

EVALUATION REPORT OF THE UNIT  
IBRAIN - Imagerie et cerveau

UNDER THE SUPERVISION OF THE  
FOLLOWING ESTABLISHMENTS AND  
ORGANISMS:

Université de Tours, Institut national de la santé et  
de la recherche médicale - INSERM

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**EVALUATION CAMPAIGN 2022-2023**  
GROUP C

Rapport publié le 27/09/2023



In the name of the expert committee<sup>1</sup> :

Mr Bogdan Draganski, Chairman of the committee

For the Hcéres<sup>2</sup> :

Thierry Coulhon, President

Under the decree n° 2021-1536 of 29th November 2021:

<sup>1</sup> The evaluation reports "are signed by the chairperson of the expert committee". (Article 11, paragraph 2);

<sup>2</sup> The president of the Hcéres "countersigns the evaluation reports established by the expert committee and signed by their chairperson." (Article 8, paragraph 5).

This report is the result of the unit's evaluation by the expert committee, the composition of which is specified below. The appreciations it contains are the expression of the independent and collegial deliberation of this committee. The numbers in this report are the certified exact data extracted from the deposited files by the supervising body on behalf of the unit.

## MEMBERS OF THE EXPERT COMMITTEE

**Chairperson:**

Mr Bogdan Draganski, Centre hospitalier universitaire vaudois, Suisse

**Experts:**

Mr Alexander Hammers, King's College London, Royaume-Uni,  
Mr Cyril Lafon, INSERM, Université de Lyon 1, Lyon,  
Ms Frédérique Liegeois, University College London, Royaume-Uni,  
Mr Philippe Marin, IGF, CNRS, Montpellier,  
Mr Philip Gorwood, IPNP, Paris, (Representative of Inserm CSS4).  
Ms Karen Chardon, UMI -01 PériTox UPJV, Amiens, (representative of CNU).  
Mr Sébastien Maifert, CIML, Marseille, (Representative of supporting personnel).

## HCÉRES REPRESENTATIVE

Ms Nadia Soussi-Yanicostas

## CHARACTERISATION OF THE UNIT

- Name: Imaging and Brain Unit (iBrain)
- Acronym: IBRAIN
- Label and number: UMR 1253
- Number of teams: 3
- Composition of the executive team: Catherine Belzung

## SCIENTIFIC PANELS OF THE UNIT

SVE Sciences du vivant et environnement

SVE5 Neurosciences et troubles du système nerveux

## THEMES OF THE UNIT

The Imaging and Brain Unit (iBrain, Inserm Unit 1253) is a multidisciplinary unit integrating research in neuropsychiatry, studies on cellular/molecular/cognitive neurosciences, human genetics and biomedical research. The unit is composed of three teams (team 1: neuro-functional psychiatry, team 2: neuro-genomics and neuronal pathophysiology and team 3: imaging, biomarkers and therapy). The unit's research is focused on using new technologies for diagnosis and treatment of neurological and neuropsychiatric disorders (particularly autism and depression) following the vision of personalised medicine. The specific objectives of the unit are: First, to characterise the biological signatures of neuropsychiatric diseases using dedicated phenotype assessment (neurophysiology, eye-tracking, cognitive and sensorial markers, behavioral and neuropsychological testing) enriched by techniques that provide detailed genomic, metabolomic, positron emission tomography (PET) and ultrasound imaging data. Second, to understand the underlying mechanisms in neuro-developmental (autism) and neuro-degenerative disorders (amyotrophic lateral sclerosis) using pathophysiological pre-clinical models and patients whilst combining cellular/molecular and integrative approaches (team 2). The last aim is to advance the development of new individually tailored diagnostic tools (imaging and metabolomic-based biomarkers) resulting in personalised treatment (team 3).

Team 1 is composed of two subgroups: Autism group with the objective to understand how sensory informations from the environment are processed, perceived and used. Three sensory modalities are studied (vision, audition and touch) in children and adults, using EEG and fMRI to localize the cerebral regions involved in information processing and studying perception and cognition mechanisms. Eye-tracking is used to study the strategies involved in environment exploration and the autonomous nervous system measurements (pupil diameter, heart rate, electro-dermal activity) used to evaluate the physiological mobilization in response to a stimulation. The Depression group uses pre-clinical models and investigates patients to tackle the question about heterogeneity of treatment response to antidepressant therapies. The current focus of the team is on the role of hippocampal neurogenesis in the regulation of stress.

The team 2 'Neurogenomics and neuronal patho-physiology' focuses on the role of genetic background in the severity of intellectual disability (ID) and amyotrophic lateral sclerosis (ALS) using multidisciplinary and translational approaches (i.e patients and pre-clinical models, *in vitro* and *in vivo* models, metabolomic and genetic analyses).

The team 3 'Imaging, biomarkers and therapy' develops new technologies and methodologies which are non-pathology-specific, and which include ultrasound brain imaging, diffusion weighted-MRI (validation of tractography using a comparative anatomical approach) and metabolomics. This team also develops new therapeutic strategies based on the use of ultrasound technology to facilitate drug penetration within target tissues using sonoporation or to stimulate brain areas that are deficient in specific pathologies.

## HISTORIC AND GEOGRAPHICAL LOCATION OF THE UNIT:

The Inserm Unit was created in 1988, which was followed by a gradual expansion through the inclusion of a CNRS team focused on genetics (2000); a linguistics and neuro-biology team (2008); a team working on genetic instability (2018); and a team investigating hedonic processes (2020). This multi-disciplinary unit is known as Inserm Unit 1253, Imaging & Brain (iBrain).

The available infrastructure is spread between the Thérèse Planiol building (1,400 m<sup>2</sup>) at the Faculty of Medicine – University Hospital Bretonneau, hosting teams 2 and 3, another Campus building for part of team 1 and the Faculty of Sciences and Techniques (6 km from the University Hospital Campus) for the preclinical group on stress-related disorders.

## RESEARCH ENVIRONMENT OF THE UNIT:

The true interdisciplinary character of the Imaging and Brain Unit is well integrated in the clinical neuroscience environment of both the Faculty of Medicine at the University Hospital and the Faculty of Sciences and Techniques of the University. This is the optimal natural habitat of a Unit that aims at integrating research in neuropsychiatry with the development of diagnostic tools and therapeutic strategies that are readily applicable in the clinical population. The rich armament of methods at the genetic, cellular and system level applied on pre-clinical models and patients with neuropsychiatric disorders, is well integrated in the technical infrastructure of both faculties.

## UNIT WORKFORCE: in physical persons at 31/12/2021

<b>Permanent personnel in active employment</b>	
Professors and associate professors	31
Lecturers and associate lecturers	29
Senior scientists (Directeur de recherche, DR) and associates	4
Scientists (Chargé de recherche, CR) and associates	6
Other scientists (Chercheurs des EPIC et autres organismes, fondations ou entreprises privées)	1
Research supporting personnels (PAR)	45
<b>Subtotal permanent personnel in active employment</b>	<b>116</b>
Non-permanent teacher researchers, researchers and associates	30
Non-permanent research supporting personnels (PAR)	4
Post-docs	5
PhD Students	47
<b>Subtotal non-permanent personnel</b>	<b>86</b>
<b>Total</b>	<b>202</b>

## DISTRIBUTION OF THE UNIT'S PERMANENTS BY EMPLOYER: NON-TUTORSHIP EMPLOYERS ARE GROUPED UNDER THE HEADING 'OTHERS'.

<b>Employer</b>	<b>EC</b>	<b>C</b>	<b>PAR</b>
Université de Tours	38	1	21
CHRU Tours	19	0	18
Inserm	0	8	6
Employeur étranger	2	0	0
Insa Centre Val de Loire	1	0	0
Employeur privé	0	1	0
CNRS	0	1	0
<b>Total</b>	<b>60</b>	<b>11</b>	<b>45</b>

## UNIT BUDGET

Recurrent budget excluding wage bill allocated by parent institutions (total over 6 years)	2,887
Own resources obtained from regional calls for projects (total over 6 years of sums obtained from AAP idex, i-site, CPER, territorial authorities, etc.)	3,639
Own resources obtained from national calls for projects (total over 6 years of sums obtained on AAP ONR, PIA, ANR, FRM, INCa, etc.)	7,392
Own resources obtained from international call for projects (total over 6 years of sums obtained)	985
Own resources issued from the valorisation, transfer and industrial collaboration (total over 6 years of sums obtained through contracts, patents, service activities, services, etc.)	744
<b>Total in euros (in K €)</b>	<b>15,647</b>

## GLOBAL ASSESSMENT

Following our virtual visit, the committee unanimously evaluated the INSERM Unit 1253, Imaging & Brain as a globally excellent research institute. This is grounded on the excellence in the main areas of evaluation:

i. excellent resources with an impressive amount of competitive funding including several EU collaborative grants mounting up to €2.1 Mio (5 H2020 Grants/7th PCRD (STIPED project, AIMS-2-TRIALS, INMIND, PPILLOW, EU Joint Programme Neurodegenerative Disease (JPND) Research – Working Group for Harmonisation and Alignment in Brain Imaging Methods for Neurodegeneration; one JPND collaborative project (Strength); Two ERANet Neuron (ADORE; Magnolia), additionally to 47 national grants with a total of €7.7 million 47 National grants (ANR, PHRC) and grants from charities (€2.1 million);

ii. excellent attractiveness that led to the recruitment of two junior researchers at Inserm researcher positions, two tenured senior researchers and five research fellows from abroad; the members of the Unit were the organisers (chairs) of several international conferences: IEEE International Ultrasonics Symposium (2016 in Tours, France, 1,400 attendees; 2021 X'ian, China, 2,500 attendees), European Network for the Cure of ALS (ENCALS 2019, in Tours, France; 400 attendees) and Assises Francophones de Génétique Humaine et Médicale (2020, in Tours, France; 1,800 attendees). Similarly, the Unit's researchers are active members of editorial boards or guest editors for peer-reviewed and internationally recognised journals and collections of various disciplines: Pharmaceutics, Frontiers in Pharmacology, IEEE T-UFFC, Ultrasound in Medicine and Biology, Frontiers in Neuroscience, Frontiers in Psychiatry, Nuclear Medicine and Biology, etc. The Unit attracted international research fellows from Le Studium (Marie-Curie international programs, Institute for advanced studies–Loire Valley): Prof. Postema (South Africa; 2017–2018), Dr. De Assis (Brazil; 2019–2020), Dr. Zaleta (EU, University of San Diego), Dr. Maldonado (Brazil; 2018 – the present), Dr. H Boutin (Univ Manchester, UK), Prof. Peter Burns, Prof Haim Einat (School of Behavioral Sciences, Tel Aviv), Jill Heathcok (Ohio State University).

iii. The scientific production of the laboratory is very good to excellent. During the 2016–2021 period, Team 1 published 297 articles, Team 2–262 articles and Team 3–718 articles. In Team 2 about 20% (53/267) of the team's scientific production is published in major speciality journals on translational, clinical or basic research work (Mol Psychiatry, Am J Hum Genet, Nat Genet), but also as review papers published in major scientific journals (Brain). Publications have been highlighted by Inserm through national press releases (Bonnet-Brilhault et al., 2016; Ung et al., 2018) and/or have been highlighted in outreach scientific journals (Sciences et Vie, La revue médicale suisse, etc.).

iv. The links with society are excellent given the high relevance of the clinical research topics with strong presence in social media, French radio and TV. Members of the Unit are invited to public conferences, in national events like the Science Festival or Utopiales, or local events like Les Mercredis de Thélème or Les Conférences du Département Recherche (at the Medecine Faculty–University of Tours) and events organised by various charities (Rotary Clubs). The Unit's members participated in debates with the general public (e.g. a debate on France 2 TV channel entitled 'Vivre avec un enfant autiste' in 2020), or directly in contact with the public following the screening of films or in Inserm communication operations (e.g. Terre de Sciences). The Unit organises visits of the lab, bringing the general public into contact with the reality of research. The Unit also created or participated in YouTube videos promoting the debunking of fake news on ASD. There are publications in Le Monde, France-Inter (La tête au carré and Grand bien vous fasse), France 3 (documentary devoted to the expertise of the Trauma Center of Tours 'La mémoire réparée', 25/11/2021), France Bleu, France Culture, TV Tours Val de Loire, Women Today, Le Figaro, Ouest France, Festival d'Avignon, etc. Additionally, they have also made a major contribution to the national scientific press: Sciences et Avenir, Cerveau & Psycho, France 5, France info, The Conversation, Journal de l'INSERM, Carnets de Science, etc. The Unit has established a 'Greenlab', which is a group of members that propose solutions in the field of environmental risk prevention

and pursuit of sustainable development. This group established the Unit's carbon footprint for 2019: it corresponds to 612 tons of CO<sub>2</sub> equivalent.

Considering the history of the Unit and its teams, the difference in their link to either clinical or basic research, there were some differences between the three teams. Team 1 (Neuro-functional psychiatry) and Team 3 (Imaging, biomarkers and therapy) were evaluated as being globally excellent on the verge of becoming outstanding. Team 2 (Neuro-genomics and neuronal patho-physiology) was rated as very good to excellent. The three teams differed according to the areas of evaluation, with ratings in specific areas ranging between very good to excellent and excellent to outstanding. The details are provided in the team-by-team assessment.

According to the committee's evaluation, the iBrain Unit has a true potential to become a national and international leader in the respective fields of research. The Unit's Principal Investigators are at key positions at the hospital, which allows for closer collaboration with clinical scientists and direct access to well-characterised clinical cohorts. iBrain is a green lab, the efforts in this direction were much appreciated. Similarly, diversity and support for disadvantaged minorities are excellent and should be honoured.

There are some threats to the Unit – of particular concern are, the unresolved question about the financial part of maintaining the much needed access to radio-ligands from a commercial supplier, the administrative load at all levels and finally, but not less importantly – a pragmatic solution for replacement of the technical staff that will avoid that low-level tasks are supported by clearly overqualified technicians.

There are some minor, but important weaknesses – the dialogue/collaboration between basic research and clinics should be encouraged and proactively supported. A good example of this is the installed 12.5% budget for translational projects. The Unit could also benefit from mutually benefitting links with industrial partners – particularly in the field of PET and ultrasound technology.

All these developments demonstrate the clear and pragmatic vision of the lab's director since 2018, who has done an excellent job of enhancing iBrains visibility and building the strong fundament for further developments and expansion. Under her lead, the Unit's atmosphere is collaborative, friendly and accommodating for both early career researchers and skilled technicians that seem to follow a common vision. The budget allocated for translational cross-cutting projects gives unique opportunities for the three teams to embark on high-risk high-gain ideas. The committee congratulates her for the success of the previous evaluation period and supports her intention to streamline the research topics/techniques at iBrain within a more coherent pragmatic vision for the short- and mid-term period.

## DETAILED EVALUATION OF THE UNIT

### A – CONSIDERATION OF THE RECOMMENDATIONS IN THE PREVIOUS REPORT

The recommendations of the previous evaluations were taken in full consideration. The comments concerned the following areas of scientific work:

A. Publications – following the previous recommendations the Unit encouraged publications in high-level journals for the cost of fewer publications in low-impact journals (e.g. Molecular Psychiatry, The American Journal of Human Genetics). The Unit also introduced a yearly 'publication award' with the expectations that these measures will maintain the positive trend.

B. Publicity – the Unit took the opportunity of social media (Twitter, YouTube) to promote itself rather than individual researchers – mini-videos on the themes of the Unit's teams were broadcast on YouTube, and radio and TV broadcasts were conducted with Radio Campus and TV Tours. Science articles accessible to the wider public have been published in the journal The Conversation. The team also contributed significantly to the national scientific press: Sciences et Avenir, Sciences et Vie, le magazine de l'INSERM, la Revue Médicale Suisse, etc. Five percent of the budget was allocated for stimulation of applications to competitive EU grants that were not successful this time. Within the Unit, collaboration and self-promotion were encouraged via establishing an intramural funding scheme for translational projects (12.5% of the budget) and a weekly newsletter. Despite the evident break due to the COVID-19 pandemics, Tours hosted well-attended national and international scientific conferences.

C. Leadership – the recommended balance between teaching/administrative load and leadership in science for the Unit's management was supported by the University with adequate adjustment of the teaching responsibilities. The administrative load remains unchanged. The recommendation to prepare the next generation of leadership was followed with the appointment of two deputy directors under the age of 50 years.

D. Attractiveness to non-Francophone early-career researchers – a common issue for the majority of French research institutions, the Unit installed a funding scheme for French courses, that is particularly targeting students who are requiring training/certificates.

E. Promote INSERM applications to Inserm management – the Unit's strategy is increasing the political weight of its currently acting members in INSERM governing bodies. The director of the unit has been elected to the Scientific Council of Inserm and three members of the Unit have been elected to Inserm CSS4 and CSS7 research committees.

F. Vision for the future – following suit, the permanent researchers staff increased from six to ten, the leadership strives for a unified and integrative vision for the future given the multitude of topics and techniques they are currently committed to.

### B – EVALUATION AREAS

#### EVALUATION AREA 1: PROFILE, RESOURCES AND ORGANISATION OF THE UNIT

##### Assessment on the unit's resources

*Strengths and possibilities:* The grant application activity is high and successful, including well funded and highly regarded national and international grants (Fondation de France ; ANR; H2020 Europe; JPND; ERA-NET; University). The long-standing integration with the University Hospital allows for closer collaboration with clinical scientists and direct access to well-characterised clinical cohorts. According to the translational character of the Unit's research activities, there is a plethora of high quality platforms serving in vivo and ex vivo research in the pre-clinical model and humans. There is a well-balanced mix between platforms under the responsibility of the Unit (free access) and ones that are supported by the University or the Hospital (user fees).

*Weaknesses and risks:* The administrative support is insufficient. The maintenance funding for access to radio-ligands from a commercial supplier is not secured, which poses a threat for the whole PET platform. There is an urgent need for a durable solution for replacement of the technical staff that will avoid that low-level task-shifting are supported by clearly overqualified technicians.



### Assessment on the scientific objectives of the unit

*Strengths and possibilities:* The scientific vision of translation between basic and clinical neurosciences to develop individually tailored therapy strategies is clear, and the unit participates actively to local and national initiatives. The creation and active involvement of the international Scientific Advisory Board are highly laudable.

*Weaknesses and risks linked to the context:* None identified

### Assessment on the functioning of the unit

*Strengths and possibilities:* iBrain is a prototypical multi-disciplinary translational Unit that successfully integrates basic and clinical neurosciences. The committee was impressed by the established culture of social and scientific exchange intertwined with regular internal and external assessments (see international SAB). The safety across different technical, pre-clinical and patient-related platforms is maintained through regular training and thorough documentation. The gender balance is well established across the different hierarchical levels.

*Weaknesses and risks:* The major risks for the maintenance of the translational character of the Unit are the unclear financial basis of the facilities and the access to PET ligands. The administrative workload for frequently overqualified technical personnel comes at the cost of scientific productivity.

*1/ The unit has resources that are suited to its activity profile and research environment.*

#### Strengths and possibilities linked to the context

Well suited to the broad spectrum of the Unit's research activities on the existing platforms for in vivo and ex vivo investigations of pre-clinical models and humans are a true asset. The combination of adequate infrastructure for stereotaxic surgery, in-vivo electrophysiology, telemetry, optogenetics, in-vivo calcium imaging, neurostimulation via TMS or transcranial ultrasound stimulation, PET/CT, neurophysiology (EEG), TMS, eye tracking, video-platform for behavioral and psychometric assessment is impressive.

The integration of data from preclinical research and well-characterised clinical cohorts is a unique opportunity that should be honed on and further developed. The ability to take advantage of the research environment and support activities is evaluated as outstanding.

#### Weaknesses and risks linked to the context

The weaknesses and risks are linked to the limited abilities to control the financial and human resources in such a way that will secure the sustainability and longevity of critical infrastructure – the facilities and the nuclear medicine imaging platform. At the same time, such control will provide the means for expansion and for the establishment of new competitive techniques and infrastructure. This issue remains critical at the moment for the PET facilities.

*2/ The unit has set itself scientific objectives, including the forward-looking aspect of its policy.*

#### Strengths and possibilities linked to the context

iBrain is an exemplary translational Unit that aims at covering the broad spectrum of studying neuropsychiatric disorders with the focus on better diagnostic and therapeutic strategies for patients. The long-standing and continuing integration of clinical researchers at all levels of expertise and project management is one of the true assets that have to be supported. As detailed in the reports of the individual teams, the quality of the research is considered excellent to outstanding. The involvement of the international SAB should be maintained.

#### Weaknesses and risks linked to the context

None identified.

*3/ The functioning of the unit complies with the regulation of human resource management, safety, the environment and the protection of scientific assets.*

Strengths and possibilities linked to the context

The sustained growth of iBrain in different although complementary domains of basic and clinical neurosciences has created a dynamic and innovation-friendly working atmosphere. The Unit's state-of-the-art policy for open science, sustainable research considering the impact on climate and environment is exemplary – the Unit has established a 'Greenlab', which is a group of members that propose solutions in the field of environmental risk prevention and pursuit of sustainable development. The fields of gender balance, support for diversity and inclusion are well established. This area was evaluated as excellent to outstanding.

Weaknesses and risks linked to the context

The valorisation and protection of intellectual property should be prioritised particularly for the areas at the interface with industry (see ultrasound). The sustainability of the research infrastructure should also be prioritised in terms of institutional financial support and human resources. The administrative workload is not adequately partitioned and a significant part is taken over by researchers and technical support staff. This creates tensions within the teams and is not favourable to scientific progress. This area was evaluated as well.

PhD students shared some concerns about the lack of information (grants, activities from others) and some tension between researchers. Although these problems are inevitable for large groups, such signal should be analysed, followed up and answered to avoid getting worse.

EVALUATION AREA 2: ATTRACTIVENESS

Assessment on the attractiveness of the unit

The iBrain unit has an excellent scientific reputation at the national level and is attractive. The attractiveness of the unit is illustrated by the recruitment of two junior researchers who were awarded an Inserm researcher position and two tenured senior researchers over the reporting period, thus expanding its scientific skills in neuropharmacology and genetic neurobiology. The unit also attracted five research fellows from abroad (two of them are applying to Inserm researcher positions) and welcomed three foreign visiting scientists, but did not attract young scientists who are holders of highly competitive grants, such as Atip/Avenir or ERC. The scientific appeal of the unit is also assessed by its very good funding capacity (more than 2 M€ raised yearly from various regional, national and international agencies or charities) and its participation in two Labex and two Fédération Hospitalo-Universitaire: University Hospital Federations (FHU).

*1/ The unit has an attractive scientific reputation and contributes to the construction of the European research area.*

Strengths and possibilities linked to the context

Members of the iBrain Unit have been invited to present their work at international congresses (IEEE International Ultrasonics Symposium, International Symposium of Therapeutic Ultrasound, European Symposium in Molecular Imaging, Metabolomics, ECNP, SFN and ENCALS) and in academic institutions (Hokkaido University, Japan; X'ian University, China, Penn State University, USA). They have chaired several major international conferences in their fields of expertise: IEEE International Ultrasonics Symposium (2016 in Tours, France, 1,400 attendees; 2021 X'ian, China, 2,500 attendees), European Network for the Cure of ALS (ENCALS 2019, in Tours, France; 400 attendees) and Assises Francophones de Génétique Humaine et Médicale (2020, in Tours, France; 1,800 attendees). They hold editorial responsibilities in several peer-reviewed and internationally recognised specialised journals (Pharmaceutics, Frontiers in Pharmacology, Frontiers in Neuroscience, Frontiers in Psychiatry, Nuclear Medicine and Biology, etc.). One member of the unit is vice-president of the IEEE UFFC society. They take part in national (scientific panels of INSERM (CSS4 and CSS7), Scientific Council of Inserm, Scientific Council of IBISA, evaluation panel of the French Institute of Research and Technology, etc.) and international (ERC Starting grant panel – vice chair –, MSCA ITN evaluation panel, European H2020 FET Open, Research Foundation Flanders, Israel

Science Foundation, New Frontiers in Research Fund–Canada–etc.) scientific committees, thereby contributing to the construction of the European research. One member of the Unit received the prestigious IUF award. Two clinicians were awarded the Scientific Emergence Prize for clinical research from the Fondation pour l'Audition and the honorary prize of the French National Academy of Pharmacy. One student was the winner of the Young Talents 2021 for the Women in Science Africa program from UNESCO and the L'Oréal Foundation.

## Weaknesses and risks linked to the context

The members of the Unit actively participate in conference organisation, editorial committees and scientific bodies but the recognition marks and awards are quite limited and only concern a minority of the scientists of the unit.

*2/ The unit is attractive for the quality of its staff hosting policy.*

## Strengths and possibilities linked to the context

During the reporting period, the Unit attracted two senior researchers and two junior researchers who were awarded a tenured Inserm researcher position and brought complementary expertise in neuropharmacology and genetic neurobiology. Taking advantage of Le Studium program (Marie-Curie international programs, Institute for advanced studies–Loire Valley), it also recruited five research fellows from several countries (2 from Brazil, one from South Africa, one from the USA and one from UK). One of them is applying to an Inserm researcher position and one to an Inserm Research director position to join Team 3. The unit also welcomed three visiting scientists (from Canada, Israel and USA). The Unit has trained and is still training many PhD students (98 over the reporting period) and the three teams have contributed to PhD supervision proportionally to their PhD training capacities. The Unit has implemented an ambitious training-through-research (TTR) program combining science and education that fosters collaborative inter-disciplinary research, develops communication skills and increases the ability to develop a personal network. This training program includes: i) the participation in weekly seminars (in English) where students have the opportunity to present their project and to discuss their last results; ii) a Student's Office that consists of annually elected students who are in charge of organizing the schedule of the weekly seminars, represent students in the Laboratory Council, relay information to and from the students, update the students' email distribution list, welcome new students and maintain an intranet webpage; iii) an internal PhD committee gathering experts in the Unit's research themes. PhD students are also encouraged to participate in: i) scientific congresses; ii) local scientific meetings/workshops that bring together different research units; and iii) scientific dissemination to the lay public events (open days, Science Festival, etc.) to communicate on the research conducted in the Unit. Collectively, the actions implemented in the frame of the TTR program provides early-stage researchers a stimulating environment and makes iBrain an attractive unit for graduate students. PhD students are the first author of the publications containing data they collected.

## Weaknesses and risks linked to the context

The Unit is attractive for PhD students, but recruited a limited number of students from abroad. A significant proportion of these are defended more than five years after the initial registration. Though the Unit has been able to attract talented young scientists from abroad thanks to Le Studium program, none of them obtained highly competitive fundings such as ANR JC/JC, ATIP/Avenir program or ERC starting/consolidator grants.

*3/ The unit is attractive because of the recognition gained through its success in competitive calls for projects.*

## Strengths and possibilities linked to the context

Over the reporting period, iBrain showed a very good capacity to raise funding in response to competitive calls from local, national and international institutions and charities (more than 2 M€ yearly). The Unit's staffs were partners of four H2020/7th PCRD Grants (665 k€) and two ERANet Neuron grants (386 k€). The Unit takes part of the Working Group for Harmonisation and Alignment in Brain Imaging Methods for Neurodegeneration in frame of the EU Joint Program on Neurodegenerative Disease Research (50 k€ funding). A member of the Unit obtained a grant from the Canadian Institute of Health Research as co-applicant (612 CAN\$).

At the national level, members of the Unit are coordinating or partners of fourteen ANR grants for a total funding of 2.2 M€. The Unit is part of two Labex (IRON, 374 k€ funding and MablImprove, 300 k€ funding), coordinates one FHU EXAC-T (Excellence Centre in Autism and Neurodevelopmental disorders) and is a partner of the FHU GenOMedS (Genomic Medicine and Society). Members of the Unit have also successfully responded to calls from the Unit's supervisory authorities (University of Tours, Inserm and Tours University Hospital) regional

authorities and several national and foreign charities (e.g. Fondation de France, Fondation Crédit Agricole, Association for research on SLA, Association ADN, FEANS Switzerland, Fondation John Bost etc.) for a total amount of 6.5 M€ over the reporting period. The Unit also raised funding for salaries in the frame of research contracts (PhD fellowships, including fellowships from foreign countries and Cifre fellowships, salaries for postdocs and engineers with fixed term contracts).

Finally, the Unit raised funding (APR IA Equipment – Centre-Val de Loire Region; FEDER; CPER) dedicated to the acquisition of a Vevo F2 ultrasound scanner with photoacoustics (330 k€) and PET/CT scanner models (746 k€) in close interaction with Inserm and the University of Tours.

## Weaknesses and risks linked to the context

The Unit is not currently leading a H2020 project and did not obtain highly competitive major grants such as FRM Team, ERC or ATIP/Avenir grants.

### *4/ The unit is attractive for the quality of its major equipment and technological skills.*

## Strengths and possibilities linked to the context

The research made at iBrain is supported by state-of-the-art platforms in its immediate vicinity that enable translational research from molecules to the clinic. These platforms provide tools and instruments dedicated to: *i*) molecular studies (mass spectrometry nuclear magnetic resonance spectrometry, CGH array, sequencing, electron and confocal microscopy, flow cytometry with cytometers and cell sorting devices), *ii*) cellular studies (primary neuronal cultures and optical imaging) as well as *in vivo* studies (behavioural tests, stereotaxic surgery, *in vivo* electrophysiology, telemetry, optogenetics, *in vivo* calcium imaging, neurostimulation via TMS or transcranial ultrasound stimulation, and PET/CT), and *iii*) studies in humans (children and adults) including imaging (US, PET/CT, 1.5T and 3T MRI), neurophysiology (EEG), TMS, eye tracking, neurovegetative reactivity and a video-platform for behavioural and psychometric assessment.

Some of these platforms are hosted by the Unit (free access) and handled by technical staff with expertise covering the entire range of the methods used. The iBrain scientific staff also have access to the technological platforms of the University of Tours that are shared with other local research units. These include the 'Analysis of Biological Systems platform' organized in five departments dedicated to metabolomics and chemical analyses, genomics, flow cytometry, microscopy and preclinical imaging facilities, and the PIXANIM platform located in the INRAE campus of Nouzilly and offering services in phenotyping and *in/ex vivo* imaging from the pre-clinical to the molecule. Some of these facilities have received the IBISA label or are part of National infrastructure (e.g. Metabohub), ensuring a service at high international standards. The strong commitment of the iBrain staff in the management of these shared platforms (one is chair of the 'Analysis of Biological Systems platform' and three manage three of its five departments), ensures that their scientific policy matches the technological needs of iBrain.

The iBrain staff are also strongly involved in fund-raising for the renewal of the instruments by applying to regional calls (APR IA Equipment – Centre-Val-de-Loire Region, FEDER, CPER, etc.) in close interaction with the University of Tours. Among the major equipment acquired over the reporting period, one can quote a system for *in vivo* calcium imaging via miniscopes, a Vevo F2 ultrasound scanner with a photoacoustic module and two microPET/CT scanners dedicated to models.

Collectively, these in-house and regional platforms provide all the technologies requested by the projects of the iBrain teams and contribute to the attractiveness of the Unit.

## Weaknesses and risks linked to the context

The number of technological platforms used by the Unit that received a national label (IBISA label) or are part of national infrastructure in biology and health is limited. Accordingly, these platforms mostly depend on regional funding for the renewal of their technologies, which is a risk in the long term.

## EVALUATION AREA 3: SCIENTIFIC PRODUCTION

### Assessment on the scientific production of the unit

The scientific production of the iBrain is excellent. Between 2016 and 2021, iBrain generated 1272 peer-reviewed publications original articles, 502 were as first/last/corresponding author, and 280 other publications. Team 1 has published 287 publications with 156 as first/last/corresponding author (5/year/person). Team 2 has published 283 publications with 81 as first/last/corresponding author (5.2/year/person). Team 3 has published 709 publications with 270 as first/last/corresponding author (5/year/person).

This significant scientific production (qualitatively and quantitatively) shows that the Unit has taken up the last HCERES committee's suggestion of increasing, scientific production in high quality journals (e.g. Molecular Psychiatry, The American Journal of Human Genetics).

#### *1/ The scientific production of the team meets quality criteria.*

##### Strengths and possibilities linked to the context

The overall productivity ranks between very good and excellent given the fact that the Unit works on many highly novel topics with often a strong therapeutic focus.

##### Weaknesses and risks linked to the context

We noted that relatively few members seem to exploit the visibility of publications (and recognisability of scientists as persons), on dedicated platforms like ResearchGate or Google Scholar. A tool to track output and impact (at least as measured by citations) would be helpful.

#### *2/ Scientific production is proportionate to the research potential of the unit and shared out between its personnel.*

##### Strengths and possibilities linked to the context

iBrain is a prolific unit with reference to scientific output, however, with an even stronger potential to increase both volume and quality of its research productivity. The unit has the unique opportunity to become a leader in the field given the Unit's very nature – translational, multi-disciplinary and well equipped.

##### Weaknesses and risks linked to the context

The Unit has shown major improvement in its scientific productivity over the current evaluation period; however, the evaluation committee sees more room for further improvement mainly in terms of publications in high-visibility disciplinary journals or even in multidisciplinary prestigious journals.

#### *3/ The scientific production of the unit complies with the principles of research integrity, ethics and open science.*

##### Strengths and possibilities linked to the context

There is substantial emphasis on the principles of good science, research integrity, prevention of plagiarism and fabrication throughout the document, with specific measures detailed. Paper and/or electronic notebooks seem widespread and well controlled.

There were several safeguards and recommendations against falling prey to openly 'predatory' journals, and the induction of new staff members (often in English in addition to French to ensure good uptake) seems solid as described.

##### Weaknesses and risks linked to the context

While policies and procedures are in place, the Unit is potentially at risk of adverse events and/or adverse publicity as it works with: 1) human research subjects including vulnerable psychiatric patients; 2) pre-clinicals, including pre-clinical models; 3) novel technologies like focused ultrasound that are by definition less well-explored than well-established methods; and 4) radiation.

It is therefore important to remain ever vigilant to keep up high standards.

## EVALUATION AREA 4: CONTRIBUTION OF RESEARCH ACTIVITIES TO SOCIETY

### Assessment on the inclusion of the unit's research in society

Capitalising on the societal impact and translational potential of its research programs, the iBrain unit has established numerous collaborations and partnerships with the non-academic world, including industrial partners, clinicians, especially clinicians of the University Hospital of Tours, charities and patient associations. The Unit is strongly involved in the dissemination of scientific information to the lay public through the active participation of its staff in scientific mediation events such as, for instance, 'la Fête de la Science' or 'la Semaine du Cerveau'. The Unit's staff are active in media and social networks and are engaged in continuing education to the benefit of non-academic actors, such as clinicians and pharmaceutical companies.

Overall, the inclusion of the Unit's research in society is excellent, but its interactions with the non-academic world should be extended to the international level. The Unit should intensify its relations with the clinics and pursue its efforts to increase its funding through industrial contracts and to licence its patents. It should also consider the creation and/or hosting start-ups to reinforce its relationships with the industrial sector.

### *1/ The unit stands out by the quality of its non-academic interactions.*

#### Strengths and possibilities linked to the context

The Unit collaborates with nonacademic entities (FAB Lab – Fabrique d'Usages Numériques –, Fondation Orange, Imagine-VR, STARSTIM-Neuroelectrics, University Hospital of Tours) to develop digital tools and environments as well as immersive reality devices for people with autism spectrum disorders, but also patients with other psychiatric disorders of neuro-developmental origin.

The Unit is engaged in citizen science activities, as illustrated by the construction of a representative cohort with the association 'Life for Paris' and the participation of one Unit's staff in a working group of citizen councils on the ethics in the frame of the Espace de Réflexion Ethique de la Région Centre-Val de Loire (ERERC), as part of an international reflection on the ethical and epistemological stakes of the human genome.

The Unit has developed strong interactions with patient associations (e.g. the National Union of Friends and Families of the Mentally ill and the French-speaking Society for Multiple Sclerosis). One can also quote the partnership with ARAPI association, one of the leading national advocates for people with autism created in Tours in 1983, which has been one of the cornerstones of the Excellence Center and FHU ExAC-T and has yielded the creation of the INSERM GRAM, a national think-tank on policies that govern partnerships and dialog between INSERM and patient organisations.

Overall, the Unit has obtained numerous grants from charities and foundations (Fondation de France — 6 projects —, Fondation Crédit Agricole, Association for Research on SLA, Association AND, Fondation Paul Bennetot, Fondation for rare diseases, FEANS, Fondation John Bost, Fondation pour l'audition etc.) representing more than 2 M€ funding, and actively participates in fund-raising events for charities (e.g. Rotary Club).

In line with the translational potential of its research projects, the Unit has been involved in fourteen clinical trials. Based on their expertise, the Unit's staff have participated in the drafting of standards (e.g. ISO and AFNOR standards) and recommendations to the benefit of health authorities (HAS), learned societies, clinicians, etc., such as for example, recommendations on prevention of inadvertent perioperative hypothermia in adults and recommendations for the French Association for Psychiatric Biology and Neuropsychopharmacology (AFPBN). Overall, they performed 35 technical expertise for different national and international organisations.

The Unit is strongly involved in continuing education (~75 h/year) for professionals from different sectors, including teachers employed by the Ministry of Education, speech-language therapists, physicians, psychologists, nurses, etc.

#### Weaknesses and risks linked to the context

Most of the non-academic interactions of the unit involve national organisations. Its interactions with international organisations remain sparse.

## *2/ The unit develops products for the socio-economic world.*

### Strengths and possibilities linked to the context

The Unit has established collaborations and partnerships with industry in the fields of imaging (Vermon, Supersonic Imaging and Siemens), metabolomics (Alice and Waters), healthcare (Irlynx, Carestream SA, Bracco SA and EXCAT) and pharmacy (Biofortis Mérieux NutriSciences, Terali, Allergan/Abbvie, Prexton Therapeutics/Lundbeck/BeeTerapi, Key-Obs, etc.). This yielded thirteen collaborations contracts over the reporting period including seven with the funding of the Unit for a total amount of 627 k€, mostly in the fields of neuropsychiatric (depression and post-traumatic stress disorder), neurodevelopmental (autism and other neurodevelopmental disorders) and neurodegenerative (amyotrophic lateral disorders, Alzheimer's and Parkinson's diseases) disorders but also other diseases (e.g. cancer, lung infections, and hearing loss).

The Unit has obtained three Cifre PhD fellowships, has filled eleven patents (including one licenced patent) and has published a psychometric scale.

The Unit has designed ultrasound devices and protocols to cure treatment-resistant depression by ultrasoundneuromodulation in collaboration with Vermon S A.

Team 1 (Depression group) hosts the Innovation Manager of SAM Sensory and Consumer Research who is half-time associate teacher at the Agrosiences department of the University of Tours. Team 3 hosted several staff of its industrial partners (e.g. one R&D engineer from Carestream SA, which co-funded three Cifre PhD fellowships for ultrasound imaging applications in association with ANR, and one R&D officer from Alice) through research hosting agreements.

### Weaknesses and risks linked to the context

Although eleven patents from the Unit have been filled over the reporting period, only one of them has been licenced. The Unit has obtained a significant number of industrial contracts (13), but only half of them provided funding to the teams. Overall, the funding raised by the Unit in the frame of industrial contracts (627 k€) is somewhat modest with respect of the funding raised from other sources. There is no start-up hosted by the unit.

## *3/ The unit shares its knowledge with the general public and takes part in debates in society.*

### Strengths and possibilities linked to the context

The Unit is strongly involved in local scientific outreach activities (e.g. la Fête de la Science, la Semaine du Cerveau, la Maison pour la Science, les Jeudi de la santé, Les Mercredis de Thélème, etc.) in collaboration with the University Hospital of Tours and the City Council of Tours. Its members also participated in debates with the general public (e.g. a debate on France 2 TV channel entitled 'Vivre avec un enfant autiste' in 2020), or directly in contact with the public following the screening of films or in the frame of Inserm communication operations (e.g., Terre de Sciences).

Many members of the Unit are regularly invited for interviews or make interventions in various print and audiovisual media, such as Le Monde, France-Inter (La tête au carré and Grand bien vous fasse), France 3, France 5, France info, France Bleu, France Culture, TV Tours Val de Loire, Women Today, Le Figaro, Ouest France, Festival d'Avignon, etc. They also made several contributions to the national scientific press such as Sciences et Avenir, Cerveau & Psycho, Journal de l'INSERM, Carnets de Science, etc. They published books intended for the lay public, such as 'Le Trauma : comment s'en sortir ?' and informative readings in the Encyclopaedia Universalis (Jacques Monod — Le hasard et la nécessité ; François Jacob — La logique du vivant ; l'épigénétique).

The Unit actively participates in awareness-raising actions for primary, middle and high school pupils. It regularly organises visits of its laboratories (ultrasound, MRI and metabolomics) and technological platforms (metabolomics and small imaging) and repeatedly hosts middle school and high school interns. Its members contribute to outreaching actions for young people and teachers at primary and secondary levels. They also contributed to the editorial committee of the multimedia Philosophical Encyclopaedia in French (<https://encyclo-philo.fr/>) intended for teenagers, their teachers and the general public.

### Weaknesses and risks linked to the context

There is no major weakness in the diffusion of the Unit's knowledge to the lay public and its participation in debates in society. The Unit's staff members are very active in these fields.

## C – RECOMMENDATIONS TO THE UNIT

### *Recommendations regarding the Evaluation Area 1: Profile, Resources and Organisation of the Unit*

The committee endorses the continuation of the external Scientific Advisory Board and recommends regular yearly formal evaluations and discussions. The successful attraction of competitive financial resources has to remain at least at the same level, the Unit should focus on more efficient support for ERC grants applicants. PhD students mentioned tensions between researchers (quoted for all teams and for the unit), the management of the unit should take this aspect into account, with an easier way to knock at the door of direct supervisors, but also of supervisors with higher responsibilities in case of difficulties.

### *Recommendations regarding the Evaluation Area 2: Attractiveness*

The committee recommends iBrain to strengthen its attractiveness toward foreign students and postdocs by applying to Marie Skłodowska-Curie Postdoctoral Fellowships or taking part in Innovative Training Networks for the funding of Marie Skłodowska-Curie PhD fellowships.

The committee also recommends iBrain to pursue its efforts to attract talented young scientists and to encourage them to apply to Atip/Avenir or ERC Starting/Consolidator grants.

### *Recommendations regarding Evaluation Area 3: Scientific Production*

The Unit has shown major improvement in its scientific productivity over the current evaluation period; however, the evaluation committee sees more room for further improvement mainly in terms of publications in high-ranked journals rather than volume.

### *Recommendations regarding Evaluation Area 4: Contribution of Research Activities to Society*

The committee recommends iBrain to better exploit the translational potential of its research programs by intensifying its interactions with clinicians and the industrial sector. In this regard, the committee recommends the Unit to consider the creation and/or the hosting of start-up companies.



## TEAM-BY-TEAM ASSESSMENT

**Team 1:** Neuro-functional psychiatry  
Name of the supervisor: Frédérique Bonnet-Brilhault

### THEMES OF THE TEAM

The team aims to identify the relevant brain circuits and key neurophysiological mechanisms underlying autism and depression, and predicting non-response to current therapies through a hypothesis-driven strategy based on a combination of different cognitive neuroscience methods.

The main objective of the Autism group is to identify markers of the atypical functioning of key neuronal networks and to combine them with clinical, behavioral, cognitive and sensorimotor atypicalities in order to establish specific bioclinical profiles. Three sensory modalities are studied (vision, audition and touch) from children to adults using EEG and fMRI, to:

- i) localize the cerebral regions involved in information processing and studying perception and cognition mechanisms;
- ii) and study the strategies involved in environmental exploration using eye-tracking.

The Depression group studies in humans and pre-clinicals found that the formation of new neurons in the hippocampus plays a major role in the regulation of stress.

### CONSIDERATION OF THE RECOMMENDATIONS OF THE PREVIOUS REPORT

Following the recommendations to maintain focus on the most fruitful interests and maintain the rate of publishing in high impact journals, Team 1 achieved the goals to publish in high-ranked journals. For the Autism group, 70% of the published 115 articles since 2016 (e.g. Translational Psychiatry; Genetics in Medicine; J. Child Psychol Psychiatry). Similarly, the Depression Group produced four highly cited papers during the period of 2016–2021 (top 1% compared to other papers published in the same field in the same year). For the 7.9 full-time equivalent positions in the Depression group, there are fourteen publications (e.g. an invited review in Molec Psychiatry) and six highly cited papers (Web of Science). The group published on average 45.1 papers (normalised to 1 full-time equivalent) reaching 56% on average per PI.

To address previous the recommendation regarding attracting a higher number of post-doctoral fellows, Team 1 introduced a systematic inclusion of funding requests dedicated to postdoctoral positions in their grant applications and ramped up the advertisement in (inter)national scientific communities. This resulted in obtaining four postdoctoral positions starting in 2019 thanks to funding from the Fondation de France; ANR; H2020 Europe as partner and intramural University grants.

The recommendation to increase the interaction between the Autism group and the Depression groups. Communications between researchers and teams have been facilitated (two annual seminars, five inter-thematic working groups) but does not abolish the communication difficulties in this large INSERM unit with different sites, and with researchers with different backgrounds, working on different disorders, topics or approaches.

To increase the number of senior neuroscientists, team 1 supported two INSERM candidates in 2018 and 2019 that resulted in hiring three Inserm researchers and a CNRS Research Director. Responding to the criticism of not having sufficient number of postdoctoral clinical scientists, the Autism group supported eight PhD candidates toward this academic grade and ensured that one becomes a postdoctoral researcher and five were kept on tenured or temporary university/hospital positions.

The point of criticism about the novelty and originality of the Autism focus on language impairment and perception difficulties was addressed adequately with a number of highly innovative publications and international activity that will result in holding the annual meeting of the international network on Language Abilities in Children with Autism (LACA) scheduled in Tours. The decision to focus on change detection of emotional or nonemotional information was well articulated and remained a strong line of research in the Autism group.

The Depression group allocated significant efforts to address the criticism about the design and development of a new stress independent pre-clinical model of therapy-resistant depression by shifting its focus on early depression and childhood stress events as a vulnerability factor.

Given the involvement of team 1 in various basic and clinical science initiatives at the national and international levels, the team also fulfilled the recommendation to increase the attractiveness of the Unit. Considering the impact of the COVID-19 pandemic, the unfulfilled intention to increase the number of conferences and workshops aiming at promoting the Unit should not be taken in the full account.

## WORKFORCE OF THE TEAM

<b>Permanent personnel in active employment</b>	
Professors and associate professors	7
Lecturers and associate lecturers	14
Senior scientists (Directeur de recherche, DR) and associates	1
Scientists (Chargé de recherche, CR) and associates	5
Other scientists (Chercheurs des EPIC et autres organismes, fondations ou entreprises privées)	0
Research supporting personnels (PAR)	11
<b>Subtotal permanent personnel in active employment</b>	<b>38</b>
Non-permanent teacher researchers, researchers and associates	6
Non-permanent research supporting personnels (PAR)	2
Post-docs	1
PhD Students	10
<b>Subtotal non-permanent personnel</b>	<b>19</b>
<b>Total</b>	<b>57</b>

## EVALUATION

### Overall assessment of the team

The team's scientific production was evaluated as excellent given the number of scientific publications (e.g. Transl Psychiatry, Autism res, Molec Psych) Team 1 managed to obtain an impressive amount of funding. This attracted senior neuroscientists to the team (excellent Attractiveness). Team 1 established itself as the clinical core of the Unit and maintained the focus of the public eye given the societal importance of two of the most prevalent neuropsychiatric disorders – autism and depression (Links to Society – excellent).

The goal of merging the two groups into one team set for the current evaluation period with the aim to create a critical mass is now fulfilled. The plan to split into two autonomous teams – Autism and Neurodevelopment and Experimental & Translational Psychiatry is the logical consequence of a successful period with the establishment of clear vision for the future, supported by adequate infrastructure and funding.

As areas for improvement, the evaluation committee sees the further integration of clinical scientists throughout the whole range of scientific activities. There should be a programme for regular scientific exchanges between early career clinicians and the research teams.

### Strengths and possibilities linked to the context

The global impression of PhD students was good, they indeed rank four out of five of the overall quality of their research experience, mentioning good relationships between themselves, diversity of projects, good interactions with seniors and interesting links with hospital.

Team 1 is part of many large international networks for autism which is a prerequisite for large-scale research. The subgroup on affective disorder is part of the Fondamental French network, which also offers large opportunities for very large recruitment.

An obvious and important effort is made by team 1 to promote knowledge of the global population on both autism and depression, two disorders with a very high level of stigmatisation and ignorance.

A transcranial focused ultrasound stimulation (tFUS) has been recently acquired, this technic might have an important role in the future, creating another way to increase interactions between the subgroups working on depression and autism.

## Weaknesses and risks linked to the context

Team 1 is a large group but with only six scientists (around 10% of the staff), it is therefore mainly led by clinicians who usually have many other responsibilities (therefore less availability).

## RECOMMENDATIONS TO THE TEAM

With around 10% of staff members in team 1 being full-time researchers, the recommendation to try continuing the recruitment of full-time researchers with permanent positions, although challenging everywhere, should be kept as a priority.

Mixing EEG and ultrasound technic is a new approach with many possibilities to further understand how the brain reallocate cognitive resources to resolve a cognitive challenge. Such an approach should be used in both disorders (autism and depression), which means in children and adults, as team 1 has the relatively rare opportunity to do both, creating new insights and potentially interesting results. Such efforts of using more identical tools in both disorders should be promoted, just as for the recently acquired tFUS.

Being part of large national and international networks is a very positive point of team 1, in line with their productivity. Such interactions should be increased in the future, more and more as leaders, not only partners.

**Team 2:** Neurogenomics and neuronal patho-physiology

Name of the supervisor: Frédéric Laumonier

## THEMES OF THE TEAM

The team 'Neurogenomics and neuronal pathophysiology' investigate genetics and pathophysiological landscapes in intellectual disability (ID) and in amyotrophic lateral sclerosis (ALS) using multidisciplinary and translational approaches (patients and pre-clinical models, *in vitro* and *in vivo* models, metabolomic and genetic analyses).

Among its major findings during the reporting period, the team identified a novel gene (CRMP5) involved in ID and brain malformations, from the clinical, genetic analysis to the characterisation of the pathophysiological mechanisms. Functional analyses revealed impaired dendritic outgrowth processes in young developing hippocampal primary neuronal cultures overexpressing the missense variants. The team also identified a novel synaptic pathway linked to the PTCHD1 protein involved in neurodevelopmental disorders and showed a clinical benefit of an agonist of FGF21 receptors in SOD1-G93A model, a preclinical model for ALS.

## CONSIDERATION OF THE RECOMMENDATIONS OF THE PREVIOUS REPORT

The team was advised to publish in higher impact journals. The team states that 53/267 (20%) of its publications during the reporting period was in top tier journals, including Mol Psychiatry, Am J Hum Genet, Nat Genet and Brain (1 review).

Another recommendation was to present at international meetings: the team members have presented their work at several conferences (e.g. Assises Génétique 2020, ENCALS2019, ECNP2019, IGEE2019, SFN2021) during the reporting period. As encouraged by previous reports the team published reviews in high impact journals (Brain, Annals of Neurology, Nat Rev Endocrinol and Nat Rev Neurosci.).

Increasing public engagement was supported by participation in a range of outreach activities during the period, taking part in yearly science festivals, patient forums, high school events, YouTube, television programs, publication in the Conversation.

As recommended, the team also hosted six postdocs and research associates (with upcoming increase thanks to ANR grants starting in 2021) and are involved in the Pathophysiology's Master's degree.

## WORKFORCE OF THE TEAM

<b>Permanent personnel in active employment</b>	
Professors and associate professors	7
Lecturer and associate lecturer	3
Senior scientist (Directeur de recherche, DR) and associate	1
Scientist (Chargé de recherche, CR) and associate	0
Other scientists (Chercheurs des EPIC et autres organismes, fondations ou entreprises privées)	0
Research supporting personnel (PAR)	11
<b>Subtotal permanent personnel in active employment</b>	<b>22</b>
Non-permanent teacher researchers, researchers and associates	2
Non-permanent research supporting personnel (PAR)	0
Post-docs	3
PhD Students	10
<b>Subtotal non-permanent personnel</b>	<b>15</b>
<b>Total</b>	<b>37</b>

### Overall assessment of the team

The team's production was overall excellent, with publications in top journals for the discipline and strong national grant income (very good Resources). Attractiveness and Links to Society are excellent.

Scientific highlights include the identification of new pathophysiological pathways (*PTCHD1*, *DPYSL5*) in neurodevelopmental disorders associated with ID and brain malformations, and of pathogenic variants in familial ALS. One preclinical study (mouse model of ALS) in collaboration with the Labex MablImprove identified a potential therapeutic application via the FGF21 pathway.

Areas for improvement include European/international grant income and industrial contracts.

### Strengths and possibilities linked to the context

This team comprises eleven permanent scientists and eleven support staff. They have supervised twenty PhD students over the reporting period. The team published 283 articles and averaged 5.2 per year per PI as the main author. The team published 81 articles as first/last/corresponding authors (10 in Top10% journals such as *Molecular Psychiatry*, *Am J Hum Genet* and *J. Neurol NeuroSurg Psychiatry*).

Research outputs have been impactful at the national level: they have been reported by Inserm through national press releases (Bonnet-Brilhault et al., 2016; Ung et al., 2018) and/or have been highlighted in lay scientific journals (*Sciences et Vie*, *La revue médicale suisse*). Work was disseminated via 24 invited presentations at conferences (e.g. ECNP2019, IGEE2019, SFN2021), and the team organised five international conferences. There are strong international partnerships via co-authored publications in the field of genetics (ID – GENCODYS, ALS – STRENGTH, MINE), neurology (ALS consortium) and pathophysiology (genes of interest: *PTCHD1*, *DPYSL5*). Each doctoral student has published one article as 1st author (as per doctoral rules), and all researchers have contributed to publications.

Several research projects funded by the Centre-Val de Loire Region involve non-academic partners (Encéfa, MabSilico, KeyObs etc.). The team has links with industrial partners on antibodies and intrabody development via the Labex MablImprove and a partnership with Biogene. The successful project Intrabals (2017–2020, regional funds) led to the funding of another follow-up project (SLAmait) by the region. The team has frequent interactions with patient 'associations' (intellectual disabilities-MED13L; ALS-ARSLA), and received funding from charities (Association for the Development of Neurogenetics). Team members are part of the Scientific Council and the administrative body of ARSLA; they are involved in clinical guidelines. Dissemination to the lay public is evident and frequent with yearly activities ('Fête de la science', Brain awareness week, Health Thursdays (Jeudis de la Santé) within a partnership between the University Hospital of Tours and the City Council of Tours. The team also hosts high school students via 'Inserm Jeunes antenna'.

The income over the period was 4,458 k€, 27 % was obtained through regional funding calls (1,211 k€), 63% via national/international calls (2,837 k€, 17 from charities) and 3% via partnerships. One contract (private company BIOGEN 150k€) and one three-year European contract (619 k€, JPND) were obtained by a team member as coordinator. Four contracts were in collaboration with Team 3.

One study published in *J. Neurol NeuroSurg Psychiatry* was awarded the Excellence prize in neurology from the French Society of Neurology. Three prizes were awarded (Prix Fondation Planiol; Prix the these de la ville de Tours; PEDR INSERM).

Overall, the team has made significant scientific discoveries and followed the previous recommendations provided by HCERES.

### Weaknesses and risks linked to the context

The proportion of income via national and international competitive calls is limited (<5%). Relative to teams 1 and 3, outreach activities toward the general public are lower (a few per PI).

## RECOMMENDATIONS TO THE TEAM

The committee encourages the team to pursue its efforts to publish its work in wide readership and historically recognised journals specialised in Neuroscience with high quality standard requirements and revision processes, and the team's staff to increase their contribution as first or senior authors.

There is scope for developing partnership with industry and patent generation when this is applicable.

The team members are encouraged to lead international grant applications, including at the European level.

There is scope to increase involvement in scientific debates, in outputs aimed at the general public (media), and outputs aimed at the professional world.

**Team 3:** Imaging, biomarkers and therapy  
 Name of the supervisor: Patrick Emond and Ayache Bouakaz

## THEMES OF THE TEAM

The team combines imaging technologies with developments in the fields of metabolomics and imaging and data processing to improve the understanding of the neurophysiological mechanisms of psychiatric diseases, as well as facilitating the discovery of biomarkers.

The team also develops new therapeutic strategies based on the use of ultrasound technology for brain neurostimulation and to enhance drug delivery.

They developed and applied standardised operating procedures for biological specimens as cell cultures, urine, blood, saliva, and feces using multiple analytical platforms in order to get the widest metabolome coverage to trace many metabolic pathways. More specifically, they develop quantitative LC-MS/MS for the simultaneous quantification of tryptophan metabolites. They are also developing PET tracers for different brain targets mainly involved in the neurotransmission and neuroinflammation processes.

## CONSIDERATION OF THE RECOMMENDATIONS OF THE PREVIOUS REPORT

Members of team 3 were particularly attentive to the recommendations issued by the previous HCERES committee.

A real thematic coherence can be underlined with a focus on the development of medical technologies for an application in the field of neurology (psychiatric diseases, neurodegenerative diseases and cancers). The varied panel of journals selected for publications over the last mandate (2016–2021) reflects the very broad spectrum of the work carried out by team 3, from mechanistic studies to clinical trials. Efforts are made to publish in the best journals: 47 and 25% of publications in journals (e.g. Transl Psychiatry; NeuroImage; Sci Rep; Front Med). These results can be improved and these efforts must be continued.

To strengthen the international visibility of the team, the members of team 3 have been very active in the field of scientific animation (board of ISTU, Vice President of IEEE UFFC Society, member of the scientific committee of the European Association of Nuclear Medicine, President of the Drug Development Group of the European Association of Nuclear Medicine). The organisation of the International Ultrasonic Symposium in 2016 in Tours was a genuine success which contributed significantly to the international visibility of the team.

## WORKFORCE OF THE TEAM

<b>Permanent personnel in active employment</b>	
Professors and associate professors	17
Lecturers and associate lecturers	12
Senior scientists (Directeur de recherche, DR) and associates	2
Scientists (Chargé de recherche, CR) and associates	1
Other scientists (Chercheurs des EPIC et autres organismes, fondations ou entreprises privées)	1
Research supporting personnels (PAR)	23
<b>Subtotal permanent personnel in active employment</b>	<b>56</b>
Non-permanent teacher researchers, researchers and associates	16
Non-permanent research supporting personnels (PAR)	2
Post-docs	13
PhD Students	47
<b>Subtotal non-permanent personnel</b>	<b>78</b>
<b>Total</b>	<b>134</b>

### Overall assessment of the team

This team is well integrated into its environment (37/180 joint publications with the other teams) and has shown an excellent scientific production (320 original articles) in the best journals (e.g. Transl Psychiatry; NeuroImage; Sci Rep; Front Med).  
Economic valuation could be developed through the creation of start-ups or the transfer of licenses to industrial partners.

### Strengths and possibilities linked to the context

The strength of the team lies in its interdisciplinarity and its thematic coherence in the field of neurology. The team is composed of methodological experts and clinicians who are very involved in clinical transfer. Developments in the field of quantitative metabolomics are particularly innovative. Their application to the opening of the blood-brain barrier by ultrasound opens up real prospects for understanding the mechanisms involved in this booming therapeutic technique. One can imagine similar gateways between the work carried out for the development of PET tracers in functional imaging and neuromodulation by ultrasound. In the field of PET and ultrasound imaging, the team has demonstrated its ability to lead a project from methodological design to its evaluation in the context of a clinical study. The atlas project is an excellent initiative led by this team. But the distribution of this tool and its use by other teams are not described.  
The team has developed privileged international partnerships with the University of Hokkaido in Japan and that of X'ian in China. These strong partnerships result in a large number of joint publications (20).

### Weaknesses and risks linked to the context

While clinical transfers are significant, they can be pursued in the field of therapeutic ultrasound in particular. This will require the team to acquire clinical ultrasound devices, to develop and evaluate its own devices (the team is able to do this thanks to its expertise and the CIC) or to get closer to other leading clinical teams. Our decision to focus on liver cancer research and treatment was not influenced by a lack of equipment for brain treatment. It was a strategic choice that we made more than 15 years ago, before the availability of ultrasound equipments for brain treatments.  
The numerous methodological developments deserve industrial transfers to benefit the greatest number of patients.

## RECOMMENDATIONS TO THE TEAM

The expertise of the team would justify a clinical transfer for applications of therapeutic ultrasound in the field of neurology. This would require either investing in a clinical ultrasound device, or developing collaborations with teams that have already made this transition.

Economic valuation must be developed (no licenses or creation of start-ups). The anatomical atlas of the brain is a good example of a tool that should benefit the community but whose benefit is hard to measure when reading the document.



## CONDUCT OF THE INTERVIEWS

### Date(s)

**Start:** 03 février 2023 à 8 h 30

**End:** 03 février 2023 à 18 h 30

8 h 30	<b>Start of the visit</b>
8:30 a.m.-8:45 a.m.	Closed session with the committee
8:45 a.m.-9 a.m.	Presentation of the committee
9 a.m.-9:45	Presentation of the unit by the present director Ms Catherine Belzung (Plenary session, 30' presentation + 15' discussion with the committee)
9:45-10:15	Presentation of Team 1: Neurofunctional psychiatry (Frédérique Bonnet-Brilhault). (10' presentation + 15' question + 5' in private PI committee)
10:15-10:30	coffee break
10:30-11:00	Presentation of Team 2: Neurogenomics and neuronal physiopathology (Frédéric Laumonnier). (10' presentation + 15' question + 5' in private PI committee)
11:00-11:30	Presentation of Team 3: Imaging, biomarkers and therapy (Patrick Emond and Ayache Bouakaz). (10' presentation + 15' question + 5' in private PI committee)
11:30-1 p.m.	Private meeting of the visiting committee (report preparation)
1 p.m.-2 p.m.	Lunch
2:10 p.m.-2:30 p.m.	Meeting with engineers, technicians and administrative personnel in French
2:30 p.m.-3 p.m.	Meeting with students and postdocs
3 p.m.-3:30 p.m.	Meeting with scientists, no lab director
3:30 p.m.-4 p.m.	Meeting with team leaders, no lab director
4 p.m.-4:30 p.m.	Discussion with the director Ms Catherine Belzung
4:30 p.m.-5 p.m.	Discussion with the representative of the funding bodies
5 p.m.-5:15 p.m.	coffee break
5:15 p.m.-6:30 p.m.	Private meeting of the visiting committee (report preparation, closed-door)
6:30 p.m.	<b>End of the visit</b>

**Interview conducted: on-site or online**

### INTERVIEW SCHEDULE

### PARTICULAR POINT TO BE MENTIONNED

Tutelles :

Catherine Beaumont, Université de tours  
 Frédéric Delaleu, Inserm  
 Etienne Hirsch, ITMO, Neurosciences  
 Franck Lethimonnier, Inserm



## GENERAL OBSERVATIONS OF THE SUPERVISORS

**Hcéres**  
**Département d'évaluation de la recherche**

Tours, le 23 juillet 2023

**objet : DER-PUR230023135 - IBRAIN - Imagerie et cerveau.**

Au nom de l'unité de recherche IBRAIN, j'adresse mes sincères remerciements aux membres du comité de visite HCERES pour leur rapport et leurs recommandations.

L'unité de recherche IBRAIN n'a pas d'observations de portée générale à formuler.

Je vous prie d'agréer l'expression de mes salutations distinguées.

Le Président de l'université de Tours

  
Arnaud GIACOMETTI

The Hcéres' evaluation reports are available online:  
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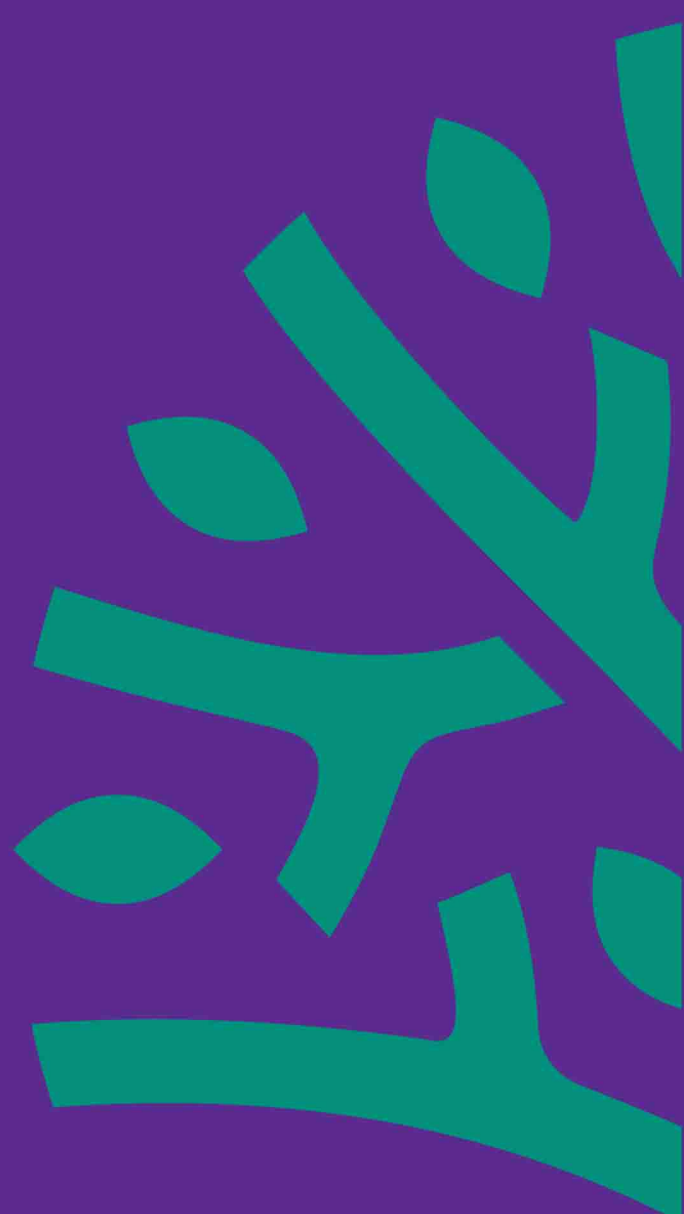
**Evaluation of Universities and Schools**

**Evaluation of research units**

**Evaluation of the academic formations**

**Evaluation of the national research organisms**

**Evaluation and International accreditation**



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