosis and/or treatment of neurological diseases;

- researchers and teachers of the U 825 mobilize each year for the “Week of the Brain” at Toulouse and offer support for this event (Conferences, cinema debates, scientific workshops, exhibitions, debates), notably in close collaboration with the Muséum d’Histoire Naturelle de Toulouse.

Short appreciation on this criterion

The interactions of the unit with its environment appears of excellent quality.

Assessment of the team's organisation and life

There is a coherence and adequation to scientific objectives of the team organisation as the main purpose of the research themes are clinical and most of the members are physicians “hospitalo-universitaires” with clinical work in the near hospital. One weakness of the common ressources is that fluorinated lab and micropet for animal studies are not on a common place. Scientific animation is very well organized in that team, as well as the representativeness of staff in steering committees, the diffusion of scientific policies and research programmes. There are minors problem concerning the updating of the website.

Short appreciation on this criterion

The unit’s organisation and life is satisfactory in a friendly athmospere.

Assessment of the team's involvement in training through research

There are 9 doctoral students in team 1 and 10 other defended their thesis over the last five years. Out of these 10, 7 students had at least 1 article at the end of the thesis. Members of the team 1 have important teaching responsibilities and teaching duties, listed below:

- director of M2R Neuropsychology;
- director of M2R Radiophysics and Medical Imaging;
- director of M2P Pharmacology and Careers in Medication;
- about 2050 h/year: first and second level of medical studies or at the undergraduate (licence) level of other scientific disciplines (biology, physics or computer science);
- about 330h/year: postgraduate medical education (EPU, Enseignement Post-Universitaire).

Short appreciation on this criterion

The unit has a high involvement in teaching and training practices, leading to the recruitment of excellent quality doctoral students.

Assessment of the strategy and the five-year plan

The team1 is involved together with the team 2 in the DEVIN project. Team 1 will be involved in the next five years in the development of imaging tools (especially for MRI analysis) and he development of new imaging markers (see below). These development wil benefit directly to all research projects planned in the unit.

Development of multimodal neuroimaging markers:

- MRI and Fluorinated Innovative biomarkers (IRON);
- imaging biomarkers development in canine model;
- clinical validation of neuroimaging markers;

- Parkinson CIC Toulouse and Spain;
- radiotherapy dose painting of high grade brain tumours institut universitaire du Cancer Toulouse;
- multimodal MRI in severely depressed patients before and after treatment with electroconvulsive therapy;
- tau imaging and mMRI markers in neuropsychiatric symptoms in Alzheimer's disease.

Short appreciation on this criterion

Excellent five years plan, with limited risks due to the results of the team's previous works.

Conclusion

- **Strengths and opportunities:**

The multidisciplinary aspect of the team.

The clinical aspect in respect to the platform.

The quality of most of the researchers: 20 out of the 29 of the team have an "Habilitation à Diriger la Recherche" (HDR), the highest French university degree for education and research.

The exceptional environment (cyclotron, CIC, CHU, Veterinary school, etc.) and the international collaborations.

- **Weaknesses and threats:**

The heterogeneity of research (from Parkinson disease to brain glioblastoma, from the diagnosis to the treatment) but with a main axis which is a methodological one.

The two modalities of clinical imaging are nearby each other but not at the same place and overall the pre-clinical one for nuclear imaging is far from the fluorinated unit.

The difficulty to find post-doctoral students and the difficulty to restructure a team dictated by the leaving of a well-known leader.

- **Recommendations:**

The experts committee recommends having a common place for the nuclear clinical and preclinical imaging next to the cyclotron. It is also recommended to boost the recruitment of postdocs, especially international postdocs, which must be a will of the new team leader. This should be easy to perform due to the excellent quality of the research in that team and the international relationships recently developed.

In conclusion, team 1 merits to be really supported due to its previous outstanding achievements (scientific production with innovative concepts using MRI and PET tools) and deserves the opportunity to develop most of its innovative projects.

Team 2: Language, memory and action in neurological diseases

Name of team leader: Mr Jean-François DEMONET, until september 2010

Workforce

Team workforce	Number as at 30/06/2014	Number as at 01/01/2016 ¹
N1: Permanent professors and similar positions	7	
N2: Permanent EPST or EPIC researchers and similar positions	1 until 2011	
N3: Other permanent staff (without research duties)	2	
N4: Other professors (PREM, ECC, etc.)		
N5: Other researchers (DREM, Postdoctoral students, visitors, etc.)		
N6: Other contractual staff (without research duties)	1	
TOTAL N1 to N6	11 (6,5 ETP)	

Team workforce	Number as at 30/06/2014	Number as at 01/01/2016
Doctoral students	6	
Theses defended	16	
Postdoctoral students having spent at least 12 months in the unit		
Number of Research Supervisor Qualifications (HDR) taken	1	
Qualified research supervisors (with an HDR) or similar positions	8	

- Detailed assessments

Assessment of scientific quality and outputs

Including 9 permanent members (5 full time equivalent) and 1 (1 full time equivalent) associate member, the team 2 aimed at examining “Language, memory and action in neurological diseases”. The former responsible of the team 2, Mr Jean-François DEMONET, moved in 2011. Studies devoted to the functional anatomy of language taking advantage of “awake surgery” were able to refine brain regions critical for handwriting, reading, calculation and to some extent, high order visual-spatial processing. Studies of the deficits underlying dyslexia are also ongoing. Studies concerning Alzheimer’s disease have mainly developed imaging biomarkers (in close collaboration with team1) with refined treatment of PET amyloid. The research work of the team is internationally known, that is reflected by the

¹ No team

number of invited communications. Team 2 has produced around 130 paper; regarding the excellent scientific quality of the papers, a significant number of articles are published in very high level journal of the medical and neurology/neurosciences topics, thus accounting for the high level of citations in this 5 years range. 56 papers mainly for Parkinson disease topic were from a corporate group. This corresponds to a scientific production of outstanding level. There also exists numerous oral and written communications in international congress, and the realisation of book chapters or whole books. 16 doctoral thesis were defended. Several papers address important issues and are at the forefront of researches in the domain of Parkinson disease, language and imaging characteristics of Alzheimer disease.

Short appreciation on this criterion

The quality of the overall scientific production is excellent.

Assessment of the team's academic reputation and appeal

The international visibility of the team 2 is outstanding. Members of the team are frequently invited to international meeting and have responsibilities in scientific societies. There exists a good recruitment of PhD students. One member has received a prize, has been one co-organizer of International Congress on Parkinson Disease and Movement Disorders (2009), coordinates the French Clinical Research Infrastructure Network, and has been elected Chairman of the European section of the International Parkinson and Movement Disorders Society.

Short appreciation on this criterion

The international visibility of team 2 is outstanding.

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

The studies developed by team 2, development of language disorders, adress very important public health issues (stroke, Alzheimer and Parkinson diseases, acquired and developmental language disorders) and is therefore in close connexions with social environment and priorities of research funds. From this point of view, team 2 has raised funds (603, 370€) including one ANR, one fund from FRM, one from Neurodon and one from Janssen pharmaceutical company. Team 2 is involved in numerous public events such as the "week of the brain".

Short appreciation on this criterion

The interactions of team 2 with the environment is excellent at all levels.

Assessment of the team's organisation and life

The laboratory is currently revising internal rules to conform to the new Inserm guidelines. During one year (April 2013 to march 2014) the General Assembly has met 5 times (research program for the forthcoming contractual period and the election of the new director). Recurrent financial means are allocated after discussion between the team leaders, the secretary-administrator and the director at the beginning of each year. Regular meetings are organized by the team, and students have the opportunity to present their protocols and results).

Short appreciation on this criterion

The overall organization appears to be adequate to the size and objective of the laboratory. It will evolve in order to reach Inserm guidelines.

Assessment of the team's involvement in training through research

All PhD students had at least 1 article at the end of the thesis (median=3 papers; 3 students with 1 paper); median duration of the thesis is 3.8 years (salary: n=6, median=4.21 yrs; contract: n=10, median=3.78 yrs). Students may participate to a monthly meeting to present their methods or results. All except one student are declared to have a post-thesis job. Regarding Masters training programmes, one member of the team is one of the coordinator of the

Research Master in Neuropsychology supported by 3 Universities (Université Toulouse 3 Paul Sabatier, Université Grenoble 2 and Université Lyon 2) and includes students from all french universities.

Short appreciation on this criterion

The thesis supervision of team 2 globally fits current recommendations and one member of the team is involved in research training.

Assessment of the strategy and the five-year plan

Team 2 is involved together with team 1 in the DEVIN project. The development of imaging tools (especially for MRI analysis) by team1 will allow to develop imaging markers of degenerative diseases, especially Alzheimer and Parkinson diseases which are major topics of the present team 2. Several projects address MRI markers of Parkinson disease and this increase the collaborations within the laboratory. The development of new imaging markers (fusion of structural and functional MRI connectivity, new fluorinated PET ligands) is ongoing and this will accelerate these studies. Other studies will address imaging markers in brain tumor, depression.

Short appreciation on this criterion

Development of new imaging markers has proven in the past to provide very interesting diagnosis and prognosis markers in brain diseases and it is still a very promising tool. This topic corresponds to an area of intensive investigations all over the world. The DEVIN team has major strenghts in this field as it includes both researchers actively involved in the development of imaging markers (with full access to imaging machines and tools) and clinicians with previous active collaborations. It will provide the opportunity to reinforce international collaborations and to increase international visibility. The overall feasibility of this 5 yrs plan appears to be good despite the very large number of parallel research projects.

Conclusion

- **Strengths and opportunities:**

The union of teams 1 and 2 of the previous plan into a unique team will give major strenghts to this team in the field of active research. The development of this team will provide the opportunity to reinforce international collaborations and to increase international visibility.

- **Weaknesses and threats:**

The large number of parallel research projects of this 5 years plan appears to be feasible and it will require a strict coordination.

- **Recommendations:**

The experts committee recommend to researchers of the ex-team 2 to continue exploration of specific cognitive and neuropsychological questions (that was indeed the strenght of the team) in the context of the new DEVIN team emphasizing methodological developments on the multimodal neuroimaging platform.

Team 3: Therapeutic innovations in cerebrovascular disease

Name of team leader: Ms Isabelle LOUBINOUX

Workforce

Team workforce	Number as at 30/06/2014	Number as at 01/01/2016
N1: Permanent professors and similar positions	8	11
N2: Permanent EPST or EPIC researchers and similar positions	1	1
N3: Other permanent staff (without research duties)	6	6
N4: Other professors (PREM, ECC, etc.)		
N5: Other researchers (DREM, Postdoctoral students, visitors, etc.)		
N6: Other contractual staff (without research duties)		
TOTAL N1 to N6	15	18

Team workforce	Number as at 30/06/2014	Number as at 01/01/2016
Doctoral students	5	
Theses defended	2	
Postdoctoral students having spent at least 12 months in the unit	7	
Number of Research Supervisor Qualifications (HDR) taken	1	
Qualified research supervisors (with an HDR) or similar positions	6	

- Detailed assessments

Assessment of scientific quality and outputs

Including 15 permanent members, the team 3 was created in 2010 under the supervision of Ms Isabelle LOUBINOUX. Main lines of research were drugs and non-invasive brain stimulations performed in healthy subjects and stroke patients with motor deficits. Team 3 also developed more recently stem cell therapy combined with nanotechnologies in rodents, and extended the research in patients with Acute Brain Injury in general (with a development in the next period). The team developed pharmacological and non-pharmacological (TMS, graft of biomaterial including stem cells) approaches to treatment and recovery of stroke. In that context, the strength of the group is in the translational approach used (from cells rodents, non-human primates to humans [healthy and pathological]). Another recent topic of research was determination of imaging characteristics of acute brain injury with MRI and PET imaging. These researches are important to a theoretical and practical viewpoints. Publications totalize 81 papers in referenced peer reviewed journals (a significant proportion of papers being outside the topic of

the team) including 50 in collaboration with team 1 and some of them are published in high-level journals (Lancet Neurology, Neurology, Neuroimage, Biomaterials, etc.).

Short appreciation on this criterion

Overall excellent scientific quality, with a potential for the future.

Assessment of the team's academic reputation and appeal

The team leader has a good international visibility. Three permanent researchers will join and reinforce the team in 2016, with one of them coming from Stanford, that emphasize the potential visibility of the team. Members of the team are frequently invited (38) to famous institutions or major congress in the domain. Some of the members are president of scientific societies.

Short appreciation on this criterion

Excellent, with potentialities for the future.

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

Based on results from a multicentre clinical trial study (FLAME, Fluoxetine for motor recovery after acute ischaemic stroke) of the team, the Pierre Fabre pharmaceutical company is promoting an european clinical trial (15 M€) and Mr François CHOLLET is the main PI of this study. In addition the team is associated to 3 studies of pharmaceutical companies testing new compounds A few participation to large audience activities (week of the brain, scientific session on one national radio). Finally the tight interaction with clinical settings (ie, Purpan hospital) is a remarkable strenght of the unit.

Short appreciation on this criterion

The interactions with the environment mainly focuses on treatment trials and Purpan hospital which is of primary importance.

Assessment of the team's organisation and life

The team accessed to (e.g. fMRI or PET) or acquired (e.g., magnetic stimulation or neuronavigation system) the material necessary to the experiments. Team 3 organizes the SLAM (Stroke lab Meeting) monthly. Further aspects (team organization, scientific animation, collegiality of decision, website), partly addressed in the document, appeared to be good during the on-site visit.

Short appreciation on this criterion

The team organization was found to be very good during the on-site visit.

Assessment of the team's involvement in training through research

Over the five year period assessed, two PhD have defended their thesis (duration = 3 years) with 3 and 6 papers each and students are now employed; 5 thesis are on going with a duration presently ≤ 2 years except in one case. Team 3 is involved in teaching in several masters and one recently recruited professor is involved in the coordination of one Master in sport science (master en science du sport et du mouvement humain, Université Paul Sabatier).

Short appreciation on this criterion

Overall very good involvement in training through research of some team members and thesis supervision perfectly fitting recommandations.

Assessment of the strategy and the five-year plan

The strategy and the five-year plan concerns the improvement of sequelae due to acute brain lesion, especially stroke. New researches have been added and concern topics that are close to the main topic of the units: post-traumatic stress disorder (PTSD), acute stroke imaging and stroke biomarkers. The recruitment of three supplementary researchers should help to perform the plan. The interdisciplinarity of the project is an advantage.

Short appreciation on this criterion

The objective of this team is ambitious and corresponds to a major objective which is developed by several teams in several western countries. The team has gained international recognition in the domain owing to its pharmacological study providing very promising results and they have developed an original approach suggesting that they will be able to guide neuronal sprouting to the target.

Conclusion

▪ Strengths and opportunities:

Topic and content of the project are its strengths and opportunities for the following reasons: it addresses a major public health issue; it is translational and innovative at least for the axis “pharmacological stimulation in stroke”; it has received a high level of funding from contracts (1,312K€); with strong relationships with pharmaceutical companies as required to boost potential translational research; it beneficiates from the recruitment of 3 “senior” researchers with acknowledged expertise in the domains covered by the project with a noticeable development of axis 3, and technical infrastructure (to the exceptions of the TEP for primates).

▪ Weaknesses and threats:

Non pharmacological stimulations needs to be validated. The determination of imaging characteristics of acute brain injury and graft of stem cells on biomaterial is very promising but still in development. The team devoted to stem cell research is recent and very restricted (with only one biologist) as underlined by the file.

▪ Recommendations:

Considering the major challenge of improving poststroke outcome, the high level of international competition in the field and their assets, it is essential to support this team very strongly.

Theme 4: 3T MRI Technological platform

Manager's name: Mr Pierre CELSIS

Workforce

Theme workforce in Full Time Equivalents	As at 30/06/2014	As at 01/01/2016
FTE for permanent professors		
FTE for permanent EPST or EPIC researchers		
FTE of other permanent staff without research duties (IR, IE, PRAG, etc.)	4	3.2
FTE for other professors (PREM, ECC, etc.)		
FTE for postdoctoral students having spent at least 12 months in the team		
FTE for other researchers (DREM, etc.) excluding postdoctoral students		
FTE for other contractual staff without research duties	0.5	0.5
FTE for doctoral students		
TOTAL	4.5	3.7

• Detailed assessments

The neuroimaging platform of UMR 825 includes a Philips 3T MRI, operational since 2010. A complete upgrade of this machine towards an all optical/digital system is planned. It would include the complete digitalization of the coil and receptor chain, and the replacement of the gradients. The total budget of this upgrade is 700 k€. Out of this sum, 400 k€ have already been provisioned by the UMR 825. The remaining 300 k€ have yet to be financed. The accessory equipment necessary for research protocols in neuroscience are present in the unit (auditory, visual, tactile stimulations, push button response systems, transcranial magnetic stimulation devices, EEG, evoked potentials). All these research examinations are provided to the clinicians on CDs and are archived on site on a dedicated PACS system).

The workforce dedicated to this MRIs includes 2 full time IR, 1 part time IR, 1 full time IE, 1 part time ARC, 2 part time MR technicians (on loan from the hospital), one computer scientist. One medical doctor (Mr Jean-Albert LOTTERIE) is specifically employed by this platform to review the MRI performed. In addition, many PUPH and PH of the neuroimaging and nuclear medicine departments of Purpan's hospital are members of the UMR 825 (Ms Isabelle BERRY, Mr Jean-François BONNEVILLE, Mr Pierre PAYOUX, Ms Isabelle CATALAA).

This equipment can perform MR studies on patients, healthy controls, and non-human primates (mostly rhesus monkeys and marmosets). Two uncommon specificities not found on most other research MR platform should be noticed:

- the possibility to explore intubated and sedated patients;
- an extensive experience on research protocols with children and infants.

A specific, wide-ranging CPP allows the performance of MR examinations on healthy volunteers, both to test sequences and to calibrate the various research protocols

The funding of this platform is extensively detailed in the unit report. This financing is “classical”, by the billing of MR time in research protocols and by performing MR examinations in clinical trials for the pharmaceutical industry. The pricing is in accordance with what is currently proposed in similar platforms.

This MRI will soon be complemented by a PET, transferred from the hospital. A cyclotron and a hot lab are present next to this machine, leading to the ability to perform advanced nuclear medicine studies. A pharmacist paid by the hospital is in charge of performing the radio chemical syntheses. However, it should be noticed that due to the current public health regulations, these radiopharmaceuticals can only be used in research studies and not for routine clinical examinations, leading to a somewhat uncomfortable situation.

As a conclusion, this platform is characterized by its excellent integration to the UMR 825 research topics, a strong involvement of the clinicians in its activity, and the possibility to provide a very large gamut of services, from sequence developments to the long-term storage of the examinations.

Conclusion

- **Strengths and opportunities**

The strengths and opportunities of the technological platform are the soon to be upgraded 3T MRI, with a strong continuous activity; an adequate support technical staff; with self financing through; and the planned transfer of a PET to the UMR 825.

- **Weaknesses and threats**

The experts committee feels that the funding for the MRI is not fully acquired and needs to be secured. The PET is in a different building from the rest of the team. The personnel of the PET is currently paid by the hospital and the continuous staff support needs to be secured when this machine will be fully transferred to the UMR 825. This is not completely clear and should be addressed. There is no small animal imaging capability

5 • Conduct of the visit

Visit dates: 6th & 7th November 2014
 Start: Thursday 6th November 2014 at 03.00 pm
 End: Friday 7th November 2014 at 03.00 pm

Visit site: CHU Purpan
 Institution: Inserm/UPS UMR 825
 Address: Pavillon Baudot, 31024 Toulouse

Specific premises visited: laboratories and 3T IRM neuroimaging platform

Conduct or programme of the visit:

Jeudi 6 novembre

14h30-15h00 : Accueil
 15h00-15h30 : Huis-clos - Présentation rôle et procédures du HCERES par le délégué scientifique du HCERES (DS) (salle 129)
 15h30-16h15 : Présentation administrative et scientifique de l'unité par les directeurs (actuel et futur : M. Pierre CELSIS, M. Pierre PAYOUX) (salle de conférence)
 16h15-17h00 : Bilan équipe 1 de l'UMR 825 (M. Pierre CELSIS) (salle de conférence)
 Projet DEVIN de l'unité TONIC (M. Patrice PERAN) (salle de conférence)
 Discussion à huis clos (salle 129)
 17h00-17h45 : Bilan équipe 3 de l'UMR 825 (M^{me} Isabelle LOUBINOUX) (salle de conférence)
 Projet iDREAM de l'unité TONIC (M^{me} Isabelle LOUBINOUX) (salle de conférence)
 Discussion à huis clos (salle 129)
 17h45-18h15 : Bilan équipe 2 de l'UMR 825 (M. Jean-François DEMONET) (salle de conférence)

Vendredi 7 novembre

08h30-09h00 : Rencontre du comité d'experts avec les chercheurs et enseignants-chercheurs (salle de conférence)
 09h00-09h30 : 2 sessions en parallèle :
 - rencontre d'une partie du comité d'experts avec les doctorants et post-doctorants (salle de conférence)
 - rencontre de l'autre partie du comité d'experts avec les techniciens et personnels administratifs (Salle 319)
 09h30-10h00 : Entretien du comité d'experts avec les représentants des organismes de tutelles (salle 129)
 10h15-10h45 : Entretien du comité d'experts avec les directeurs des écoles doctorales (salle 129)
 10h45-11h45 : Visite des locaux (Plateau Technique IRM, L2, Centre TEP)
 11h45-12h15 : Huis-clos avec les directeurs (actuel et futur : M. Pierre CELSIS, M. Pierre PAYOUX) (salle 129)
 12h15-13h15 : Déjeuner
 13h15-15h30 : Réunion en séance privée du comité d'experts pour préparer le rapport final (salle 129)
 15h30 : Fin de la visite